Clinical trial results:
Enhancing the BCG-induced trained immunity response by addition of bisphosphonate or MMR vaccine: a possible preventive approach against COVID-19 (BCG-PLUS)

Summary

EudraCT number	2020-002456-21
Trial protocol	NL
Global end of trial date	03 September 2020

Results information

Result version number	v1 (current)
This version publication date	29 July 2022
First version publication date	29 July 2022
Summary attachment (see zip file)	Synopsis BCG-PLUS (Synopsis BCG-PLUS.pdf)

Trial information

Trial identification

Sponsor protocol code	74082

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Dutch trial registry: NL74082.091.20

Notes:

Sponsors

Sponsor organisation name	Radboudumc
Sponsor organisation address	Geert grooteplein zuid 8, nijmegen, Netherlands,
Public contact	Jaap ten Oever , Radboudumc, jaap.tenoever@radboudumc.nl
Scientific contact	Jaap ten Oever , Radboudumc, 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	Interim
Date of interim/final analysis	01 November 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 September 2020
Global end of trial reached?	Yes
Global end of trial date	03 September 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the effect of bisphosphonates and the MMR vaccine on BCG-induced trained immunity as a preventive approach against COVID-19

Protection of trial subjects:

Blooddrawing and vaccination were performed by trained and experienced nurses and always in presence of a medical doctor. Subjects were monitored after the intervention. If any faintness occured adequate measures were taken to ensure the swiftly recovered. Subjects were given emergency contact information in case an adverse event occured.

Background therapy: -

Evidence for comparator:

BCG vaccine: BCG has been shown to induce trained innate immunity both in vitro and in vivo. There is evidence that BCG protects against viral infections in animal models .

MMR vaccine: To our knowledge, there are no relevant pre-clinical studies regarding the MMR vaccine as an immune modulator for BCG vaccination. However, it has been hypothesized that trained immunity is responsible for the beneficial NSEs of live vaccines other than BCG. There is also preliminary epidemiological evidence that suggests a protective effect MMR vaccination against SARS-CoV-2 infection .

Bisphosphonates: To our knowledge, there are no relevant pre-clinical studies regarding bisphosphonates as immune modulators for BCG vaccine. However, the immunomodulatory capacity of bisphosphonates is well-described. In a mouse model, bisphosphonates have been shown to exhibit potent adjuvant activities for other vaccines. Monocytes and macrophages are cells from the same myeloid lineage as osteoclasts, the originally intended target of bisphosphonates . There is evidence from in vitro experiments that bisphosphonates enhance the cytokine release of monocytes and macrophages . Furthermore, alendronate (the intended bisphosphonate of use in this study) has been shown in vitro to enhance trans-endothelial migration and pro-inflammatory cytokine production of PBMCs (29). Amongst the upregulated pro-inflammatory cytokines was interferon gamma, which is of crucial importance in the host defense against viral infections. Further in vitro evidence suggests that nitrogen-containing bisphosphonates (such as alendronic acid) activate γδ-T cells via monocytes

Actual start date of recruitment	03 June 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 104
Worldwide total number of subjects	104
EEA total number of subjects	104

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)	104
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

DATE and No. inclusions
3-6-20: n=6,
8-6-20: n=4,
12-6-20: n=11,
19-6-20: n=7,
26-6-20: n=12,
3-7-20: n=7,
10-7-20: n=9,
15-7-20: n=4,
17-7-20: n=12,
23-7-20: n=9,
31-7-20: n=9,
6-8-20: n=4,
Total: 104

Pre-assignment

Screening details:

Inclusion criteria
• Adult (18-50 years of age)
• Male or female
• Healthy

104 participants were included. 1 participant didn't meet criteria and was excluded. 5 participants dropped out (consent withdrawn by subject). 1 participant was lost to follow up.
Data was therefore complete for 97 participants.

Period 1

Period 1 title	Recruitment and first visit
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants were randomly assigned to the placebo group or one of the 4 experimental groups (1:1:1:1:1).
A single placebo vaccine (0.1 ml 0.9% NaCl,) was given intradermally in the left upper arm.
80 ml of blood was drawn before the intervention.
After 28-38 days, 80 ml of blood was drawn again.

Arm type	Placebo
Investigational medicinal product name	Natriumchloride CF 9 mg/ml, injectievloeistof
Investigational medicinal product code	RVG 50825
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Cutaneous use

Dosage and administration details:

Administered into the left upper arm slowly (intradermal), in about 10 seconds, 0.1 ml of 0.9% NaCl solution, for BCG placebo.

Arm title	BCG vaccine

Arm description:

Participants were randomly allocated in the BCG vaccination group or in one of the other 4 arms of the study using a computer algorithm, in a 1:1:1:1:1 ratio.

80 ml of blood was drawn before the intervention.
After 28-38 days, 80 ml of blood was drawn again (2nd visit)

Arm type	Experimental
Investigational medicinal product name	BCG vaccin SSI, 0,75 mg per ml, poeder en oplosmiddel voor suspensie voor injectie
Investigational medicinal product code	J 07 AN 01
Other name	
Pharmaceutical forms	Powder and solvent for suspension for injection in pre-filled syringe
Routes of administration	Cutaneous use

Dosage and administration details:

Administer into the left upper arm slowly, in about 10 seconds, intracutaneously 0.1ml of the suspended vaccine, which accounts for 0.075mg of attenuated Mycobacterium bovis.

Arm title	MMR vaccine

Arm description:

participants were randomly allocated to the MMR vaccine group or the other 4 groups in a 1:1:1:1:1 algorithm .
80 ml of blood was drawn before the intervention.
After 28-38 days, 80 ml of blood was drawn again (2nd visit)

Arm type	Experimental
Investigational medicinal product name	M-M-RVAXPRO poeder en oplosmiddel voor suspensie voor injectie
Investigational medicinal product code	J07BD52
Other name	
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Administer into the right upper arm, intramuscular. The adult dose is 0.5 ml of the resuspended vaccine, which accounts for

- Live attenuated mumps virus (strain 'Jeryl Lynn', at least 12.5 * 10^3 CCID50);
- Live attenuated measles virus (strain "Enders' Edmonston", at least 1 * 10^3 CCID50);
- Live attenuated rubella virus (strain 'Wistar RA 27/3', at least 1 * 10^3 CCID50)

Arm title	BCG+MMR

Arm description:

participants were randomply allocated to the BCG+MMR group or the other 4 groups in a 1:1:1:1:1 algorithm.
80 ml of blood was drawn before the intervention.
After 28-38 days, 80 ml of blood was drawn again (2nd visit)

Arm type	Experimental
Investigational medicinal product name	BCG vaccin SSI, 0,75 mg per ml, poeder en oplosmiddel voor suspensie voor injectie
Investigational medicinal product code	J 07 AN 01
Other name	
Pharmaceutical forms	Powder and solvent for suspension for injection in pre-filled syringe
Routes of administration	Cutaneous use

Dosage and administration details:

Administer into the left upper arm slowly, in about 10 seconds, intracutaneously 0.1ml of the suspended vaccine, which accounts for 0.075mg of attenuated Mycobacterium bovis.

Investigational medicinal product name	M-M-RVAXPRO poeder en oplosmiddel voor suspensie voor injectie
Investigational medicinal product code	J07BD52
Other name	
Pharmaceutical forms	Powder and solvent for suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Administer into the right upper arm, intramuscular. The adult dose is 0.5 ml of the resuspended vaccine, which accounts for:

- Live attenuated mumps virus (strain 'Jeryl Lynn', at least 12.5 * 10^3 CCID50);
• Live attenuated measles virus (strain "Enders' Edmonston", at least 1 * 10^3 CCID50);
• Live attenuated rubella virus (strain 'Wistar RA 27/3', at least 1 * 10^3 CCID50)

Arm title	BCG+Alendronate

Arm description:

participants were randomly allocated to the BCG+Alendronate group in a 1:1:1:1:1 algorithm.
80 ml of blood was drawn before the intervention.
After 28-38 days, 80 ml of blood was drawn again (2nd visit)

Arm type	Experimental
Investigational medicinal product name	BCG vaccin SSI, 0,75 mg per ml, poeder en oplosmiddel voor suspensie voor injectie
Investigational medicinal product code	J 07 AN 01
Other name	
Pharmaceutical forms	Powder and solvent for suspension for injection in pre-filled syringe
Routes of administration	Cutaneous use

Dosage and administration details:

Administer into the left upper arm slowly, in about 10 seconds, intracutaneously 0.1ml of the suspended vaccine, which accounts for 0.075mg of attenuated Mycobacterium bovis.

Investigational medicinal product name	Alendroninezuur Aurobindo 70 mg, tabletten
Investigational medicinal product code	RVG 103208
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Administer the alendronic acid tablet orally. The tablet should be taken at least 30 minutes before eating/drinking/taking other medication on that day. 1 tablet contains 70 mg alendronic acid. The following measures should be taken to prevent esophageal side effects: the tablet should be swallowed as a whole, together with a full glass of (flat) tap water, whilst the participant remains in an upright position. The participant should not lie down for at least 30 minutes following administration

Number of subjects in period 1	Placebo	BCG vaccine	MMR vaccine
Started	21	21	21
Completed	21	21	21

Number of subjects in period 1	BCG+MMR	BCG+Alendronate
Started	21	20
Completed	21	20

Period 2

Period 2 title	Second/last visits
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	placebo

Arm description:

Participants were randomly assigned to the placebo group or one of the 4 experimental groups (1:1:1:1:1). A single placebo vaccine (0.1 ml 0.9% NaCl,) was given intradermally in the left upper arm. 80 ml of blood was drawn before the intervention. After 28-38 days, 80 ml of blood was drawn again

Arm type	Placebo
Investigational medicinal product name	Natriumchloride CF 9 mg/ml, injectievloeistof
Investigational medicinal product code	RVG 50825
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Cutaneous use

Dosage and administration details:

Administered into the left upper arm slowly (intradermal), in about 10 seconds, 0.1 ml of 0.9% NaCl solution, for BCG placebo.

Arm title	bcg vaccine

Arm description: -

Arm type	intervention group

No investigational medicinal product assigned in this arm

Arm title	mmr vaccine

Arm description: -

Arm type	intervention group

No investigational medicinal product assigned in this arm

Arm title	bcg + mmr

Arm description: -

Arm type	intervention group

No investigational medicinal product assigned in this arm

Arm title	bcg + alendronate

Arm description: -

Arm type	intervention group

No investigational medicinal product assigned in this arm

Number of subjects in period 2	placebo	bcg vaccine	mmr vaccine
Started	21	21	21
Completed	18	21	21
Not completed	3	0	0
Consent withdrawn by subject	2	-	-
exclusion/screening failure	1	-	-
Lost to follow-up	-	-	-

Number of subjects in period 2	bcg + mmr	bcg + alendronate
Started	21	20
Completed	19	18
Not completed	2	2
Consent withdrawn by subject	2	1
exclusion/screening failure	-	-
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants were randomly assigned to the placebo group or one of the 4 experimental groups (1:1:1:1:1). A single placebo vaccine (0.1 ml 0.9% NaCl,) was given intradermally in the left upper arm. 80 ml of blood was drawn before the intervention. After 28-38 days, 80 ml of blood was drawn again.	
Reporting group title	BCG vaccine
Reporting group description:	
Participants were randomly allocated in the BCG vaccination group or in one of the other 4 arms of the study using a computer algorithm, in a 1:1:1:1:1 ratio. 80 ml of blood was drawn before the intervention. After 28-38 days, 80 ml of blood was drawn again (2nd visit)	
Reporting group title	MMR vaccine
Reporting group description:	
participants were randomly allocated to the MMR vaccine group or the other 4 groups in a 1:1:1:1:1 algorithm . 80 ml of blood was drawn before the intervention. After 28-38 days, 80 ml of blood was drawn again (2nd visit)	
Reporting group title	BCG+MMR
Reporting group description:	
participants were randomply allocated to the BCG+MMR group or the other 4 groups in a 1:1:1:1:1 algorithm. 80 ml of blood was drawn before the intervention. After 28-38 days, 80 ml of blood was drawn again (2nd visit)	
Reporting group title	BCG+Alendronate
Reporting group description:	
participants were randomly allocated to the BCG+Alendronate group in a 1:1:1:1:1 algorithm. 80 ml of blood was drawn before the intervention. After 28-38 days, 80 ml of blood was drawn again (2nd visit)	

Reporting group values	Placebo	BCG vaccine	MMR vaccine
Number of subjects	21	21	21
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)	18	21	21
From 65-84 years	0	0	0
85 years and over	0	0	0
Not Recorded	3	0	0
Gender categorical Units: Subjects			
Female	10	16	12
Male	11	5	9

Reporting group values	BCG+MMR	BCG+Alendronate	Total
Number of subjects	21	20	104
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)	19	18	97
From 65-84 years	0	0	0
85 years and over	0	0	0
Not Recorded	2	2	7
Gender categorical Units: Subjects			
Female	16	11	65
Male	5	9	39

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Participants were randomly assigned to the placebo group or one of the 4 experimental groups (1:1:1:1:1).
A single placebo vaccine (0.1 ml 0.9% NaCl,) was given intradermally in the left upper arm.
80 ml of blood was drawn before the intervention.
After 28-38 days, 80 ml of blood was drawn again.

Reporting group title	BCG vaccine

Reporting group description:

Participants were randomly allocated in the BCG vaccination group or in one of the other 4 arms of the study using a computer algorithm, in a 1:1:1:1:1 ratio.
80 ml of blood was drawn before the intervention.
After 28-38 days, 80 ml of blood was drawn again (2nd visit)

Reporting group title	MMR vaccine

Reporting group description:

participants were randomly allocated to the MMR vaccine group or the other 4 groups in a 1:1:1:1:1 algorithm .
80 ml of blood was drawn before the intervention.
After 28-38 days, 80 ml of blood was drawn again (2nd visit)

Reporting group title	BCG+MMR

Reporting group description:

participants were randomply allocated to the BCG+MMR group or the other 4 groups in a 1:1:1:1:1 algorithm.
80 ml of blood was drawn before the intervention.
After 28-38 days, 80 ml of blood was drawn again (2nd visit)

Reporting group title	BCG+Alendronate

Reporting group description:

participants were randomly allocated to the BCG+Alendronate group in a 1:1:1:1:1 algorithm.
80 ml of blood was drawn before the intervention.
After 28-38 days, 80 ml of blood was drawn again (2nd visit)

Reporting group title	placebo

Reporting group description:

Participants were randomly assigned to the placebo group or one of the 4 experimental groups (1:1:1:1:1). A single placebo vaccine (0.1 ml 0.9% NaCl,) was given intradermally in the left upper arm. 80 ml of blood was drawn before the intervention. After 28-38 days, 80 ml of blood was drawn again

Reporting group title	bcg vaccine

Reporting group description: -

Reporting group title	mmr vaccine

Reporting group description: -

Reporting group title	bcg + mmr

Reporting group description: -

Reporting group title	bcg + alendronate

Reporting group description: -

Primary: IL6

End point title	IL6[1]

End point description:

raw cytokine data

End point type	Primary

End point timeframe:

T1 (baseline) cytokine measurements and T2 (1 month after vaccination) cytokine measurements

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Kruskal wallis test was used to compare cytokine production capacity between groups

End point values	Placebo	BCG vaccine	MMR vaccine	BCG+MMR
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	21	21	19
Units: pg/ml				
number (not applicable)	0	0	0	0

End point values	BCG+Alendronate			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: pg/ml				
number (not applicable)	0			

Attachments (see zip file)	IL6-raw /IL6_dataset_wide.xlsx

Statistical analyses

No statistical analyses for this end point

Primary: TNFa

End point title	TNFa[2]

End point description:

Raw data

End point type	Primary

End point timeframe:

T1 (baseline) cytokine measurements and T2 (1 month after vaccination) cytokine measurements

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Kruskal wallis test was used to compare cytokine production capacity between groups

End point values	Placebo	BCG vaccine	MMR vaccine	BCG+MMR
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	21	21	19
Units: pg/ml				
number (not applicable)	0	0	0	0

End point values	BCG+Alendronate			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: pg/ml				
number (not applicable)	0			

Attachments (see zip file)	TNF-raw data/TNF_dataset_wide.xlsx

Statistical analyses

No statistical analyses for this end point

Primary: IL1Ra

End point title	IL1Ra[3]

End point description:

raw data

End point type	Primary

End point timeframe:

T1 (baseline) cytokine measurements and T2 (1 month after vaccination) cytokine measurements

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Kruskal wallis test was used to compare cytokine production capacity between groups

End point values	Placebo	BCG vaccine	MMR vaccine	BCG+MMR
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	21	21	19
Units: pg/ml				
number (not applicable)	0	0	0	0

End point values	BCG+Alendronate			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: pg/ml				
number (not applicable)	0			

Attachments (see zip file)	IL1Ra-raw data/IL1RA raw.xlsx

Statistical analyses

No statistical analyses for this end point

Primary: IFNy

End point title	IFNy[4]

End point description:

raw data

End point type	Primary

End point timeframe:

T1 (baseline) cytokine measurements and T2 (1 month after vaccination) cytokine measurements

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Kruskal wallis test was used to compare cytokine production capacity between groups

End point values	Placebo	BCG vaccine	MMR vaccine	BCG+MMR
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	21	21	19
Units: pg/ml				
number (not applicable)	0	0	0	0

End point values	BCG+Alendronate			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: pg/ml				
number (not applicable)	0			

Attachments (see zip file)	IFNy-raw/IFNy_dataset_wide.xlsx

Statistical analyses

No statistical analyses for this end point

Primary: IP10

End point title	IP10[5]

End point description:

raw data

End point type	Primary

End point timeframe:

T1 (baseline) cytokine measurements and T2 (1 month after vaccination) cytokine measurements

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Kruskal wallis test was used to compare cytokine production capacity between groups

End point values	Placebo	BCG vaccine	MMR vaccine	BCG+MMR
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	21	21	19
Units: pg/ml				
number (not applicable)	0	0	0	0

End point values	BCG+Alendronate			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: pg/ml				
number (not applicable)	0			

Attachments (see zip file)	IP10-raw/IP10 raw.xlsx

Statistical analyses

No statistical analyses for this end point

Primary: IFNa

End point title	IFNa[6]

End point description:

raw data

End point type	Primary

End point timeframe:

T1 (baseline) cytokine measurements and T2 (1 month after vaccination) cytokine measurements

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Kruskal wallis test was used to compare cytokine production capacity between groups

End point values	Placebo	BCG vaccine	MMR vaccine	BCG+MMR
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18	21	21	19
Units: pg/ml				
number (not applicable)	0	0	0	0

End point values	BCG+Alendronate			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: pg/ml				
number (not applicable)	0			

Attachments (see zip file)	IFNa-raw/IFNa raw.xlsx

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

From start of the trial until 3 months after the trial.

Assessment type	Non-systematic

Dictionary used

Dictionary name	SNOMED CT
Dictionary version	20210901

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants were randomly assigned to the placebo group or one of the 4 experimental groups (1:1:1:1:1).
A single placebo vaccine (0.1 ml 0.9% NaCl,) was given intradermally in the left upper arm.
80 ml of blood was drawn before the intervention.
After 28-38 days, 80 ml of blood was drawn again.

Reporting group title	BCG vaccine

Reporting group description:

Participants were randomly allocated in the BCG vaccination group or in one of the other 4 arms of the study using a computer algorithm, in a 1:1:1:1:1 ratio.
80 ml of blood was drawn before the intervention.
After 28-38 days, 80 ml of blood was drawn again (2nd visit)

Reporting group title	MMR vaccine

Reporting group description:

participants were randomly allocated to the MMR vaccine group or the other 4 groups in a 1:1:1:1:1 algorithm .
80 ml of blood was drawn before the intervention.
After 28-38 days, 80 ml of blood was drawn again (2nd visit)

Reporting group title	BCG+MMR

Reporting group description:

participants were randomply allocated to the BCG+MMR group or the other 4 groups in a 1:1:1:1:1 algorithm.
80 ml of blood was drawn before the intervention.
After 28-38 days, 80 ml of blood was drawn again (2nd visit)

Reporting group title	BCG+Alendronate

Reporting group description:

participants were randomly allocated to the BCG+Alendronate group in a 1:1:1:1:1 algorithm.
80 ml of blood was drawn before the intervention.
After 28-38 days, 80 ml of blood was drawn again (2nd visit)

Serious adverse events	Placebo	BCG vaccine	MMR vaccine
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 21 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	BCG+MMR	BCG+Alendronate	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
number of deaths (all causes)	0	0	

number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Placebo	BCG vaccine	MMR vaccine
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 21 (0.00%)	0 / 21 (0.00%)	0 / 21 (0.00%)

Non-serious adverse events	BCG+MMR	BCG+Alendronate	
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: n/a

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