Synopsis BCG-PLUS

Name of Sponsor/Company: Radboudumc		
Name of Finished Product: Not applicable		
Name of Active Ingredient: For the 5 arms of this study: Bacillus Calmette-Guerin (BCG) vaccine "BCG-SSI" (1); mumps-measles-rubella (MMR) vaccine "M-M-RVAXPRO" (2); BCG + Alendronate "Aurubindo" (3); BCG + MMR (4); 0.9% NaCl (placebo; 5).		
Title of Study: Enhancing the BCG-induced trained immunity response by addition of bisphosphonate or MMR vaccine: a possible preventive approach against COVID-19 (BCG-PLUS)		
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Study centre(s): Radboudumc (single centre trial).		
Publication (reference): Not yet published.		
Studied period (years): First enrolment: 3rd of June, 2020 Last completed: 3rd of September, 2020	**Phase of development:** Not applicable	
Objectives: To investigate the effect of bisphosphonates and the MMR vaccine on BCG-induced trained immunity as a preventive approach against COVID-19		
Methodology: Participants were randomly assigned to the placebo group or one of the 4 experimental groups (1:1:1:1:1). 80 ml of blood was drawn before the intervention for baseline analysis. After 28-38 days, 80 ml of blood was drawn again to assess the effects of intervention.		
Number of patients (planed and analysed): 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participants were included. 1 participant didn't meet criteria and was excluded. 5 participants dropped out (consent withdrawn by subject). 1 participant was lost to follow up.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.		
Diagnosis and main criteria for inclusion: Diagnosis not applicable. Inclusion criteria: - Adult (18 – 50 years of age); - Male or Female; - Healthy.		
Test product, dose and mode of administration, batch number: **Placebo arm:** **Investigational medicinal product name**: Natriumchloride CF 9 mg/ml, injectievloeistof; **Investigational medicinal product number:** RVG 50825; **Pharmaceutical form:** solution for injection; **Route 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. **(continued on next page)**		

Test product, dose and mode of administration, batch number (*cont.*):

BCG vaccine arm:
Investigational medicinal product name: BCG vaccin SSI, 0,75 mg per ml, poeder en oplosmiddel voor suspensie voor injectie;
Investigational medicinal product number: J 07 AN 01;
Pharmaceutical form: Powder and solvent for suspension for injection in pre-filled syringe;
Route 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*.

MMR vaccine arm:
Investigational medicinal product name: M-M-RVAXPRO poeder en oplosmiddel voor suspensie voor Injectie;
Investigational medicinal product number: J07BD52;
Pharmaceutical form: Powder and solvent for suspension for injection;
Route 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)

BCG vaccine + MMR vaccine arm:
Investigational medicinal product name: BCG vaccin SSI, 0,75 mg per ml, poeder en oplosmiddel voor suspensie voor injectie;
Investigational medicinal product number: J 07 AN 01;
Pharmaceutical form: Powder and solvent for suspension for injection in pre-filled syringe;
Route 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 number: J07BD52;
Pharmaceutical form: Powder and solvent for suspension for injection;
Route 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)

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Test product, dose and mode of administration, batch number (*cont.*):

BCG vaccine + alendronate arm:
Investigational medicinal product name: BCG vaccin SSI, 0,75 mg per ml, poeder en oplosmiddel voor suspensie voor injectie;
Investigational medicinal product number: J 07 AN 01;
Pharmaceutical form: Powder and solvent for suspension for injection in pre-filled syringe;
Route 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 number: RVG 103208;
Pharmaceutical form: Tablet;
Route 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.

Duration of treatment:
The intervention treatment or placebo was administered once on the day of enrolment.

Reference therapy, dose and mode of administration, batch number:
Placebo arm:
Investigational medicinal product name: Natriumchloride CF 9 mg/ml, injectievloeistof;
Investigational medicinal product number: RVG 50825;
Pharmaceutical form: solution for injection;
Route 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.

Criteria for evaluation:

Efficacy:
The treatment efficacy was assessed by comparing between study arms the cytokine production capacity of peripheral blood mononuclear cells (on the intervention day and 28-38 days later). The cytokines TNF, IL-6, IL-1RA, IFN-γ, IFN-α, and IP-10 were measured.

Safety:
The safety of the treatments and placebo was assessed at two timepoints. 1: Participants were observed by a medical doctor during the intervention. 2: At the follow-up visit 28-38 days later, participants were asked to indicate any adverse events.

Statistical methods:
The Kruskal-Wallis test was used to compare cytokine production capacities between groups.

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SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

No significant differences in cytokine production capacity were observed between the groups.

SAFETY RESULTS:

No serious adverse events were recorded.

12 participants (11.65%) reported adverse effects of the intervention. Of these, 3 participants were in the BCG arm; 3 were in the BCG+alendronate arm; 6 were in the BCG+MMR arm; 0 were in the MMR arm; 0 were in the placebo arm.

Of the 12 participants reporting adverse effects, 10 reported 1 adverse effect. 2 participants reported 2 adverse effects.

5 participants reported local skin reaction (BCG: 2; BCG+MMR: 3).
1 participant reported fever (BCG: 1).
4 participants reported gastrointestinal effects (BCG+alendronate: 2; BCG+MMR: 2).
3 participants reported headache (BCG: 1; BCG+MMR: 2).
1 participant reported a muscle ache in the left arm (BCG+alendronate: 1).

CONCLUSION:

Based on the analyses of the data we conclude there was no significant effect of the interventions in the setup of this study.

Date of the report: 30th of June, 2022