Clinical trial results:
Danish:
BCG vaccination og sygelighed blandt danske småbørn.
En prospektivt, randomiseret, klinisk lægemiddelafprøvning.
English:
Bacille Calmette Guérin immunisation at birth and childhood morbidity in Danish children. A prospective, randomised, clinical trial.

Summary

EudraCT number	2010-021979-85
Trial protocol	DK
Global end of trial date	06 February 2015

Results information

Result version number	v1 (current)
This version publication date	13 May 2022
First version publication date	13 May 2022
Summary attachment (see zip file)	Published manuscript primary outcome (archdischild-2016-310760.pdf) Adverse event publication (adverse event BCG trial.pdf)

Trial information

Trial identification

Sponsor protocol code	2009-323

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01694108
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	The Child and Adolescent Clinic (formerly The Pediatric Clinics), The Juliane Marie Center, The Danish National University Hospital "Rigshospitalet"
Sponsor organisation address	9-Blegdamsvej, Copenhagen East, Denmark, DK-2100
Public contact	Lone Graff Stensballe, Research Leader, The Child and Adolescent Clinic, The Juliane Marie Center, The Danish National University Hospital , lgn@ssi.dk
Scientific contact	Lone Graff Stensballe, Research Leader, The Child and Adolescent Clinic, The Juliane Marie Center, The Danish National University Hospital , +45 35459727, lone.graff.stensballe@regionh.dk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No	No

1901/2006 apply to this trial?	
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	02 March 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 February 2015
Global end of trial reached?	Yes
Global end of trial date	06 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To test the hypothesis that Danish infants who are Bacille Calmette Guérin (BCG) immunised at birth experience less hospitalisations during early childhood than non-BCG-immunised infants.

Protection of trial subjects:

The protocol of the trial was approved by the Committees on Biomedical Research Ethics (J.no. H-3-2010-087), the Danish Data Protection Board (J.no. 2009-41-4141), and the Danish Medicines Agency (J.no. 2612-4356. EudraCT 2010-021979-85. Protocol 2009-323). The study was registered at www.ClinicalTrials.gov with trial registration number NCT01694108. The trial was supervised by the Good Clinical Practice Units of the Capital Region and the Region of Southern Denmark. The study was monitored by an independent Data Safety Monitoring board with three members who evaluated the study status, patterns of adverse reactions, and the distribution of baseline characteristics and outcome by allocation. All parents gave written informed consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 October 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	80 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 4262
Worldwide total number of subjects	4262
EEA total number of subjects	4262

Notes:

Subjects enrolled per age group

In utero	0

Preterm newborn - gestational age < 37 wk	145
Newborns (0-27 days)	4117
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

From October 2012 to November 2013 all parents planning to give birth at Rigshospitalet, Hvidovre Hospital, and Kolding Hospital in Denmark received a letter in the 2nd or 3rd trimester of pregnancy with information about the Danish Calmette Study and an invitation to participate in the study.

Pre-assignment

Screening details:

The inclusion criteria were gestational age of at least 32 weeks, a birth weight of at least 1000 g, and a signed consent form from the parents. Exclusion criteria were maternal intake of immune modulating medicine during pregnancy or signs of severe illness or major malformation in the newborn. Only parents fluent in Danish were included.

Period 1

Period 1 title	Period of allocation (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind[1]
Roles blinded	Monitor, Carer, Subject

Blinding implementation details:

Since no placebo injection was administered, the parents and the health person who administered the BCG-vaccine were not blinded to the allocation. Hence the infant itself was also not considered blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention

Arm description:

BCG vaccine

Arm type	Experimental
Investigational medicinal product name	BCG vaccine Danish Strain 1331
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intradermal use

Dosage and administration details:

Standard dose of 0.05 ml in the upper, lateral part of the left shoulder

Arm title	Control

Arm description:

Control children (no intervention)

Arm type	No intervention

No investigational medicinal product assigned in this arm

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.
Justification: Not possible to fully blind since the intervention leads to a local skin reaction

Number of subjects in period 1	Intervention	Control
Started	2129	2133
Completed	2129	2133

Baseline characteristics

Reporting groups	
Reporting group title	Intervention
Reporting group description: BCG vaccine	
Reporting group title	Control
Reporting group description: Control children (no intervention)	

Reporting group values	Intervention	Control	Total
Number of subjects	2129	2133	4262
Age categorical Units: Subjects			
Newborns	2129	2133	4262
Gender categorical Units: Subjects			
Female	1025	996	2021
Male	1104	1137	2241

Subject analysis sets	
Subject analysis set title	Intention to treat
Subject analysis set type	Intention-to-treat
Subject analysis set description: Data on time in days to the first hospitalization in the period from randomization to 15 months of age were obtained for all randomized children and analysed according to randomization group.	
Subject analysis set title	Per protocol
Subject analysis set type	Per protocol
Subject analysis set description: Children who did not follow the allocation were excluded in the per protocol analyses. For the remaining children, time to the first hospitalization in the period from randomization to 15 months of age was defined as time since vaccination for the BCG-group and time since randomization for controls.	

Reporting group values	Intention to treat	Per protocol	
Number of subjects	4262	4215	
Age categorical Units: Subjects			
Newborns	2129	2133	
Gender categorical Units: Subjects			
Female	1022	979	
Male	1096	1118	

End points

End points reporting groups

Reporting group title	Intervention
Reporting group description: BCG vaccine	
Reporting group title	Control
Reporting group description: Control children (no intervention)	
Subject analysis set title	Intention to treat
Subject analysis set type	Intention-to-treat
Subject analysis set description: Data on time in days to the first hospitalization in the period from randomization to 15 months of age were obtained for all randomized children and analysed according to randomization group.	
Subject analysis set title	Per protocol
Subject analysis set type	Per protocol
Subject analysis set description: Children who did not follow the allocation were excluded in the per protocol analyses. For the remaining children, time to the first hospitalization in the period from randomization to 15 months of age was defined as time since vaccination for the BCG-group and time since randomization for controls.	

Primary: All cause hospitalisation

End point title	All cause hospitalisation[1]
End point description:	
End point type	Primary
End point timeframe: Randomisatio/vaccination within 7 days after birth to 15 months of age	

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: Statistical analysis described in detail in publication PMID 27443836

End point values	Intervention	Control	Intention to treat	Per protocol
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	2129	2133	4262	4215
Units: 1188	1047	1003	4262	4215

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: October 1 2012, to January 17, 2015.	
Adverse event reporting additional description: Published in detail in PMID 27060379	
Assessment type	Systematic

Dictionary used	
Dictionary name	Groups of diagnoses
Dictionary version	1

Frequency threshold for reporting non-serious adverse events: 0.01 %

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: Adverse event history described in detail in PMID 27060379

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