Clinical trial results:
A phase IIa specificity trial of the diagnostic agent C-Tb, when given intradermally by the Mantoux technique to healthy volunteers previously vaccinated with BCG

Summary

EudraCT number	2009-017296-17
Trial protocol	GB
Global end of trial date	17 October 2011

Results information

Result version number	v1 (current)
This version publication date	17 July 2016
First version publication date	17 July 2016

Trial information

Trial identification

Sponsor protocol code	TESEC-03

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Statens Serum Institut
Sponsor organisation address	Artillerivej 5, Copenhagen, Denmark, 2300
Public contact	Toxicology and Clinical Development Unit, Statens Serum Institut, kjmo@ssi.dk
Scientific contact	Toxicology and Clinical Development Unit, Statens Serum Institut, kjmo@ssi.dk

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	03 May 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 October 2011
Global end of trial reached?	Yes
Global end of trial date	17 October 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the specificity of the C-Tb skin test as a function of the cut-off value (i.e., the smallest size of induration measured in mm resulting in a negative outcome of the C-Tb test) when the test is administered intradermally by the Mantoux technique to healthy BCG vaccinated adults.

The present phase IIa (TESEC-03) trial in a healthy BCG vaccinated population collected data on the distribution of the induration response, if any, to C-Tb in this population. The specificity of the C-Tb test was defined as the relative frequency of subjects in a healthy population (i.e., no exposure to MTb) who have an induration response < cut-off after a C-Tb test.

Protection of trial subjects:

Based on previous trials, 0.01 and 0.1 µg was considered safe and well tolerated.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 May 2011
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	United Kingdom: 151
Worldwide total number of subjects	151
EEA total number of subjects	151

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)	151
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This clinical trial was conducted at Surrey Clinical Research Centre, University of Surrey, Guildford, United Kingdom.
First subject´s first visit: 09 May 2011
Last subject´s last visit: 17 October 2011

Pre-assignment

Screening details:

The screening visit (visit 1) took place up to 28 days before the inclusion visit (visit 2)

Period 1

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

Blinding implementation details:

C-Tb and PPD RT 23 SSI were manufactured as solutions for injection and both appeared as clear and colourless liquids. Each subject was administered 1 injection of the IMP C-Tb (0.1 µg / 0.1 mL) in one arm and 1 injection of the comparator PPD RT 23 SSI (2 T.U. / 0.1 mL) in the other arm according to split body design using a randomisation code by the Mantoux injection technique, which is the currently approved injection technique for the comparator

Arms

Arm title	All subjects

Arm description: -

Arm type	Experimental
Investigational medicinal product name	C-Tb + PPD RT 23 SSI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intradermal use

Dosage and administration details:

Each subject was administered 1 injection of the IMP C-Tb (0.1 µg / 0.1 mL) in one arm and 1 injection of the comparator PPD RT 23 SSI (2 T.U. / 0.1 mL) in the other arm according to a randomisation code by use of the Mantoux injection technique, which is the currently approved injection technique for the comparator.

A disposable graduated 1 mL syringe equipped with a short-bevelled needle sized 26 gauges was used for the injection.

Stretching the skin slightly and holding the needle almost parallel to the skin with the bevelled side upwards the needle was inserted through the epidermis into the flexor surface of the right or left volar part of the forearm 5-10 cm below the elbow point. The needle was visible through the epidermis before 0.1 mL of the test solution was injected slowly intradermally.

Number of subjects in period 1	All subjects
Started	151
Completed	149
Not completed	2
Consent withdrawn by subject	2

Baseline characteristics

Reporting groups

Reporting group title	Safety set

Reporting group description: -

Reporting group values	Safety set	Total	
Number of subjects	151	151	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	33.7		
full range (min-max)	18 to 65	-	
Gender categorical Units: Subjects			
Female	92	92	
Male	59	59	

Subject analysis sets

Subject analysis set title	Per protocol set
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol set consists of all subjects who have complied with the protocol and who have a non-missing diagnostic read out of C-Tb

Reporting group values	Per protocol set		
Number of subjects	147		
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	34		
full range (min-max)	18 to 65		
Gender categorical Units: Subjects			
Female	89		
Male	58		

End points

End points reporting groups

Reporting group title	All subjects
Reporting group description: -	
Subject analysis set title	Per protocol set
Subject analysis set type	Per protocol

Subject analysis set description:

The Per Protocol set consists of all subjects who have complied with the protocol and who have a non-missing diagnostic read out of C-Tb

Primary: Specificity of C-Tb

End point title	Specificity of C-Tb[1]

End point description:

End point type	Primary

End point timeframe:

Days 2-3 after administration of C-Tb

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: No parametric model for the distribution was proposed,so the empirical cumulative distribution function,defined on the range from 0mm to the maximal observed diameter will constitute the main outcome of the study. For each value of d (diameter of C-Tb) in this range, an exact 95% CI for the true value of F(d) will be calculated. The estimated value of F(d) can be interpreted as the specificity of a MTb test using the value d+1 as cut-off, i.e. values above d were considered MTb test positive

End point values	Per protocol set			
Subject group type	Subject analysis set			
Number of subjects analysed	147			
Units: percent				
number (confidence interval 95%)				
Diameter 0 mm	97.3 (93.2 to 99.3)			
Diameter 5 mm	99.3 (96.3 to 100)			
Diameter 6 mm	99.3 (96.3 to 100)			
Diameter 10 mm	100 (97.5 to 100)			
Diameter 15 mm	100 (97.5 to 100)			

Attachments (see zip file)	Figure for T-03 EudraCT.docx

Statistical analyses

No statistical analyses for this end point

Primary: Specificity of PPD

End point title	Specificity of PPD[2]

End point description:

End point type	Primary

End point timeframe:

Day 2-3 after administration of PPD RT 23 SSI

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: No parametric model for the distribution is proposed,so the empirical cumulative distribution function,defined on the range from 0mm to the maximal observed diameter will constitute the main outcome of the study. For each value of d (diameter of PPD) in this range, an exact 95% CI for the true value of F(d) will be calculated. The estimated value of F(d) can be interpreted as the specificity of a MTb test using the value d+1 as cut-off, i.e. values above d are considered MTb test positive

End point values	Per protocol set			
Subject group type	Subject analysis set			
Number of subjects analysed	147			
Units: Percentage				
number (confidence interval 95%)				
Diameter 0 mm	60.5 (52.2 to 68.5)			
Diameter 5 mm	62.6 (54.2 to 70.4)			
Diameter 6 mm	66 (57.7 to 73.6)			
Diameter 10 mm	76.9 (69.2 to 83.4)			
Diameter 15 mm	91.8 (86.2 to 95.7)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The duration of the safety follow-up period was
1. First hour after the administration of skin tests
2. 26-30 days

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups

Reporting group title	Safety set

Reporting group description: -

Serious adverse events	Safety set		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 151 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Safety set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	97 / 151 (64.24%)		
Nervous system disorders			
Headache			
subjects affected / exposed	28 / 151 (18.54%)		
occurrences (all)	33		
Dizziness			
subjects affected / exposed	2 / 151 (1.32%)		
occurrences (all)	2		
Migraine			
subjects affected / exposed	2 / 151 (1.32%)		
occurrences (all)	2		
General disorders and administration site conditions			

Injection site haematoma			
subjects affected / exposed	42 / 151 (27.81%)		
occurrences (all)	44		
Injection site pruritus			
subjects affected / exposed	25 / 151 (16.56%)		
occurrences (all)	28		
Injection site pain			
subjects affected / exposed	5 / 151 (3.31%)		
occurrences (all)	7		
Injection site rash			
subjects affected / exposed	4 / 151 (2.65%)		
occurrences (all)	4		
Injection site discomfort			
subjects affected / exposed	2 / 151 (1.32%)		
occurrences (all)	2		
Injection site erythema			
subjects affected / exposed	2 / 151 (1.32%)		
occurrences (all)	2		
Injection site vesicles			
subjects affected / exposed	2 / 151 (1.32%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	2 / 151 (1.32%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	2 / 151 (1.32%)		
occurrences (all)	2		
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	6 / 151 (3.97%)		
occurrences (all)	6		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	5 / 151 (3.31%)		
occurrences (all)	5		
Diarrhoea			

subjects affected / exposed	5 / 151 (3.31%)		
occurrences (all)	5		
Nausea			
subjects affected / exposed	2 / 151 (1.32%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	2 / 151 (1.32%)		
occurrences (all)	2		
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	5 / 151 (3.31%)		
occurrences (all)	5		
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	7 / 151 (4.64%)		
occurrences (all)	7		
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	2 / 151 (1.32%)		
occurrences (all)	2		
Rash			
subjects affected / exposed	2 / 151 (1.32%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 151 (1.99%)		
occurrences (all)	3		
Back pain			
subjects affected / exposed	3 / 151 (1.99%)		
occurrences (all)	3		
Myalgia			
subjects affected / exposed	2 / 151 (1.32%)		
occurrences (all)	2		
Pain in extremity			

subjects affected / exposed occurrences (all)	2 / 151 (1.32%) 2		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Tonsillitis subjects affected / exposed occurrences (all)	 16 / 151 (10.60%) 17 2 / 151 (1.32%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 May 2011	Administrative changes, such as the outsourcing of the statistical reporting of the trial from Statens Serum Institut (SSI) to OnQ (CRO based in Johannesburg, SA)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/23691171