Clinical trial results:
A phase III contact tracing trial comparing the diagnostic performance of C-Tb to QuantiFERON®-TB Gold In-Tube, in combination with a double blind randomized split body safety assessment of C-Tb versus 2 T.U. Tuberculin PPD RT23 SSI

Summary

EudraCT number	2011-005617-36
Trial protocol	ES
Global end of trial date	02 October 2014

Results information

Result version number	v1 (current)
This version publication date	29 May 2016
First version publication date	29 May 2016

Trial information

Trial identification

Sponsor protocol code	TESEC-06

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01631266
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Statens Serum Institut
Sponsor organisation address	Artillerivej 5, Copenhagen, Denmark, 2300
Public contact	Clinical Trials Department, Statens Serum Institut, +45 3268 3416, btg@ssi.dk
Scientific contact	Clinical Trials Department, Statens Serum Institut, +45 3268 3416, btg@ssi.dk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001156-PIP01-11
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 December 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 October 2014
Global end of trial reached?	Yes
Global end of trial date	02 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

-To demonstrate an increasing trend in C-Tb positivity across the 4 risk (exposure) groups with positivity defined as an induration ≥ 5 mm

Protection of trial subjects:

The dose-finding trial TESEC-02 in recently diagnosed TB patients concluded from a clinical perspective that injection of 0.1 µg/0.1 mL C-Tb was safe and resulted in an induration response similar to the response of PPD RT 23 SSI. Both TESEC-03 and TESEC-04 confirmed that the injection of 0.1 µg/0.1 mL of C-Tb was safe and well tolerated. It was therefore concluded that subjects injected with this dosage would be exposed to minimal risks in the present TESEC-06 trial, such as local reversible adverse reactions at the injection sites.
The DSMB was established prior to the start of the trial and the members consisted of 3 independent medical doctors. The board had an advisory function and, if requested by the national PI, evaluated critical events in the trial to ensure the safety of all subjects. Safety reports were to be sent to the DSMB 2 times during the trial for evaluation: after 200 and after 500 subjects had completed the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 July 2012
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	Spain: 979
Worldwide total number of subjects	979
EEA total number of subjects	979

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)	16
Children (2-11 years)	61
Adolescents (12-17 years)	44

Adults (18-64 years)	853
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Each of the 13 sites in Spain recruited subjects under the responsibility of a site investigator.
First subject´s first visit: 24 July 2012
Last subject´s last visit: 02 October 2014

Pre-assignment

Screening details:

At visit1, screening visit (day -28–0). Informed consent was obtained and examinations were performed in order to determine if the subject fulfils the inclusion and exclusion criteria for the trial.
A total of 993 patients were screened, of which 14 (1.4%) were screening failures.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

This is a split-body double blind trial where the mode of injection of skin tests were randomised in split-body design where neither the investigator nor the subject knew which skin test was administered to each forearm. Thus this trial was not a blinded trial in a conventional sense as all subjects were given C-Tb and PPD RT 23 SSI (except 50 subjects in the Negative control group who received only a single injection of C-Tb) and there was no placebo.

Arms

Arm title	All subjects

Arm description:

The trial aimed to evaluate C-Tb's positive response rates in 4 groups defined and ranked by ascending risk of Mtb infection to demonstrate a similar trend in positive responses to C-Tb:

-Negative Control group: participants must have not had history of exposure to a TB index case and have no signs or symptoms of TB

-Occasional Contact group: participants must have been in contact with a pulmonary TB index case (sputum or broncho smear positive, subsequently confirmed by Culture, GeneXpert or PCR) between 6 hours/week and 6 hours/day

-Close Contact group: participants must have been in close contact with a pulmonary TB index case (sputum or broncho smear positive, subsequently confirmed by Culture, GeneXpert or PCR) for more than 6 hours/day for at least 5 days

-Positive Control group: participants must have had TB disease within the last 3 years confirmed by culture, GeneXpert or PCR

Arm type	Experimental and Active comparator
Investigational medicinal product name	C-Tb
Investigational medicinal product code	C-Tb
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intradermal use

Dosage and administration details:

Concomitantly one injection of C-Tb (0.1 µg/0.1 mL) in one forearm and one injection of the PPD RT 23 SSI in the opposite forearm immediately one after each other according to the randomisation code.

The Mantoux technique was employed for injection. A disposable graduated 1 mL syringe equipped with a short-bevelled needle sized 26 gauges was used for injection. According to this method, the skin was stretched slightly, and the needle held almost parallel to the skin with the bevelled side upwards. The needle was then inserted through the epidermis into the flexor surface of the right or left volar part of the forearm at a 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 and intradermally.

Number of subjects in period 1	All subjects
Started	979
Completed	970
Not completed	9
Discontinued	1
Lost to follow-up	8

Baseline characteristics

Reporting groups

Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	979	979	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	30.6		
standard deviation	± 14.5	-	
Gender categorical Units: Subjects			
Female	524	524	
Male	455	455	
BCG status Units: Subjects			
BCG vaccinated	366	366	
BCG unvaccinated	509	509	
BCG unknown	104	104	

Subject analysis sets

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects enrolled, randomised and tested irrespective of any results obtained

Reporting group values	Full Analysis Set		
Number of subjects	979		
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	30.6		
standard deviation	± 14.5		
Gender categorical Units: Subjects			
Female	524		
Male	455		
BCG status Units: Subjects			
BCG vaccinated	366		

BCG unvaccinated	509		
BCG unknown	104		

End points

End points reporting groups

Reporting group title	All subjects

Reporting group description:

The trial aimed to evaluate C-Tb's positive response rates in 4 groups defined and ranked by ascending risk of Mtb infection to demonstrate a similar trend in positive responses to C-Tb:

-Negative Control group: participants must have not had history of exposure to a TB index case and have no signs or symptoms of TB

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-Positive Control group: participants must have had TB disease within the last 3 years confirmed by culture, GeneXpert or PCR

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects enrolled, randomised and tested irrespective of any results obtained

Primary: C-Tb positivity

End point title	C-Tb positivity[1]

End point description:

Number of subjects in each group:

Negative control group = 263
Occasional contact group = 299
Close contact group = 316
Positive control group = 101

End point type	Primary

End point timeframe:

The test positive subject was defined as an individual with an observation at day 2–3 (Visit 3) after the injection above the cut-off value of:

- C-Tb: induration diameter ≥ 5 mm

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: Test positivity rates for C-Tb were tabulated descriptively in total and split into risk groups. No statistical analysis was performed

End point values	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	979			
Units: Subjects with positive C-Tb results				
Negative control group	9			
Occasional contact group	49			
Close contact group	136			
Positive control group	68			
Overall	262			

Statistical analyses

No statistical analyses for this end point

Primary: Binary response of C-Tb positivity across risk groups

End point title	Binary response of C-Tb positivity across risk groups

End point description:

End point type	Primary

End point timeframe:

The test positivity rate was defined as the prevalence of test positives, in a given subgroup of the trial population of interest at the time of test reading (Visit 3, 2–3 days after the injection)

End point values	All subjects	Full Analysis Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	979	979		
Units: Odds ratio				
number (confidence interval 95%)				
Positive – Negative	47.603 (21.222 to 106.78)	47.603 (21.222 to 106.78)		
Close – Negative	17.852 (8.713 to 36.579)	17.852 (8.713 to 36.579)		
Occasional – Negative	4.643 (2.205 to 9.778)	4.643 (2.205 to 9.778)		
Positive – Occasional	10.253 (6.045 to 17.391)	10.253 (6.045 to 17.391)		
Close – Occasional	3.845 (2.617 to 5.65)	3.845 (2.617 to 5.65)		
Positive – Close	2.666 (1.646 to 4.319)	2.666 (1.646 to 4.319)		

Statistical analyses

Statistical analysis title	Logistic regression model
Comparison groups	All subjects v Full Analysis Set

Number of subjects included in analysis	1958
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	≤ 0.05
Method	Regression, Logistic
Confidence interval	
sides	2-sided
lower limit	2.62
upper limit	5.65
Variability estimate	Standard error of the mean
Dispersion value	1

Notes:

[2] - Purpose of analysis is to demonstrate a rising trend in C-Tb test positivity across 4 predefined risk groups of subjects . The contrast between close and occasional contact groups is selected as the most central below.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (both systemic AEs and injection site reactions) were collected and assessed at Visit 2, Visit 3 and Visit 4. Reporting of SAEs was in accordance with the defined procedure in trial protocol

Adverse event reporting additional description:

This is a split-body double blind trial where C-Tb and PPD RT 23 SSI were each injected as per the randomisation scheme into each forearm. All subjects were given C-Tb and PPD RT 23 SSI (except 50 subjects in the Negative control group who received only single injection of C-Tb)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Safety set

Reporting group description:

Threshold for non-serious adverse event reporting is: 5%

Serious adverse events	Safety set		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 979 (0.10%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Aspartate transferase increased	Additional description: AST increased - Increased AST, more than 9.7 times normal upper limit Secondary SAEs in this subject were: Bilirubin increased ALT increased Alkaline phosphatase increased Platelets decreased		
subjects affected / exposed	1 / 979 (0.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	396 / 979 (40.45%)		
General disorders and administration site conditions			

Injection site reactions	Additional description: Overall, 565 Injection site reactions in 341 (34.8%) subjects were reported.		
subjects affected / exposed	318 / 979 (32.48%)		
occurrences (all)	484		
Systemic adverse events	Additional description: Overall, 550 systemic AEs in 317 (32.4%) subjects were reported		
subjects affected / exposed	137 / 979 (13.99%)		
occurrences (all)	171		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 March 2012	Added the word 'double' to indicate that double reading of the induration at V3 (day 2–3) and V4 (day 28±2) to be performed. The word 'double' reading was added throughout the protocol where relevant. Deleted 'sputum smear microscopy' activity from V1 (day -28–0) as the test was not needed A single cut-off for PPD of ≥ 6 mm was to be used according to the subject information leaflet for PPD Cut-off for C-Tb was to be calculated from the specificity trial (TESEC-03) and sensitivity trial (TESEC-04)
24 August 2012	Secondary objectives changed A new group of 50 subjects was added to the Negative Control group. This group was to be tested with C-Tb alone. Index cases to be enrolled in the Occasional and Close Contact groups should have positive sputum smear and either positive culture, GeneXpert or PCR Subjects to be enrolled in the Positive Control group could have a negative sputum smear but must have positive culture or GeneXpert At least 80 paediatric subjects should be enrolled, stratified by 4 age groups. Double reading of the induration should be independently performed by 2 staff members Double reading should be recorded in the source notes together with a consensus diameter. Only consensus diameter was to be recorded in the CRF Only the first 550 subjects would have safety blood samples taken Of the 120 paediatric subjects, at least 80 of them must be enrolled in the Occasional and Close Contact groups and divided by the 4 age groups: • 6 weeks–23 months: 20 subjects • 2–4 years: 20 subjects • 5–11 years: 20 subjects • 12–17 years: 20 subjects
10 December 2012	Primary objectives and endpoints changed Secondary objectives and endpoints changed Index cases in the Occasional and Close Contact groups must have either a positive sputum smear or broncho smear Changes in the SAP

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported