Clinical trial results:
A Phase III trial in subjects suspected to have tuberculosis, comparing the diagnostic performance of C-Tb to QuantiFERON®-TB Gold In-Tube, in combination with a double blind randomised splitbody safety assessment of C-Tb versus 2 T.U. Tuberculin PPD RT 23 SSI (PPD)

Summary

EudraCT number	2011-005078-40
Trial protocol	Outside EU/EEA
Global end of trial date	30 September 2014

Results information

Result version number	v1 (current)
This version publication date	15 September 2016
First version publication date	15 September 2016

Trial information

Trial identification

Sponsor protocol code	TESEC-05

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01642888
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Statens Serum Institut
Sponsor organisation address	Artillerivej 5, Copenhagen, Denmark, 2300
Public contact	Bettine Borregaard Jørgensen, Statens Serum Institut, btg@ssi.dk
Scientific contact	Bettine Borregaard Jørgensen, Statens Serum Institut, 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 January 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2014
Global end of trial reached?	Yes
Global end of trial date	30 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1) To evaluate the diagnostic performance of C-Tb in relation to age, HIV status and CD4 counts:
a) To evaluate C-Tb induration diameters as a function of age, with emphasis on children
b) To evaluate C-Tb induration diameters as a function of HIV status
c) To evaluate C-Tb induration diameters as a function of CD4 counts in HIV-positive participants
d) To evaluate C-Tb positivity as a function of age, with emphasis on children using the 5 mm cut-off to define positivity
e) To evaluate C-Tb positivity according to HIV status using the 5 mm cut-off to define positivity
f) To evaluate C-Tb positivity according to CD4 counts in HIV-positive participants using the 5 mm cut-off to define positivity

2) To evaluate the clinical safety of C-Tb with emphasis on children and HIV-positive participants

Protection of trial subjects:

The IMP C-Tb and the comparator PPD RT 23 SSI were to be administered on one occasion at V2 (day 0). At the follow-up V3 (day 2–3) and V4 (day 28)), assessment of the induration and safety were to be performed. As these procedures did not expose a trial subjects to any further risks, there were no pre-defined medical events or conditions which could lead to the withdrawal of a subject in TESEC-05.

The trial could be terminated at any time if the sponsor, Principal investigator I, Ethics Committee or Competent Authority concluded that the trial posed an unacceptable risk to the trial subjects. If, for any reason, a subject wished to discontinue her or his participation in the trial, or if the subject was to be withdrawn for any reason, the date and reason (if possible) for drop-out or withdrawal were to be recorded in the eCRF.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 September 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	South Africa: 1190
Worldwide total number of subjects	1190
EEA total number of subjects	0

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)	99
Children (2-11 years)	407
Adolescents (12-17 years)	96
Adults (18-64 years)	588
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 1278 subjects were screened and 1190 subjects were enrolled at 8 sites in South Africa.
First subject´s first visit: 05 September 2012
Last subject´s last visit: 30 September 2014

Pre-assignment

Screening details:

Visit 1: screening visit (day -28–day 0). Informed consent (and assent form for children 7–17 years of age) was to be obtained from each subject or legal guardian. General medical examination and vital signs were to be performed and safety blood samples collected to see if the subject had fulfilled the inclusion and exclusion criteria for the trial

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 splitbody 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 CTb and PPD RT 23 SSI.

Arms

Arm title	All subjects

Arm description:

The trial subjects included children (28 days to 4 years of age) with either TB symptoms or known Mtb exposure, children (5 to 17 years of age) and adults with TB symptoms, and 100 healthy children (negative control) with no TB symptoms or known exposure to Mtb.

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:

A dose of 0.1 µg C-Tb refers to a test solution consisting of 0.05 µg rdESAT-6 and 0.05 µg rCFP-10 per 0.1 mL.

0.1 mL of C-Tb was administered in one forearm and 0.1 mL of the comparator PPD was administered in the other forearm as indicated by the randomisation code. The 2 injections were administered intradermally using the Mantoux technique. The ratio of rdESAT-6 and rCFP-10 in C-Tb was 1:1 in solution.

Number of subjects in period 1	All subjects
Started	1190
Completed	1165
Not completed	25
Consent withdrawn by subject	2

Death	3
Other reasons	2
Lost to follow-up	17
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	1190	1190	
Age categorical Units: Subjects			
0-1 years	99	99	
2-4 years	137	137	
5-11 years	270	270	
12-17 years	96	96	
18-39 years	311	311	
40-65 years	277	277	
Gender categorical Units: Subjects			
Female	589	589	
Male	601	601	
BCG vaccination status Units: Subjects			
Vaccinated	882	882	
Not vaccinated	264	264	
Unknown	44	44	
HIV status Units: Subjects			
HIV-negative	730	730	
HIV-positive	299	299	
HIV-unknown	161	161	

End points

End points reporting groups

Reporting group title	All subjects

Reporting group description:

The trial subjects included children (28 days to 4 years of age) with either TB symptoms or known Mtb exposure, children (5 to 17 years of age) and adults with TB symptoms, and 100 healthy children (negative control) with no TB symptoms or known exposure to Mtb.

Primary: C-Tb induration by age among responders

End point title	C-Tb induration by age among responders[1]

End point description:

End point type	Primary

End point timeframe:

The primary endpoints were the C-Tb induration and C-Tb positivity measured at V3 (2–3 days after injection) according to 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: C-Tb induration diameters according to age were tabulated descriptively.

End point values	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	1190			
Units: Millimeter				
arithmetic mean (standard deviation)				
0-<2 years	9.8 (± 7.5)			
2-4 years	15.6 (± 8.3)			
5-11 years	21.5 (± 12)			
12-17 years	24.4 (± 17.2)			
18-39 years	21.4 (± 12)			
40-65 years	23 (± 13.7)			

Statistical analyses

No statistical analyses for this end point

Primary: C-Tb positivity by age using 5 mm cut-off to define positivity

End point title	C-Tb positivity by age using 5 mm cut-off to define positivity[2]

End point description:

The percentage of subjects positive for C-Tb can be calculated by taking the ratio of number of subjects positive for C-Tb according to age and the total number of subjects enrolled according to age.

End point type	Primary

End point timeframe:

The primary endpoints were the C-Tb induration and C-Tb positivity measured at V3 (2–3 days after injection) according to age

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: Test-positive rates for C-Tb according to age were tabulated descriptively.

End point values	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	1190			
Units: Sbjects				
0-<2 years	14			
2-4 years	35			
5-11 years	75			
12-17 years	45			
18-39 years	153			
40-65 years	154			

Statistical analyses

No statistical analyses for this end point

Primary: C-Tb induration according to HIV status among responders

End point title	C-Tb induration according to HIV status among responders[3]

End point description:

End point type	Primary

End point timeframe:

The primary endpoints were the C-Tb induration and C-Tb positivity measured at V3 (2–3 days after injection) according to HIV status

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: C-Tb induration diameters according to HIV status were tabulated descriptively.

End point values	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	1190			
Units: millimeter(s)				
arithmetic mean (standard deviation)				
HIV-positive	20.4 (± 13.6)			
HIV-negative	22.4 (± 13.1)			
HIV-unknown	14.2 (± 8.3)			

Statistical analyses

No statistical analyses for this end point

Primary: C-Tb positivity according to HIV status using 5 mm cut-off to define

positivity	
End point title	C-Tb positivity according to HIV status using 5 mm cut-off to define positivity[4]

End point description:

The percentage of subjects positive for C-Tb by HIV status can be calculated by taking the ratio of number of subjects positive for C-Tb according to HIV-status and the total number of subjects enrolled according to HIV-status.

End point type	Primary

End point timeframe:

The primary endpoints were the C-Tb induration and C-Tb positivity measured at V3 (2–3 days after injection) according to HIV status

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: Test-positive rates for C-Tb according to HIV status were tabulated descriptively.

End point values	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	1190			
Units: Subjects				
HIV-positive	113			
HIV-negative	327			
HIV-unknown	36			

Statistical analyses

No statistical analyses for this end point

Primary: C-Tb induration according to CD4 counts in HIV-positive responders	
End point title	C-Tb induration according to CD4 counts in HIV-positive responders[5]

End point description:

End point type	Primary

End point timeframe:

The primary endpoints were the C-Tb induration and C-Tb positivity measured at V3 (2–3 days after injection) according to CD4 counts in HIV-positive responders

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: C-Tb induration diameters according to CD4 counts were tabulated descriptively.

End point values	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	1190			
Units: millimeter(s)				
arithmetic mean (standard deviation)				
<100	13.6 (± 7.3)			
100-199	18.2 (± 13.9)			
200-299	21.2 (± 18.5)			
300-399	23.6 (± 14.7)			

400-499	19.7 (± 10.8)			
500-599	19.8 (± 8)			
>600	22.4 (± 14.9)			

Statistical analyses

No statistical analyses for this end point

Primary: C-Tb positivity according to CD4 count using 5 mm cut-off to define positivity

End point title	C-Tb positivity according to CD4 count using 5 mm cut-off to define positivity[6]

End point description:

The percentage of subjects positive for C-Tb can be calculated by taking the ratio of number of subjects positive for C-Tb according to CD4 and the total number of subjects enrolled according to CD4.

End point type	Primary

End point timeframe:

The primary endpoints were the C-Tb induration and C-Tb positivity measured at V3 (2–3 days after injection) according to CD4 counts in HIV-positive responders

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: Test-positive rates for C-Tb according to CD4 counts were tabulated descriptively.

End point values	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	1190			
Units: Subjects				
<100	7			
100-199	16			
200-299	20			
300-399	15			
400-499	16			
500-599	19			
>600	16			

Statistical analyses

No statistical analyses for this end point

Primary: Injection site reactions (ISRs) in C-Tb injected arms

End point title	Injection site reactions (ISRs) in C-Tb injected arms[7]

End point description:

End point type	Primary

End point timeframe:

ISRs collected & assessed at V2, V3 & V4.
-Since all subjects received C-Tb & PPD same time, systemic AEs were presumed to be attributed to

either of the skin tests
-SAEs: Cryptococcosis & Pneumonia were possibly related to skin tests by Sponsor

Notes:

[7] - 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: Injection site reactions were reported

End point values	All subjects			
Subject group type	Reporting group			
Number of subjects analysed	1188			
Units: Subjects	282			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (both systemic adverse events 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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

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	15 / 1190 (1.26%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events			
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 1190 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Febrile convulsion			
subjects affected / exposed	1 / 1190 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Grand mal convulsion			
subjects affected / exposed	1 / 1190 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Death			

subjects affected / exposed	2 / 1190 (0.17%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	1 / 1190 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 1190 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cryptococcosis			
subjects affected / exposed	1 / 1190 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 1190 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 1190 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tuberculosis			
subjects affected / exposed	1 / 1190 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Disseminated tuberculosis			
subjects affected / exposed	1 / 1190 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Upper respiratory tract infection			
subjects affected / exposed	1 / 1190 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lobar pneumonia			
subjects affected / exposed	1 / 1190 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumocystis pneumonia			
subjects affected / exposed	1 / 1190 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
End stage AIDS			
subjects affected / exposed	1 / 1190 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Malnutrition			
subjects affected / exposed	1 / 1190 (0.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Safety set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	557 / 1190 (46.81%)		
General disorders and administration site conditions			
Injection site reactions			
subjects affected / exposed	340 / 1190 (28.57%)		
occurrences (all)	844		
Systemic adverse events			
subjects affected / exposed	332 / 1190 (27.90%)		
occurrences (all)	533		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 August 2012	First amendment: 1. The number of participants to be enrolled in the TESEC-05 trial has been reduced by 450 (from 1625 in the initial protocol to 1175 participants in the amended protocol) due to a novel parallel trial TESEC-07. The 450 participants has been transferred to the TESEC-07 trial. 2. Safety tests will not be done on all trial participants from 5 years of age and above as stated in the initial protocol but will only be done on the first 550 participants. The reason for this is that no severe systemic adverse reactions have been observed in the completed phase I and II TESEC trials. 3. The number of participants on whom GeneXpert tests will be done has been increased. In the initial protocol GeneXpert analysis was only done on sputum smear negative / HIV positive participants. In the amended protocol GeneXpert analysis will also include sputum smear positive participants. 4. The rapid HIV test kits which will be used during screening have been specified, which they were not in the initial protocol. 5. It is clarified in the amended protocol that children between 28 days and 4 years of age may have an unknown HIV status and may receive antiretroviral therapy (ART) or have breastfeeding mothers on ART. 6. The procedure for reading and recording the induration responses has been described in detail, which it was not in the initial protocol. 7. The cut-off for C-Tb has been clarified, which it was not in the initial protocol. 8. The trial statistician has been changed to Henrik Wachmann instead of Prof. Schoeman
03 January 2013	Amendment 2: 1. The primary objectives have been revised to investigate the performance of C-Tb in children and in HIVpositive participants to see whether the induration response is altered at a certain age or a certain CD4 count. The statistical analysis section of the amended protocol has been updated accordingly. 2. The secondary objectives have been revised and the statistical analysis section of the amended protocol has been updated accordingly. As it has been of SSI's perception that the MCC would not accept a reduced safety testing SSI decided to follow MCC's advice and has changed back the safety sample testing to include all trial participants from 5 years of age and above. 3. It has been specified that infants, toddlers and children between 28 days and 4 years must either have symptoms or signs of TB or be in close contact to a smear positive pulmonary TB case (more than 6 hours/day for at least five days).
04 April 2014	Third amendment: 1. The role as National Principal Investigator was transferred from Prof. Diacon to Prof. Dheda on 02. Apr. 2014 due to Prof. Diacon having an extensive work load and travel activity (Ref. Note to File no. 14, dated 02. Apr. 2014). 2. Søren Tetens Hoff took over the role as medically responsible in the TESEC-05 trial from Trine R. Nielsen on 12. August 2013 (ref. NTF no. 08, date 10. Sep. 2013). By mistake this was not corrected in the Clinical Trial Protocol v. 3.0, date 03 January 2013 (Ref. Note to File no. 15, dated 04. Apr. 2014).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported