# 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<br>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<br>Units: Subjects | | | |
| Female | 589 | 589 | |
| Male | 601 | 601 | |
| BCG vaccination status<br>Units: Subjects | | | |
| Vaccinated | 882 | 882 | |
| Not vaccinated | 264 | 264 | |
| Unknown | 44 | 44 | |
| HIV status<br>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:<br><br>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.<br>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.<br>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.<br>4. The rapid HIV test kits which will be used during screening have been specified, which they were not in the initial protocol.<br>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.<br>6. The procedure for reading and recording the induration responses has been described in detail, which it was not in the initial protocol.<br>7. The cut-off for C-Tb has been clarified, which it was not in the initial protocol.<br>8. The trial statistician has been changed to Henrik Wachmann instead of Prof. Schoeman |
| 03 January 2013 | Amendment 2:<br><br>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.<br>2. The secondary objectives have been revised and the statistical analysis section of the amended protocol has been updated accordingly.<br>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.<br>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:<br><br>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).<br>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