Clinical trial results:
Immunogenicity and safety of a tetanus, diphtheria and mono component acellular pertussis (TdaP) vaccine in comparison to a tetanus and diphtheria (Td) vaccine when given as a booster vaccination to adults

Summary

EudraCT number	2009-013411-36
Trial protocol	DK
Global end of trial date	03 August 2010

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	VTdaP-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01033877
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, btc@ssi.dk
Scientific contact	Toxicology and Clinical Development Unit, Statens Serum Institut, btc@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	02 May 2011
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 August 2010
Global end of trial reached?	Yes
Global end of trial date	03 August 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

-To demonstrate anti-pertussis toxin (anti-PTx) booster responses in at least 60 % of TdaP booster vaccinated adults, defined from pre- and post-vaccination anti-PTx antibody concentrations.

-To demonstrate the non-inferiority of TdaP compared to Td when given as a booster vaccination to adults, defined from the percentage of subjects with post-vaccination anti-diphtheria antibody concentrations and anti-tetanus antibody concentrations ≥ 0.1 IU/mL

Protection of trial subjects:

The investigational TdaP Vaccine SSI and the comparative Td Vaccine SSI had both been registered medicinal products in Denmark for several years at the time of conducting the present clinical trial. TdaP indicated for use in children and Td for children (≥ 5 years of age) and adults.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 January 2010
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	Denmark: 802
Worldwide total number of subjects	802
EEA total number of subjects	802

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)	802

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

At Visit 1 the subject's eligibility was assessed according to the pre-defined in/exclusion criteria, demography, medical history data, oral temperature and vital signs were recorded, and a pregnancy test was performed for females. If the subject was eligible for inclusion and vaccination, a pre-vaccination blood sample was drawn

Period 1

Period 1 title	Overall trial (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:

It was not possible to identify the type of vaccine (TdaP or Td) by visual inspection of the suspension for injection in the pre-filled syringe, the inner- or outer packaging materials or inner- or outer labels.

Arms

Are arms mutually exclusive?	Yes
Arm title	TdaP Vaccine SSI

Arm description: -

Arm type	Experimental
Investigational medicinal product name	TdaP Vaccine SSI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Diphtheria toxoid, SSI.....≥ 2 I.U. (6.25 Lf)
Tetanus toxoid, SSI.....≥ 20 I.U. (6.25 Lf)
Pertussis toxoid.....20 µg
Aluminium hydroxide corr. to al.....0.5 mg
Sodium hydroxide.....q.s. ad pH 7
Sodium chloride.....4.0 mg
Water for injections.....to 0.5 ml

All vaccinations were administered intramuscularly, perpendicular to the skin in the LEFT deltoid muscle. A 23 gauge, 25 mm, blue Terumo needle was used for the injection.

Arm title	Td Vaccine SSI

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Td Vaccine SSI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Diphtheria toxoid, SSI.....≥ 2 I.U. (6.25 Lf)
Tetanus toxoid, SSI..... ≥ 20 I.U. (6.25 Lf)
Aluminium hydroxide corr. to al.....0.5 mg
Sodium hydroxide.....q.s. ad pH 7

Sodium chloride.....4.0 mg
Water for injections.....to 0.5 ml

All vaccinations were administered intramuscularly, perpendicular to the skin in the LEFT deltoid muscle. A 23 gauge, 25 mm, blue Terumo needle was used for the injection.

Number of subjects in period 1	TdaP Vaccine SSI	Td Vaccine SSI
Started	401	401
Completed	401	400
Not completed	0	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	TdaP Vaccine SSI
Reporting group description: -	
Reporting group title	Td Vaccine SSI
Reporting group description: -	

Reporting group values	TdaP Vaccine SSI	Td Vaccine SSI	Total
Number of subjects	401	401	802
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	26.5	26.1	
standard deviation	± 8	± 8.1	-
Gender categorical Units: Subjects			
Female	190	208	398
Male	211	193	404

Subject analysis sets	
Subject analysis set title	All subjects
Subject analysis set type	Full analysis
Subject analysis set description: All subjects randomised were included in this analysis set	

Reporting group values	All subjects		
Number of subjects	802		
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	26.3		
standard deviation	± 8.1		
Gender categorical Units: Subjects			
Female	398		
Male	404		

End points

End points reporting groups

Reporting group title	TdaP Vaccine SSI
Reporting group description: -	
Reporting group title	Td Vaccine SSI
Reporting group description: -	
Subject analysis set title	All subjects
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects randomised were included in this analysis set

Primary: Anti-pertussis toxin (anti-PT) booster response in the TdaP group

End point title	Anti-pertussis toxin (anti-PT) booster response in the TdaP group[1][2]

End point description:

Demonstrate that at least 60% of the subjects in the TdaP group have an anti-PT booster response, defined as an at least a 4-fold increase in the anti-PT antibody level, if the pre-vaccination antibody level is low (< 20 IU/mL), and by at least a 2-fold increase in the anti-PTx antibody level if the pre-vaccination antibody level is high (≥ 20 IU/mL).

End point type	Primary

End point timeframe:

The booster response was assessed one month (28-35 days) after the administration of the booster vaccination from pre-vaccination and post-vaccination anti-pertussis toxin levels in the TdaP group

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: The relative frequency of vaccinees with an adequate booster response was estimated via the normal approximation to the binomial distribution with corresponding approximate 95% confidence intervals. The objective was considered proved as the lower limit of the 2-sided 95% confidence interval was above 0.60.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The primary objective was only to demonstrate anti-pertussis antibody booster responses in TdaP booster vaccinated adults.

End point values	TdaP Vaccine SSI			
Subject group type	Reporting group			
Number of subjects analysed	401			
Units: Percentage				
number (confidence interval 95%)	92 (88.9 to 94.5)			

Statistical analyses

No statistical analyses for this end point

Primary: Non-inferiority of TdaP compared to Td: Tetanus protection

End point title	Non-inferiority of TdaP compared to Td: Tetanus protection[3]

End point description:

The non-inferiority of the investigational TdaP vaccine to the comparative Td vaccine as regards protection against tetanus (defined as post-vaccination anti-tetanus antibody concentrations ≥ 0.1 IU/mL), when given as a booster vaccination to adults. The non-inferiority limit was 10%.

End point type	Primary

End point timeframe:

The proportion of subjects with protection against tetanus was assessed one month (28-35 days) after the administration of the booster vaccination from post-vaccination tetanus antibody levels

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: The non-inferiority of the protection rate against tetanus after TdaP-vaccination compared to that after Td-vaccination is tested with the 2-sided Wilson method. The non-inferiority limit of 10%.

End point values	TdaP Vaccine SSI	Td Vaccine SSI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	401	399		
Units: Percentage				
number (not applicable)	100	100		

Statistical analyses

No statistical analyses for this end point

Primary: Non-inferiority of TdaP compared to Td: Diphtheria protection

End point title	Non-inferiority of TdaP compared to Td: Diphtheria protection[4]

End point description:

The non-inferiority of the investigational TdaP vaccine to the comparative Td vaccine as regards protection against diphtheria (defined as post-vaccination and anti-diphtheria antibody concentrations ≥ 0.1 IU/mL), when given as a booster vaccination to adults. The non-inferiority limit was 10%

End point type	Primary

End point timeframe:

The proportion of subjects with protection against diphtheria was assessed one month (28-35 days) after the administration of the booster vaccination from post-vaccination diphtheria antibody levels

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: The non-inferiority of the protection rate against diphtheria after TdaP-vaccination compared to that after Td-vaccination is tested with the 2-sided Wilson method. The non-inferiority limit of 10%.

End point values	TdaP Vaccine SSI	Td Vaccine SSI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	401	399		
Units: Percentage				
number (not applicable)	98.5	99.5		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

A thermometer, ruler and diary with instructions for use were given to the subjects on the day of the vaccination. At the follow-up visit 28-35 days later, adverse events and concomitant medications were assessed and recorded.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10.0

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 / 802 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

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	528 / 802 (65.84%)		
General disorders and administration site conditions			
All injection site reactions			
subjects affected / exposed	297 / 802 (37.03%)		
occurrences (all)	345		
Systemic adverse events related to vaccination			
subjects affected / exposed	290 / 802 (36.16%)		
occurrences (all)	534		

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

Online references

http://www.ncbi.nlm.nih.gov/pubmed/22776216