Clinical trial results:
A single blind, randomized comparative and multicentre clinical trial of the immunogenicity and safety of booster immunisation with tetanus monovalent vaccines VACTETA 40 IU/0,5 ml (BIODRUG) and TETAVAX (Sanofi Pasteur SA) in healthy adults.

Summary

EudraCT number	2016-004934-11
Trial protocol	CZ
Global end of trial date	29 May 2017

Results information

Result version number	v1 (current)
This version publication date	19 August 2017
First version publication date	19 August 2017
Summary attachment (see zip file)	Study report synopsis TeVaTri042017 v1.3 (Study Report Synopsis TeVaTri042017 version 1.3.pdf)

Trial information

Trial identification

Sponsor protocol code	TeVaTri042017

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	BIODRUG s.r.o.
Sponsor organisation address	Boženy Němcovej 8, Bratislava, Slovakia, 811 04
Public contact	Clinical Trial Information Desk, RECLINMED s.r.o., +420 608 881 826, info@reclinmed.cz
Scientific contact	Clinical Trial Information Desk, RECLINMED s.r.o., +420 608 881 826, info@reclinmed.cz

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	20 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 May 2017
Global end of trial reached?	Yes
Global end of trial date	29 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluation of immunogenicity of tetanus monovalent vaccine Vacteta after booster immunisation of health adults compared with that induced by vaccine Tetavax.

Protection of trial subjects:

The risk to subjects enrolled in this study is not higher than the general risks of adverse reactions after tetanus vaccination because both commercial vaccines are registered in the Czech Republic. Subjects will not be exposed to more stress or pain than they are from the vaccination or blood sampling.

Background therapy:

Healthy adults

Evidence for comparator:

The control vaccine, further called as reference vaccine, was chosen as it is the only one monovalent vaccine against tetanus available and authorised in the Czech Republic. There was no other reason of this selection.

Actual start date of recruitment	28 March 2017
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	Czech Republic: 200
Worldwide total number of subjects	200
EEA total number of subjects	200

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)	200

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In the study was planned to enrol a total of 200 subjects recruited from healthy adults. All patients were selected from outpatient's clinic (clinical sites) according to inclusion and exclusion criteria. In one clinical site, there were planned to enrol a total of 50 subjects.

Pre-assignment

Screening details:

Subjects must have written confirmation on previous immunisation against tetanus not later than 15.9 years and not early than 9.9 years

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Subject

Blinding implementation details:

The single blinding was achieved by simple overlapping of subject eyes with a mask before the administration of vaccine. So a subject did not know which vaccine had been administered to him. The single blinding helped especially to objectively assess any adverse events.

Arms

Are arms mutually exclusive?	Yes
Arm title	Test medication

Arm description:

Subjects received one dose of test vaccine Vacteta.

Arm type	Experimental
Investigational medicinal product name	Vacteta 40 IU/0.5 ml
Investigational medicinal product code	SUB12609MIG
Other name	TETANUS TOXOID ADSORBED
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

The vaccine was administered intramuscularly to minimize the occurrence of local adverse reactions as it is recommended by the manufacture. The recommended site of the application was deltoid region in adults.
The vaccine dose was the same for both vaccines, i.e. volume of 0.5 ml. The concentration of dose was also identical for both vaccines, i.e. at least 40 IU/0.5 ml. The volume of dose, including the way of administration was in accordance of SmPC of both study vaccines.

Arm title	Reference medication

Arm description:

Subjects received one dose of reference vaccine Tetavax.

Arm type	Active comparator
Investigational medicinal product name	Tetavax
Investigational medicinal product code	SUB12609MIG
Other name	TETANUS TOXOID ADSORBED
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

The vaccine was administered intramuscularly to minimize the occurrence of local adverse reactions as it is recommended by the manufacture. The recommended site of the application was deltoid region in adults.

The vaccine dose was the same for both vaccines, i.e. volume of 0.5 ml. The concentration of dose was also identical for both vaccines, i.e. at least 40 IU/0.5 ml. The volume of dose, including the way of administration was in accordance of SmPC of both study vaccines.

Number of subjects in period 1	Test medication	Reference medication
Started	100	100
Completed	100	100

Baseline characteristics

Reporting groups	
Reporting group title	Test medication
Reporting group description:	
Subjects received one dose of test vaccine Vacteta.	
Reporting group title	Reference medication
Reporting group description:	
Subjects received one dose of reference vaccine Tetavax.	

Reporting group values	Test medication	Reference medication	Total
Number of subjects	100	100	200
Age categorical			
The study stratification was performed on the base of sex and age as follows: 24.1-29.9 years, 30- 49.9 years, 50-64.9 years for both males and females.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Adults 24.1-29.9	24	24	48
Adults 30-49.9	44	44	88
Adults 50-64.9	32	32	64
Gender categorical			
Units: Subjects			
Female	50	50	100
Male	50	50	100

Subject analysis sets	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The primary objective of proving non-inferiority based on primary analysis of variables performed on the ITT set (intention-to-treat) subjects is conservative in approach. This set included all subjects since each subject had the primary endpoint, i.e. the concentration of tetanus-specific antibodies at the started and completed milestone.	

Reporting group values	ITT		
Number of subjects	200		
Age categorical			
The study stratification was performed on the base of sex and age as follows: 24.1-29.9 years, 30- 49.9 years, 50-64.9 years for both males and females.			

Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	0		
From 65-84 years	0		
85 years and over	0		
Adults 24.1-29.9	48		
Adults 30-49.9	88		
Adults 50-64.9	64		
Gender categorical			
Units: Subjects			
Female	100		
Male	100		

End points

End points reporting groups

Reporting group title	Test medication
Reporting group description:	
Subjects received one dose of test vaccine Vacteta.	
Reporting group title	Reference medication
Reporting group description:	
Subjects received one dose of reference vaccine Tetavax.	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The primary objective of proving non-inferiority based on primary analysis of variables performed on the ITT set (intention-to-treat) subjects is conservative in approach. This set included all subjects since each subject had the primary endpoint, i.e. the concentration of tetanus-specific antibodies at the started and completed milestone.	

Primary: seroconversion rate

End point title	seroconversion rate
End point description:	
The seroconversion rate was evaluated positive if the increase in antibody levels is at least 4-fold. If the tetanus-specific antibody concentrations prior to administering the booster dose was equal to or less than 0.1 IU/ml, then the seroconversion rate was positive when the post-vaccination concentration was at least 4-fold higher than the pre-vaccination concentration and the post-vaccination concentration was at least 0.4 IU/ml.	
End point type	Primary
End point timeframe:	
Between started and completed milestone	

End point values	Test medication	Reference medication		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	100		
Units: 10	71	68		

Statistical analyses

Statistical analysis title	difference between test and reference vaccine
Statistical analysis description:	
Fisher’s exact test; asymptotic interval	
Comparison groups	Test medication v Reference medication

Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.05 [2]
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.76
upper limit	15.8
Variability estimate	Standard error of the mean
Dispersion value	6.51

Notes:

[1] - The efficacy objective was met if the seroconversion rate induced with Vacteta vaccine was not worse than 10% compared to reference vaccine-induced seroconversion rate (i.e. seroconversion rates of test minus reference vaccine, including the lower limit of the 95% confidence interval of this difference was not lower than -10%).
[2] - The significance level was determined 0.05 for the test of null hypothesis of non-inferiority at a two-sided 95% confidence interval because this study was designed to be non-inferior based on the substantial similarity of both tetanus vaccines.

Secondary: geometric mean of antibodies specific against tetanus

End point title	geometric mean of antibodies specific against tetanus

End point description:

A secondary objective is to confirm not a worse immune response demonstrated with the 95% confidence interval of geometric mean of tetanus-specific antibody concentrations after booster immunisation with the test vaccine compared to that of the reference one.

End point type	Secondary

End point timeframe:

completed milestone

End point values	Test medication	Reference medication		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	100		
Units: IU/ml				
geometric mean (confidence interval 95%)	7.4 (6.6 to 8.2)	8.3 (7.6 to 9.1)		

Statistical analyses

Statistical analysis title	ratio of geometric means - test/reference

Statistical analysis description:

It was computed as a difference of logarithms of both geometric means. It was reasonable to assume that two populations (antibody concentrations) have the same standard deviation, therefore a procedure known as the pooled t procedure could be.

Comparison groups	Test medication v Reference medication

Number of subjects included in analysis	200
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	ratio
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.02
Variability estimate	Standard error of the mean
Dispersion value	0.224

Notes:

[3] - If the lower limit of this ratio interval (i.e. anti-T [Vacteta] / anti-T [Tetavax]) is ≥0.5 and the two-sided confidence interval will contain 1, then the criterion of non-inferiority will be met.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

started and completed milestone

Adverse event reporting additional description:

The measures of safety used in this study were routine clinical procedures. They were chosen to capture known undesirable effects of tetanus vaccination from the SmPC. Safety measures were conducted by the investigators. They included close vigilance for reporting of reactions on the day of immunisation and 4 weeks after immunisation

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20

Reporting groups

Reporting group title	test vaccine
Reporting group description: -	
Reporting group title	reference vaccine

Reporting group description: -

Serious adverse events	test vaccine	reference vaccine	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 100 (0.00%)	0 / 100 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	test vaccine	reference vaccine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 100 (29.00%)	35 / 100 (35.00%)	
Nervous system disorders			
Headache			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 100 (1.00%)	1 / 100 (1.00%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Pain in extremity	Additional description: Arm/Shoulder pain		

subjects affected / exposed	3 / 100 (3.00%)	7 / 100 (7.00%)	
occurrences (all)	3	7	
Injection related reaction	Additional description: Pain at injection site, Swelling at injection site, Spot at injection site, Burning at injection site, Itching at injection site, Redness at injection site, Induration at the injection site, Elevated temperature at injection site		
subjects affected / exposed	18 / 100 (18.00%)	22 / 100 (22.00%)	
occurrences (all)	28	43	
Fatigue			
subjects affected / exposed	5 / 100 (5.00%)	1 / 100 (1.00%)	
occurrences (all)	5	1	
subfebrilia			
subjects affected / exposed	0 / 100 (0.00%)	4 / 100 (4.00%)	
occurrences (all)	0	4	
Skin and subcutaneous tissue disorders			
Pruritus	Additional description: Pruritus - Exacerbation of eczema		
alternative assessment type: Systematic			
subjects affected / exposed	1 / 100 (1.00%)	1 / 100 (1.00%)	
occurrences (all)	1	1	
Infections and infestations			
Viraemia	Additional description: Virosis		
alternative assessment type: Systematic			
subjects affected / exposed	1 / 100 (1.00%)	1 / 100 (1.00%)	
occurrences (all)	1	1	

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Not applicable.

Notes: