1. TITLE PAGE

CLINICAL STUDY REPORT

Protocol identifying number: TeVaTri042017

EudraCT code: 2016-004934-11

Study title:

A single blind, randomised 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.

Name of test drug	VACTETA 40 IU/0,5 ml
Indication studied	Tetanus Imunoprophylaxis; booster immunisation
Development phase of study	Post-registration study, phase IV
Study initiation date	28.3.2017
Study completion date	29.5.2017
Name and address of the sponsor	BIODRUG s.r.o., Boženy Němcovej 8, 811 04 Bratislava, Slovakia, tel: +421905349706, email: fisera@biodrug.sk
Contract research organisation	RECLINMED s.r.o., Průběžná 41/387,100 87 Praha 10, Czech Republic, tel: +420 608 881 826, email: info@reclinmed.cz
Principle investigator	MUDr. Lenka Pennigrová CSc. Alergologie Třeboňská s.r.o., Třeboňská 530/4, 140 00 Praha 4 – Michle, Czech Republic, Tel: 244 400 413, e-mail: alpenn@volny.cz
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Date	21.7.2017
Version	version 1.3
Protocol amendment	None

This study was performed in compliance with Good Clinical Practices.
This final report has been prepared in accordance
with the principles CPMP/ICH/137/95 and its annexes.

2. SYNOPSIS

Name of sponsor: BIODRUG s.r.o., Bratislava, Slovakia	STUDY REPORT SYNOPSIS **Protocol identifying number:** **TeVaTri042017** **EudraCT code: 2016-004934-11** Final version 1.3
Name of investigational product: VACTETA 40 IU/0,5 ml TETAVAX	
Name of active ingredient: Tetani anatoxinum (min. 40 IU/0,5 ml)	

Title of Study:
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.

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Publication (reference)
WHO Expert Committee on Biological Standardization. Replacement of Annex 2 of WHO Technical Report Series, No. 800, and Annex 5 of WHO Technical Report Series, No. 927.

Study duration: 9 weeks **Date of first enrolment:** 28.3.2017 **Date of last completed:** 29.5.2017	**Clinical phase:** IV

Objectives of the trial:
1. Primary objective of this trial was to demonstrate non-inferior immunogenicity (represented by seroconversion rate) induced by the immunization with the test vaccine (Vacteta) over the reference one (Tetavax) in the set of healthy adults.
2. Secondary objective was to confirm not a worse immune response demonstrated with the geometric mean of concentrations of tetanus-specific antibodies after booster immunization with the test and reference vaccine.
3. Safety objective was to evaluate safety of the test vaccine (Vacteta).

Methodology
The study followed a randomized, single-blind comparative and multicentre design with healthy adult subjects requiring a booster dose of tetanus vaccine. To assess the immune response after vaccination

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two blood samples was taken, i.e. before immunisation and 4 weeks after immunisation. One half of the subjects received the test vaccine (Vacteta) and the other half received the reference vaccine (Tetavax).
The measurements of antibody concentrations were performed by ELISA method with the VaccZyme Anti-Tetanus Toxoid IgG Enzyme Immunoassay Kit (code: MK010).

Number of patients
Planned: 200; Analysed: 200

Diagnosis and main criteria for inclusion

1. Subjects had to have signed an approved informed consent after complete information
2. Subjects had to have written confirmation on previous immunisation against tetanus not later than 15.9 years and not early than 9.9 years
3. Healthy men and women aged 24.1- 64.9 years.

Test product, dose and mode of administration, batch number
Vacteta 40 IU/0,5 ml; intramuscular application; batch number: 03716001, expiration: 06.2019

Duration of treatment
Length of follow-up: 28 days (4 weeks)

Reference therapy, dose and mode of administration, batch number
Tetavax (40 IU/0,5 ml); intramuscular application; batch number: M74627V, expiration: 31.08.2018

Criteria for evaluation:
Efficacy (immunogenicity endpoints):
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%).
The immune response expressed with the GMCs of tetanus antibodies (secondary endpoint) induced with Vacteta vaccine was not worse if the lower limit of 95% confidence interval for the GMCs ratio of both vaccinations (i.e. anti-T [Vacteta] GMCs / anti-T [Tetavax] GMCs) was ≥0.5 and the two-sided confidence interval contained 1.

Safety:
If the proportion of adverse events between the two groups was not statistically significant, the safety of the test vaccine was similar or equal to that of the reference vaccine.

Statistical methods
Two subsets of categorical variable (seroconversion rate, sex, smoker, etc.) were assessed by the Fisher's exact test and more than two subsets with the chi-square test. The two-sided confidence interval of difference between two proportions (i.e. seroconversion rates) was calculated as simple asymptotic. Statistical significance was set a 0.05.

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It was decided to analyse continuous variables (such as antibody concentrations, age, BMI, post-vaccination period etc.) by nonparametric tests, because groups and subgroups of continuous variables did not mostly pass the normality test (D'Agostino and Pearson test). If the significance P was in the range 0.02-0.1 then the parametric test was applied to verify the result of the nonparametric test (verification of significance). If there was no agreement between the results of parametric and non-parametric tests then the significance of parametric test was accepted if at least two subsets passed the test of normality.
If the comparison of more than two subgroups was performed, then it was used the Kruskal-Wallis test or the ordinary one-way ANOVA test with correction for multiple comparisons using statistical hypothesis testing with Dunn's multiple comparisons test or Bonferroni's multiple comparisons test, respectively.

Summary - Conclusions

Efficacy Results

1. The primary objective of this trial was achieved; the seroconversion rate induced by the test vaccine (Vacteta) was not worse than that induced by the reference vaccine (Tetavax), i.e. the difference in the seroconversion rates was 3.0 % (95% CI: -9.76 to 15.80%).
2. The seroconversion rate of the test group (71%; 95% CI: 61.1 to 79.6%) and the reference one (68%; 95%CI: 57.9 to 77%) was similar with no statistically significant difference.
3. The primary objective was demonstrated also in the subset of subjects with pre-vaccination concentrations lower than 1.0 IU/ml since both study groups achieved the seroconversion rate of 100% and the difference of rates was 0% (95%CI: -2.4 to 2.4%).
4. The seroconversion rate of the test group was not worse than that of the reference group after the mutual adjustment for covariates with the logistic regression.
5. The secondary objective was also achieved in the ratio of geometric mean concentrations of tetanus antibodies. The pre-specified GMCs ratio of Vacteta to Tetavax vaccine complied at least 0.5 IU/ml of the lower limit of two-sided 95% confidence interval and this interval contained 1. The ratio of GMCs was 0.88 (95%CI: 0.76 to 1.02).
6. A 7.8-fold rise in concentrations of tetanus antibodies after booster dose of Vacteta was like 7.3-fold rise after booster dose of Tetavax. The geometric mean concentrations were 7.4 IU/ml (6.6 to 8.2 IU/ml) and 8.3 IU/ml (7.6 to 9.1 IU/ml) 4 weeks after booster dose of Vacteta and Tetavax, respectively.

Safety Results

1. A total of 64 subjects reported adverse events, i.e. 32% (95% CI: 25.6 to 38.9%). A total of 29 subjects (29%; 95% CI: 20.4 to 38.9%) received the test vaccine (Vacteta) and 35 subjects (35%; 95% CI: 25.7-45.2%) the reference one (Tetavax). No statistical difference in number of subjects of both study groups was found.
2. Neither serious nor severe adverse events were observed. No death was recorded during the entire study.
3. Moderate severity of adverse events was documented by 15.6% of subjects; all related adverse events spontaneously disappeared with no treatment and its outcome was full recovery.
4. The test vaccine (Vacteta) had the same safety profile as the reference one (Tetavax) because

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no significant difference in adverse events related to vaccination was confirmed between them.

5. The very common occurring adverse event was pain at injection site in 10.5% of immunised independently of the used vaccine. Common adverse events were in accordance with SmPC of both study vaccines, i.e. redness, swelling, induration, elevated temperature, itching and spot at injection site, arm or shoulder pain, fatigue, subfebrilia and headache.

Conclusion

Vacteta vaccine did not induced worse immune response than Tetavax vaccine and therefore it provides the suitable protection against tetanus as it is expected consistently with the manufacturer's recommendations. The safety profile of Vacteta vaccine was as Tetavax vaccine and it demonstrated good acceptance. The study did not reveal any new facts that would not be displayed in the current SmPCs of both authorised vaccines.

The clinical trial protocol will be submitted for approval by the national authority and ethical committees.
During its formation, the principles of the Declaration of Helsinki and of Good Clinical Practice have been followed. The clinical trial will be conducted in accordance with the principles of Good Clinical Practice.