Clinical trial results:
Prospective Multicentre Randomized Double-Blind Placebo-Controlled Parallel Group Study on the Efficacy and Tolerability of StroVac® in Patients With Recurrent Symptomatic Bacterial Urinary Tract Infections

Summary

EudraCT number	2010-020882-25
Trial protocol	DE
Global end of trial date	19 March 2015

Results information

Result version number	v1 (current)
This version publication date	24 February 2018
First version publication date	24 February 2018

Trial information

Trial identification

Sponsor protocol code	SU5.6

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Strathmann GmbH & Co. KG
Sponsor organisation address	Sellhopsweg 1, Hamburg, Germany, 22459
Public contact	Medizinisch-Wissenschaftliche Abteilung, Strathmann GmbH & Co. KG, +49 (0)40559050, Verteiler_MW@strathmann.de
Scientific contact	Medizinisch-Wissenschaftliche Abteilung, Strathmann GmbH & Co. KG, +49 (0)40559050, Verteiler_MW@strathmann.de

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	22 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 March 2015
Global end of trial reached?	Yes
Global end of trial date	19 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the clinical efficacy and tolerability of the inactivated germs of specified enterobacteria contained in StroVac® in recurrent acute uncomplicated symptomatic bacterial urinary tract infections as compared to placebo.

Protection of trial subjects:

This trial was conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World Medical Association. The planning and conduct of this trial followed the respective national laws in Germany, the principles and guidelines for good clinical practice laid down in Directives 2001/20/EC [9] and 2005/28/EC [10] of the European Parliament and the Consensus paper of the International Conference on Harmonisation on good clinical practice (ICH-GCP) and the Pharmalog SOPs that are based on the ICH-GCP guidelines.
The risk profile of StroVac® has been well established in more than 25 years both in published studies and via spontaneous reporting. Two large non-interventional studies including more than 2.000 patients treated with StroVac® showed that the product is efficacious and well tolerated under medical routine conditions.
Placebo is considered to be an adequate comparator to study the effect of immunization as compared to the natural course without immunization. In case of intolerability to the first or second vaccination the patient was withdrawn from the study. In addition, in compliance with GCP patients were free to leave the study at any time they wish. In order to follow the risks adequately the Investigator saw the patients frequently or was in telephone contact with them according to the study scheme provided in protocol. The study protocol included study withdrawal criteria on patient and study basis to reduce individual risks.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 January 2012
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	Germany: 376
Worldwide total number of subjects	376
EEA total number of subjects	376

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)	304
From 65 to 84 years	72
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Adult outpatients with the inclusion diagnosis “history of at least one year of confirmed recurrent uncomplicated symptomatic bacterial urinary tract infections” were eligible for study participation if they meet all of the inclusion and exclusion criteria.

Period 1

Period 1 title	Screening assessments
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	No arms defined yet

Arm description:

Prior to randomisation, the Investigator must ensure that the patient meets the inclusion diagnosis “history of at least one year of confirmed recurrent uncomplicated symptomatic bacterial urinary tract infections” and all of the corresponding inclusion and exclusion criteria. No arms defined yet.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	No arms defined yet
Started	376
Completed	376

Period 2

Period 2 title	Immunization
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

To ensure balancing regarding known and unknown influencing factors for both treatments, a randomized block design stratification by menopausal condition (pre-/ and postmenopausal) of the patients was used to allocate StroVac® or placebo to the patient.
Male patients were included in the premenopausal stratum.

Arms

Are arms mutually exclusive?	Yes

Arm title	StroVac®

Arm description:

Basic suspension and dried active substance for the preparation of a suspension for injection purposes. One unit of dried active substance contains at least 10**9 inactivated germs including Escherichia coli 7.5 x 10**8, Morganella morganii 3.75 x 10**7, Proteus mirabilis 3.75 x 10**7, Klebsiella pneumoniae 1.5 x 10**8, and Enteroccocus faecalis 2.5 x 10**7

Arm type	Experimental
Investigational medicinal product name	StroVac®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Three single injections every two weeks ± 7 days

Arm title	Placebo

Arm description:

Basic suspension and dried placebo substance for the preparation of a suspension for injection purposes. One unit of dried placebo substance contains excipients only.

Arm type	Placebo
Investigational medicinal product name	Placebo suspension for i.m. injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Three single injections every two weeks ± 7 days

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Baseline period starts with Visit 2 (=randomisation date). Prior to randomisation (=Period 1, screening assessments), the Investigator must ensure that the patient meets the inclusion diagnosis "history of at least one year of confirmed recurrent uncomplicated symptomatic bacterial urinary tract infections" and all of the corresponding in- and exclusion criteria (e.g. at least 5 UTIs during a period of 12 months prior to study inclusion = baseline value)

Number of subjects in period 2	StroVac®	Placebo
Started	188	188
Completed	184	187
Not completed	4	1
Consent withdrawn by subject	2	1
Adverse event, non-fatal	1	-
Poor compliance	1	-

Period 3

Period 3 title	Post- Immunization
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind

Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

No further IMP dispensed. Blinding and randomization of period 2 was kept.

Arms

Are arms mutually exclusive?	Yes
Arm title	StroVac®

Arm description:

Same arm like in Period 2 / no further injections

Arm type	Experimental
Investigational medicinal product name	StroVac®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Same arm like in Period 2 / no further injections

Arm title	Placebo

Arm description:

Same arm like in Period 2 / no further injections

Arm type	Placebo
Investigational medicinal product name	Placebo suspension for i.m. injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Same arm like in Period 2 / no further injections

Number of subjects in period 3	StroVac®	Placebo
Started	184	187
Completed	167	170
Not completed	17	17
Consent withdrawn by subject	4	5
Administrative	1	1
Poor compliance	2	1
Lost to follow-up	2	4
Lack of efficacy	1	1
Protocol deviation	7	5

Baseline characteristics

Reporting groups	
Reporting group title	StroVac®
Reporting group description:	
Basic suspension and dried active substance for the preparation of a suspension for injection purposes. One unit of dried active substance contains at least 10**9 inactivated germs including Escherichia coli 7.5 x 10**8, Morganella morganii 3.75 x 10**7, Proteus mirabilis 3.75 x 10**7, Klebsiella pneumoniae 1.5 x 10**8, and Enteroccocus faecalis 2.5 x 10**7	
Reporting group title	Placebo
Reporting group description:	
Basic suspension and dried placebo substance for the preparation of a suspension for injection purposes. One unit of dried placebo substance contains excipients only.	

Reporting group values	StroVac®	Placebo	Total
Number of subjects	188	188	376
Age categorical 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
age (≥18 and ≤80 years)	188	188	376
Gender categorical Units: Subjects			
Female	186	184	370
Male	2	4	6

End points

End points reporting groups

Reporting group title	No arms defined yet

Reporting group description:

Prior to randomisation, the Investigator must ensure that the patient meets the inclusion diagnosis "history of at least one year of confirmed recurrent uncomplicated symptomatic bacterial urinary tract infections" and all of the corresponding inclusion and exclusion criteria. No arms defined yet.

Reporting group title	StroVac®

Reporting group description:

Basic suspension and dried active substance for the preparation of a suspension for injection purposes. One unit of dried active substance contains at least 10**9 inactivated germs including Escherichia coli 7.5 x 10**8, Morganella morganii 3.75 x 10**7, Proteus mirabilis 3.75 x 10**7, Klebsiella pneumoniae 1.5 x 10**8, and Enteroccocus faecalis 2.5 x 10**7

Reporting group title	Placebo

Reporting group description:

Basic suspension and dried placebo substance for the preparation of a suspension for injection purposes. One unit of dried placebo substance contains excipients only.

Reporting group title	StroVac®

Reporting group description:

Same arm like in Period 2 / no further injections

Reporting group title	Placebo

Reporting group description:

Same arm like in Period 2 / no further injections

Primary: Number of bacterial urinary tract recurrences with confirmed bacterial origin over a period of 13.5 months

End point title	Number of bacterial urinary tract recurrences with confirmed bacterial origin over a period of 13.5 months

End point description:

The primary endpoint was compared statistically in a confirmatory test approach on superiority of StroVac® compared to placebo. The respective statistical test was performed using the generalized linear model (GLM) in the following form:
It was assumed that the number of confirmed infection recurrences during exposure time t=13.5 months could be described by Poisson distributions where the recurrence rate depended on treatment and disease severity at baseline, which was defined as confirmed UTI recurrences in the 12 months previous to study start.

End point type	Primary

End point timeframe:

Over a period of 13.5 months starting after randomization.

End point values	StroVac®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	187	188		
Units: no. of bacterial UTIs	1024	1018		

Statistical analyses

Statistical analysis title	Main analysis
Comparison groups	Placebo v StroVac®
Number of subjects included in analysis	375
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.6324
Method	Poisson regression
Parameter estimate	Mean difference (final values)
Point estimate	-0.0595
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.3031
upper limit	0.1842
Variability estimate	Standard error of the mean
Dispersion value	0.1243

Notes:

[1] - superiority of StroVac® compared to placebo

Post-hoc: Analysis of patients with No. of UTIs above average

End point title	Analysis of patients with No. of UTIs above average

End point description:

An additional post-hoc analysis of patients with infections above average prior to randomisation versus UTIs during the study was performed. 13.9 % of the patients had 7 or more infections prior randomisation in the StroVac® group and in the placebo group 17.0 % of the patients, in mean 7.4 UTIs.
In the period of 13.5 months after randomisation (= after start of first vaccination) 7 or more UTIs prior to inclusion reduced in the StroVac® group to 2.3 UTIs compared to 4.4 UTIs during placebo treatment with significant differences in the ITT (p-value 0.0482).
This significance was verified in the FAS and PP (p-value 0.0487 and 0.0286, respectively). Furthermore a significant difference could also be shown in the period of 12 months (=after completion of vaccination) in the PP (p-value 0.0469).

End point type	Post-hoc

End point timeframe:

In the period of 13.5 months after randomisation

End point values	StroVac®	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	32		
Units: No. of bacterial UTIs	189	242		

Statistical analyses

Statistical analysis title	Analysis of pts with No. of UTIs above average
Comparison groups	Placebo v StroVac®

Number of subjects included in analysis	58
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.0482
Method	Poisson regression
Parameter estimate	Median difference (final values)
Point estimate	-0.555
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.1056
upper limit	-0.0044
Variability estimate	Standard error of the mean
Dispersion value	0.2809

Adverse events

Adverse events information

Timeframe for reporting adverse events:

1) "Within the treatment period": start date on/after Day 1 (=V2, start of immunization) until the last day of the immunization period (V5–1 day).
2) "after the treatment period": start on on the first day of the post-immunization period (V5)

Adverse event reporting additional description:

According to the study protocol fever > 38.5 °C occurring up to 72 hours after the injection and chills were to be documented as SAEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Within the treatment period / StroVac®
Reporting group description: -	
Reporting group title	Within the treatment period / Placebo
Reporting group description: -	
Reporting group title	After the treatment period / StroVac®
Reporting group description: -	
Reporting group title	After the treatment period / Placebo
Reporting group description: -	

Serious adverse events	Within the treatment period / StroVac®	Within the treatment period / Placebo	After the treatment period / StroVac®
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 188 (12.77%)	5 / 188 (2.66%)	15 / 188 (7.98%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma			
subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer female			
subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Thrombophlebitis			

subjects affected / exposed	0 / 188 (0.00%)	1 / 188 (0.53%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	1 / 188 (0.53%)	0 / 188 (0.00%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystectomy			
subjects affected / exposed	1 / 188 (0.53%)	0 / 188 (0.00%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian operation			
subjects affected / exposed	1 / 188 (0.53%)	0 / 188 (0.00%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicectomy			
subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystocele repair			
subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal resection			

subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salpingectomy			
subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillectomy			
subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transurethral bladder resection			
subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Haemorrhage in pregnancy			
subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Labour pain			
subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chills			
subjects affected / exposed	14 / 188 (7.45%)	2 / 188 (1.06%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	15 / 15	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	8 / 188 (4.26%)	2 / 188 (1.06%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	8 / 8	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vaccination site swelling			
subjects affected / exposed	1 / 188 (0.53%)	0 / 188 (0.00%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea exertional			
subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Intentional self-injury			
subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Multiple injuries			
subjects affected / exposed	1 / 188 (0.53%)	0 / 188 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 188 (0.00%)	1 / 188 (0.53%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiomyopathy			
subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Dizziness			
subjects affected / exposed	1 / 188 (0.53%)	0 / 188 (0.00%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids thrombosed			
subjects affected / exposed	0 / 188 (0.00%)	1 / 188 (0.53%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatitis acute			
subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Musculoskeletal discomfort			
subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Helicobacter gastritis			

subjects affected / exposed	0 / 188 (0.00%)	1 / 188 (0.53%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast abscess			
subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mastitis			
subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	0 / 188 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis			
subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	1 / 188 (0.53%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 188 (0.00%)	0 / 188 (0.00%)	2 / 188 (1.06%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	After the treatment period / Placebo		

Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 188 (5.32%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Breast cancer female			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Thrombophlebitis			
subjects affected / exposed	0 / 188 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertensive crisis			
subjects affected / exposed	0 / 188 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombosis			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Abortion induced			
subjects affected / exposed	0 / 188 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystectomy			
subjects affected / exposed	0 / 188 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Ovarian operation				
subjects affected / exposed	0 / 188 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Appendicectomy				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cystocele repair				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal resection				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Salpingectomy				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tonsillectomy				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transurethral bladder resection				
subjects affected / exposed	0 / 188 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pregnancy, puerperium and perinatal conditions				
Haemorrhage in pregnancy				
subjects affected / exposed	0 / 188 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Labour pain			
subjects affected / exposed	0 / 188 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 188 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	0 / 188 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vaccination site swelling			
subjects affected / exposed	0 / 188 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	0 / 188 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea exertional			
subjects affected / exposed	0 / 188 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Intentional self-injury			
subjects affected / exposed	0 / 188 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			

Multiple injuries			
subjects affected / exposed	0 / 188 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 188 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiomyopathy			
subjects affected / exposed	0 / 188 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 188 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sciatica			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	0 / 188 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemorrhoids thrombosed			
subjects affected / exposed	0 / 188 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatitis acute			

subjects affected / exposed	0 / 188 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Musculoskeletal discomfort			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Helicobacter gastritis			
subjects affected / exposed	0 / 188 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Breast abscess			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	0 / 188 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	0 / 188 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	1 / 188 (0.53%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Mastitis				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Meningitis				
subjects affected / exposed	0 / 188 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				
subjects affected / exposed	1 / 188 (0.53%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Within the treatment period / StroVac®	Within the treatment period / Placebo	After the treatment period / StroVac®
Total subjects affected by non-serious adverse events			
subjects affected / exposed	115 / 188 (61.17%)	83 / 188 (44.15%)	81 / 188 (43.09%)
Investigations			
Body temperature increased			
subjects affected / exposed	11 / 188 (5.85%)	2 / 188 (1.06%)	2 / 188 (1.06%)
occurrences (all)	14	2	2
Nervous system disorders			
Headache			
subjects affected / exposed	15 / 188 (7.98%)	11 / 188 (5.85%)	1 / 188 (0.53%)
occurrences (all)	16	13	1
General disorders and administration site conditions			
Feeling cold			
subjects affected / exposed	6 / 188 (3.19%)	0 / 188 (0.00%)	0 / 188 (0.00%)
occurrences (all)	8	0	0
Influenza like illness			
subjects affected / exposed	22 / 188 (11.70%)	9 / 188 (4.79%)	10 / 188 (5.32%)
occurrences (all)	27	9	14
Pyrexia			

subjects affected / exposed	15 / 188 (7.98%)	5 / 188 (2.66%)	3 / 188 (1.60%)
occurrences (all)	17	5	3
Vaccination site erythema			
subjects affected / exposed	13 / 188 (6.91%)	2 / 188 (1.06%)	1 / 188 (0.53%)
occurrences (all)	21	2	1
Vaccination site pain			
subjects affected / exposed	70 / 188 (37.23%)	10 / 188 (5.32%)	1 / 188 (0.53%)
occurrences (all)	124	15	1
Vaccination site reaction			
subjects affected / exposed	9 / 188 (4.79%)	0 / 188 (0.00%)	0 / 188 (0.00%)
occurrences (all)	16	0	0
Vaccination site swelling			
subjects affected / exposed	12 / 188 (6.38%)	0 / 188 (0.00%)	0 / 188 (0.00%)
occurrences (all)	17	0	0
Chills			
subjects affected / exposed	14 / 188 (7.45%)	2 / 188 (1.06%)	1 / 188 (0.53%)
occurrences (all)	16	2	1
Gastrointestinal disorders			
Diarrhea			
subjects affected / exposed	4 / 188 (2.13%)	6 / 188 (3.19%)	3 / 188 (1.60%)
occurrences (all)	5	6	4
Nausea			
subjects affected / exposed	8 / 188 (4.26%)	4 / 188 (2.13%)	3 / 188 (1.60%)
occurrences (all)	9	5	3
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	6 / 188 (3.19%)	2 / 188 (1.06%)	0 / 188 (0.00%)
occurrences (all)	6	2	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 188 (0.00%)	2 / 188 (1.06%)	3 / 188 (1.60%)
occurrences (all)	0	2	3
Nasopharyngitis			
subjects affected / exposed	9 / 188 (4.79%)	12 / 188 (6.38%)	9 / 188 (4.79%)
occurrences (all)	10	13	12
Vulvovaginal mycotic infection			

subjects affected / exposed	2 / 188 (1.06%)	6 / 188 (3.19%)	4 / 188 (2.13%)
occurrences (all)	2	8	4

Non-serious adverse events	After the treatment period / Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	84 / 188 (44.68%)		
Investigations			
Body temperature increased			
subjects affected / exposed	2 / 188 (1.06%)		
occurrences (all)	2		
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 188 (4.26%)		
occurrences (all)	17		
General disorders and administration site conditions			
Feeling cold			
subjects affected / exposed	0 / 188 (0.00%)		
occurrences (all)	0		
Influenza like illness			
subjects affected / exposed	7 / 188 (3.72%)		
occurrences (all)	11		
Pyrexia			
subjects affected / exposed	6 / 188 (3.19%)		
occurrences (all)	7		
Vaccination site erythema			
subjects affected / exposed	0 / 188 (0.00%)		
occurrences (all)	0		
Vaccination site pain			
subjects affected / exposed	0 / 188 (0.00%)		
occurrences (all)	0		
Vaccination site reaction			
subjects affected / exposed	0 / 188 (0.00%)		
occurrences (all)	0		
Vaccination site swelling			
subjects affected / exposed	0 / 188 (0.00%)		
occurrences (all)	0		

Chills subjects affected / exposed occurrences (all)	1 / 188 (0.53%) 1		
Gastrointestinal disorders Diarrhea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	 7 / 188 (3.72%) 8 6 / 188 (3.19%) 8		
Musculoskeletal and connective tissue disorders Pain in extremity subjects affected / exposed occurrences (all)	 2 / 188 (1.06%) 2		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Vulvovaginal mycotic infection subjects affected / exposed occurrences (all)	 8 / 188 (4.26%) 8 8 / 188 (4.26%) 11 7 / 188 (3.72%) 9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 January 2013	Amendment No. 2, valid since 07 JAN 2013 (forming integrated CSP, Version 3.0, 04 DEC 2012): The age limit was extended up to 80 years provided that people elder than 70 years are physically and mentally able to participate in the study in the opinion of the investigator. Participating investigators confirmed that several patients elder than 70 years would be eligible and access to study participation should be possible. Exclusion criterion no. 18 was extended by "e.g. patients are physically or mentally not able to collect a qualitative sample of midstream urine or to complete the diary" in the opinion of the investigator. From previous studies where patients elder than 70 years were treated with StroVac® no indication for different tolerability or response to the immunisation were obvious. If a sufficient number of patients (per treatment group) with an age ≥ 70 years was included in this study a corresponding subgroup analyses was conducted. The subgroup analysis of male patients was added. Due to the delayed recruitment rate the blinded sample size review was performed with less patients in order to be able to make decisions regarding the sample size correspondingly to the results of the analysis in a timely manner and the recruitment period was prolonged.
26 November 2013	Amendment No. 3, valid since 26 NOV 2013 (forming integrated CSP, Version 4.0, 11 OCT 2013): Changes due to Amendment No. 3 referred mainly to the statistical analyses and adapted this protocol part to the "charter to the interim analysis". The reason for the change of section 13.1 in the protocol (primary endpoint) regarded minor changes in wording and some more details to the endpoint evaluation applied during this analysis. The change of section 13.3 in the protocol (blinded sample size review- blinded interim analysis) described the results and consequences of the blinded sample size review for the further conduct of the study. Section 13.6 in the protocol (initial sample size estimation) had also minor changes in wording and some more details to the initial sample size estimation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported