1 TITLE PAGE

Integrated Study Report **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**	
EudraCT Number:	2010-020882-25
Protocol Code:	SU 5.6 / 10404
Clinical Phase:	IV
Name of the Investigational Product (test product):	StroVac®
Indication studied:	Recurrent Symptomatic Bacterial Urinary Tract Infections
Dose and Duration:	One intramuscular unit of StroVac® each at V2, V3, V4 two weeks apart
Patient Population:	Females and males
Study Initiation Date: Study Completion Date:	24 JAN 2012 (first patient first visit) 19 MAR 2015 (last patient last visit)
Co-ordinating Investigator:	Dr. Goetz Geiges Lietzenburger Str. 54 10719 Berlin (Germany)
Clinical Research Organization (CRO):	Pharmalog Institut für klinische Forschung GmbH Neumarkter Straße 18 81673 Munich, Germany
Project Manager CRO:	Dr. K. Fuchs / Dr. J. Milde Pharmalog Institut für klinische Forschung GmbH
Sponsor:	Strathmann GmbH & Co. KG Sellhopsweg 1 22459 Hamburg (Germany)
Sponsor's Representative:	Bert Behnke, PhD Sellhopsweg 1 22459 Hamburg (Germany)
Sponsor's Clinical Project Manager:	Joerg Heyer, PhD Lorentzenstr. 44a 23843 Bad Oldesloe (Germany)
Name of Sponsor's Signatory:	Claudia Möckel, MD Sellhopsweg 1 22459 Hamburg (Germany)
Date of the Clinical Study Report:	22 FEB 2016

2 SYNOPSIS

Name of Sponsor/Company: Strathmann GmbH & Co. KG Name of Finished Product: StroVac® Name of Active Ingredient: at least 10^9 inactivated germs including E. coli, Morganella morganii, Proteus mirabilis, Klebsiella pneumoniae, and Enteroccocus faecalis	Individual Study Table Referring to Part Of the Dossier Volume: Page:	(For National Authority Use only)

EudraCT no.	2010-020882-25
Study code	RUDIS (**R**ecurrent **U**rinary Tract Infections **D**efense **I**mmunization with **S**troVac)
Title of study	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
Phase of development	Phase IV
Principal investigator	Dr. Goetz Geiges; Lietzenburger Str. 54; 10719 Berlin (Germany)
Study centres	48 investigational sites were approved by the EC and initiated (see attached list) 40 investigational sites were actively recruiting patients.
Country	Germany
Publication (reference)	None
Studied period	Approx. 13.5 months for each patient Study initiation date (first patient first visit): 24 JAN 2012 Study completion date (last patient last visit): 19 MAR 2015
Objectives	To demonstrate the clinical efficacy and tolerability of the inactivated germs of specified enterobacteria contained in StroVac® in recurrent urinary tract infections [RUTIs] as compared to placebo
Study duration	39 months[1]
Study visits	7 (+ 2 Phone) scheduled visits; additional unscheduled visits could have taken place any time during the study in case of UTI symptoms V1 (Days -14 to -1) Screening and baseline assessment V2 (Day 1) Randomization, first immunization V3 (Day 15 ± 7) Second immunization, Efficacy and safety assessments V4 (Day 29 ± 7) Third immunization, Efficacy and safety assessments V5 (Day 43 ± 7) Efficacy and safety assessments V6 (M4 ± 14 days) Assessments via telephone call V7 (M7.5 ± 14 days) Efficacy and safety assessments V8 (M11 ± 14 days) Assessments via telephone call V9 (M13.5 ± 14 days or premature discontinuation) Final visit: Efficacy and safety assessments Unscheduled visits UV1 to UVx Efficacy and safety assessments

[1] Changed from 27 to 39 months by Amendment No. 2 (valid since 07 JAN 2013) (for details please refer to Appendix 16.1.1)

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Methodology and study procedures	*STUDY PROCEDURE*	*TIME*
	• Patient information, patient's written informed consent	• Visit1 (Day -14 to -1)
	• Demographic data (date of birth, gender, ethnic origin, height, weight)	• Visit 1 (Day -14 to -1)
	• Sexual anamnesis (menopausal status, contraception, sexual behaviour, gynaecological infections, relationship between intercourses and occurrence of urinary tract infections, frequency of intercourses)	• Visit 1 (Day -14 to -1) • Visit 9 (M[1] 13.5 ± 14 days) [1] *M = month*
	• Medical history (previous and concomitant diseases), including confirmation of UTIs of uncomplicated origin by ultrasound of kidney and bladder and termination of residual amount of urine in the bladder; duration of history of recurrent acute symptomatic bacterial UTIs; number of UTIs in the year prior to study inclusion	• Visit 1 (Day -14 to -1)
	• Previous and concomitant medication	• Visit 1 (Day -14 to -1)
	• Changes in concomitant diseases and concomitant treatment	• Visit 2 (Day 1) • Visit 3 (Day 15 ± 7) • Visit 4 (Day 29 ± 7) • Visit 5 (Day 43 ± 7) • Visit 6 (M 4 ± 14 days) • Visit 7 (M 7.5 ± 14 days) • Visit 8 (M 11 ± 14 days) • Visit 9 (M 13.5 ± 14 days)
	• Check of inclusion/exclusion criteria	• Visit 2 (Day 1)
	• Documentation of acute UTIs (symptoms, urinary dipstick rest, and urinary dipslide test)	• Visit 1 (Day -14 to -1) till Visit 9 (M 13.5 ± 14 days) • Unscheduled Visits (UV1 to UVx)
	• Quality of life Questionnaire	• Visit 1 (Day -14 to -1) • Visit 9 (M 13.5 ± 14 days)
	• Investigator's global judgement of efficacy	• Visit 7 (M 7.5 ± 14 days) • Visit 9 (M 13.5 ± 14 days)
	• Patient's satisfaction with treatment	• Visit 7 (M 7.5 ± 14 days) • Visit 9 (M 13.5 ± 14 days)
	• Investigator's and patient's global judgement on tolerability	• Visit 5 (Day 43 ± 7)

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Methodology and study procedures (cont.)

• Vital signs (pulse rate, blood pressure, body temperature)	• Visit 1 (Day -14 to -1) • Visit 2 (Day 1) • Visit 3 (Day 15 ± 7) • Visit 4 (Day 29 ± 7) • Visit 5 (Day 43 ± 7) • Visit 7 (M 7.5 ± 14 days) • Visit 9 (M 13.5 ± 14 days)
• Urine pregnancy test *Only for female patients of childbearing potential* (for details see below)	• Visit 1 (Day -14 to -1) • Visit 2 (Day 1) • Visit 3 (Day 15 ± 7) • Visit 4 (Day 29 ± 7) • Visit 9 (M 13.5 ± 14 days)
• Blood sample collection for safety laboratory tests (for details see below)	• Visit 1 (Day -14 to -1) • Visit 5 (Day 43 ± 7) • Visit 9 (M 13.5 ± 14 days)
• Adverse events (AEs)	• Visit 2 (Day 1) • Visit 3 (Day 15 ± 7) • Visit 4 (Day 29 ± 7) • Visit 5 (Day 43 ± 7) • Visit 6 (M 4 ± 14 days) • Visit 7 (M 7.5 ± 14 days) • Visit 8 (M 11 ± 14 days) • Visit 9 (M 13.5 ± 14 days)

<u>Safety laboratory</u>
The safety laboratory included the assessment of the following parameters in blood/serum:

- Haematology
  Haemoglobin (Hb), haematocrit, Red blood cell count (RBC), white blood count (WBC), platelet count
- Serum chemistry
  Sodium, potassium, chloride, calcium, blood urea nitrogen (BUN), creatinine, glucose, uric acid, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin (total and direct), C-reactive protein (CRP)

<u>Urine pregnancy test</u>

- A urinary pregnancy test was performed in women of childbearing age (exception: posthysterecomy or sterilized partner or menopause with last period at least 6 months prior to study start) at V1 and V9 and before each vaccination. A medically accepted method of contraception had to be used by female patients of childbearing potential.

Number of patients (planned and analysed)

Planned: 370 patients (185 patients per dose group)

Treatment	Randomised	Premature termination	Completed	Analysed SEP	Analysed ITT	Analysed FAS	Analysed PP
Screening failure	36						
StroVac®	188	21	167	188	187	168	151
Placebo	188	18	170	188	188	160	141
Total	412	39	337	376	375	328	292

SEP = Safety Evaluable Population; ITT = Intention to treat; FAS = Full Analyses Set ; PP = Per Protocol

Name of Sponsor/Company: Strathmann GmbH & Co. KG Name of Finished Product: StroVac® Name of Active Ingredient: at least 10^9 inactivated germs including E. coli, Morganella morganii, Proteus mirabilis, Klebsiella pneumoniae, and Enteroccocus faecalis	Individual Study Table Referring to Part Of the Dossier Volume: Page:	(For National Authority Use only)

Inclusion criteria	1. Males and females aged 18 to ~~70~~ *80* years[2]. 2. Patients with a history of at least one year of confirmed recurrent uncomplicated symptomatic bacterial urinary tract infections 3. Patients with at least five confirmed episodes of uncomplicated symptomatic bacterial urinary tract infections during a period of twelve months prior to study inclusion 4. Patients who had given their signed declaration of consent and data protection declaration after having been informed about the nature, relevance and the scope of the study and about the expected desired and undesired effects of the investigative medicinal product
Exclusion criteria	1. Complicated urinary tract infections or other diseases of the urinary tract such as nonbacterial cystitis or diseases/anomalies associated with an obstruction such as bladder or kidney stones, strictures of ureter or benign prostatic hyperplasia with urinary retention. (Confirmation by ultrasound of kidney and bladder and determination of residual amount of > 50 ml urine). 2. Patients suffering from overactive bladder (> 8 micturitions per day and clinically not significant urinanalysis) 3. Contraindications for the application of the investigational medicinal product − Acute infectious diseases, excluding urogenital diseases − Active tuberculosis − Severe diseases of the hematopoietic system − Severe cardiac or renal disease − Diseases of the immune system − Hypersensitivity towards StroVac® 4. Malfunction of immunity as a result of diseases like diabetes mellitus with instable metabolic status or presence of manifest late diabetic complications or liver insufficiency 5. Any malignancy in the recent 5 years (expect basal cell carcinoma) 6. Any radiation therapy of the abdomen (without time limitation) or radiation therapy of another body part within the last 5 years prior to start of study or planned during study 7. Intake of not permitted previous therapy (see Section 9.4.6.1) 8. Planned intake or application of concomitant therapy which was not permitted during the study (see Section 9.4.6.2) 9. Hospitalization within the last 12 months prior to study start or planned during study 10. Inhabitants of nursing homes or comparable institutions (12 months before study and during study) 11. Pregnancy and lactation 12. Women of childbearing age, who did not use a medically accepted method of contraceptional method unless in case of posthysterecomy or sterilized partner or menopause with last period at least 6 months prior to study start 13. Current or previous abuse of alcohol or drugs 14. Patients in custody by juridical or official order

[2] Changed from 70 to 80 years by Amendment No. 2 (valid since 04 JAN 2012) (see also Appendix 16.1.1)

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Exclusion criteria (cont.)	15. Other severe physical or mental diseases which challenged the conduct of the study according to protocol or impact the evaluation of the efficacy or safety of the product or the safety of the patient 16. Patient was incapable of contracting or other circumstances which did not allow the patient to understand type, relevance and reach of the clinical study 17. Unreliability or lack of cooperation by the patient 18. Other reasons against participation in the study in the opinion of the Investigator (e.g. patient's physical or mental disability to collect a qualitative sample of midstream urine or to complete the diary)[3] 19. Participation in another clinical study within 12 weeks prior to study start and during study 20. Patients who were part of the staff of the study centre, the Investigator him/herself or close relatives of the Investigator
Investigational medicinal product (IMP)	
<u>Test drug:</u>	StroVac®
Form:	Basic suspension and dried active substance for the preparation of a suspension for injection purposes
Active ingredients/form:	One unit of dried active substance contained at least 109 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)
Substance class	vaccination (ATC code: J07AX53)
Mode of administration	Intramuscular injection
Batch number	103SU (dried substance) 2011SU (basic suspension)
Duration of treatment	Three single injections every two weeks ± 7 days
<u>Reference product:</u>	Placebo
Form	Basic suspension and dried placebo substance for the preparation of a suspension for injection purposes
Active ingredients/form:	One unit of dried placebo substance contains excipients only.
Substance class	None
Mode of administration	Intramuscular injection
Batch number	103SU (dried substance) 2011SU (basic suspension)

[3] Addition of "*e.g. patient's physical or mental disability to collect a qualitative sample of midstream urine or to complete the diary*" by Amendment No. 2 (valid since 07 JAN 2013) (see also Appendix 16.1.1)

Name of Sponsor/Company: Strathmann GmbH & Co. KG Name of Finished Product: StroVac® Name of Active Ingredient: at least 10^9 inactivated germs including E. coli, Morganella morganii, Proteus mirabilis, Klebsiella pneumoniae, and Enteroccocus faecalis	Individual Study Table Referring to Part Of the Dossier Volume: Page:	(For National Authority Use only)

Duration of treatment	Three single injections every two weeks ± 7 days
Criteria for evaluation PRIMARY OBJECTIVE	Number of bacterial urinary tract recurrences with confirmed bacterial origin over a period of 13.5 months starting after randomization and adjusted by the respective "Baseline" value (Baseline = number of confirmed UTI recurrences during the 12 months-period prior to study inclusion).
SECONDARY OBJECTIVES	The secondary endpoints analysed for bacterial UTIs with confirmed bacterial origin[4] in this study were: 1. Number of bacterial UTI recurrences with confirmed bacterial origin within a period of 12 months starting after finalization of the immunization scheme (FAS and PP-population) 2. Time interval until occurrence of the first recurrent infection after finalisation of the randomization starting starting at – V2 (randomization - for the ITT-population) – V5 (after finalisation of the immunization scheme - for the FAS and PP-population) 3. The area under the "number of recurrences versus time" curve from for the periods V2-V5, V2-V9 - for the ITT population- and the periods V5-V6 (6 weeks), V5-V7 (6 months), V5-V8 (9.5 months) and V5-V9 (12 months) - for the FAS and PP population - separately for each period including "Baseline" and "Duration of period" as covariates and treatment and menopausal status (pre-/postmenopausal) as factors. 4. Frequency of UTI recurrences during the first six months after finalisation of the immunization scheme (V5-V7) as compared to months 7 to 12 (V7-V9) were performed separately for each treatment for the FAS and PP-population. 5. Difference in the percentage of patients with no recurrences in the period of – 13.5 starting after randomization (for the ITT population) – 12 months starting after finalisation of the immunization scheme (for the FAS and PP population) between StroVac® and placebo. <u>Other investigations for evaluation of efficacy</u>: 6. Quality of life 7. Investigator's and patient's global judgement on efficacy [score] 8. Difference in the percentage of patients classified as responders (treatment responders [%]) by the global investigator and patient's assessment (very good or good) between StroVac® and placebo. <u>Sensitivity Analysis</u> 1. Patient Characteristics The primary endpoint and the secondary endpoints were analysed for the subgroup(s) of – patients with infection rates above average during the period of 12 months prior to study inclusion – pre- and postmenopausal women

[4] Addition of "*bacterial UTIs with confirmed bacterial origin*" by Amendment No. 4 (valid since 21 MAY 2015) (see also Appendix 16.1.1)

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SECONDARY OBJECTIVES (cont.)	– male patients (if a minimum of five male patients in each treatment group was available) – patients with an age ≥70 years (if a sufficient number of patients per treatment group was included in this study)[5] 2. Centre Effects Because it was expected that the number of patients per centre was low, centre effects were only considered for sensitivity analysis using the ITT set. For this sensitivity analysis no subgroup calculations were done and all centres with less than 5 patients were pooled. The sensitivity analysis was performed as follows: – for the ANCOVA analysis, the factor centre was included into the model – for nonparametric calculations (i.e. Mann-Whitney Test) the Van Elteren-test (controlling for centres) was used – for categorical analysis (e.g. Chi-Square Test) the Cochran-Mantel-Haenszel test controlling for centres was used – for life-table analysis, centre was added as strata variable into the log-rank Test 3. Different Definitions of UTIs[6] The following at least suspected UTIs: (a) clinical cystitis (two or more typical symptoms reported but bacterial origin not confirmed), (b) patient reported UTIs or (c) monosymptomatic bacteriuria (one symptom reported and either positive urinary dipstick test or positive urinary dipslide test) and (a) + (b) + (c) + bacterial UTIs with confirmed bacterial origin were analysed in the same manner as the primary and the secondary endpoints.
SECONDARY OBJECTIVES Safety endpoints	1. Frequency and severity of systemic and local adverse events (AE) [N/%] 2. Change in vital signs (blood pressure, pulse rate, temperature) 3. Change in laboratory parameters 4. Investigator's and patient's global judgement on tolerability [score] 5. Evaluation of safety in the subgroup of patients who had a urinary tract infection during the immunization period If a minimum of five male patients in each treatment group was available a corresponding safety analysis was conducted. If a sufficient number of patients (per treatment group) with an age ≥70 years was included in this study a corresponding safety analysis was conducted for this subgroup in addition.[7]
Statistical methods	<u>Randomisation</u> Patients were randomised to one of the two treatment groups in a balanced fashion. Randomisation was carried out in blocks and stratified by menopausal condition (pre-/ and postmenopausal) of the patients. For female patients after hysterectomy the allocation to the strata was dependent on their age: women after hysterectomy elder than 45 years were included in the postmenopausal stratum, women younger or equal to 45 years were included in the premenopausal stratum. Male patients were included in the premenopausal stratum. <u>Statistical analyses</u>

[5] Addition of "*bullet point •male patients (if a minimum of five male patients in each treatment group was available) and •patients with an age ≥70 years (if a sufficient number of patients per treatment group was included in this study)"* by Amendment No. 4 (valid since 21 MAY 2015) (see also Appendix 16.1.1)
[6] Addition of "*No.3: Different definitions of UTIs"* by Amendment No. 4 (valid since 21 MAY 2015) (see also Appendix 16.1.1)
[7] Addition of "*If a sufficient number of patients (per treatment group) with an age ≥70 years was included in this study a corresponding safety analysis was conducted for this subgroup in addition"* by Amendment No. 2 (valid since 07 JAN 2013) (see also Appendix 16.1.1)

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Statistical methods (cont.)	The Safety Evaluable Population (SEP) included all patients randomised with at least one documented application of the medicinal product and post-treatment safety evaluation. The efficacy analyses were performed using the Intention To Treat (ITT) set which included all randomised patients having at least one efficacy data after randomization available in order to calculate the primary endpoint. The Full Analysis Set (FAS) was performed for the efficacy analyses and included all randomised patients who • had complied with the study indication (see inclusion criterion), • had documented all three applications of the investigational drug • had at least one efficacy data for the 12-months follow-up period (starting after finalization of the immunization scheme) available in order to calculate the primary endpoint. Thus, the frequency of recurrent UTI had to be available after Visit 5 for that patient. The analysis of the Per Protocol (PP) set was performed additionally as a sensitivity analysis for the efficacy analyses and included all FAS patients who did not show any "relevant" protocol deviation and were classified as clinically evaluable. Except for the primary endpoint, all analyses and statistical tests for difference between treatment groups were performed in an exploratory manner. Continuous data were described by the number of valid observations (N_{valid}), the number of missing observations (N_{miss}), mean, standard deviation (SD), minimum (Min), median and maximum (Max) and calculated separately for each treatment group. Categorical data were displayed separately for each treatment group using absolute frequencies (N) and percentages (%). Time-to-event data were described by medians and quartiles calculated by Kaplan-Meier life-table methods separately for each treatment group. (Means, standard deviations and other statistical parameters commonly used for continuous variables were not used because they might have been biased due to censored data.) Changes in categorical variables from an earlier visit to a later visit were examined by shift-tables. Summary statistics for continuous data and time-to-event data were presented with the same number of decimal places as the observed data, apart from the means, medians and standard deviations, which were presented with one more decimal place than that observed. Using explorative methods, treatment groups were analysed for homogeneity on the basis of patients' baseline characteristics. **STUDY HYPOTHESIS AND PRIMARY ENDPOINT (CONFIRMATORY) ANALYSIS** 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)[8] in the following form: It was assumed that the number of confirmed infection recurrences during exposure time t=13.5 months could 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. This was modelled through a Poisson regression (GLM with log link function)[9] with covariate "baseline frequency of UTI" with factors for treatment (1 degree of freedom=df) and menopausal status (pre-/postmenopausal; 1 degree of freedom=df). The null hypothesis of interest was whether the rate ratio for treatment was larger or equal to 1 (i.e. log rate ratio was larger or equal to 0).

[8] Addition of "*GLM"* by Amendment No. 3 (valid since 28 NOV 2014) (see also Appendix 16.1.1)
[9] Addition of *"GLM with log link function"* by Amendment No. 3 (valid since 28 NOV 2014) (see also Appendix 16.1.1)

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Statistical methods (cont.)	Differences in the duration of exposure were adjusted by the offset variable which was (the natural) logarithm of the treatment duration. The analysis was adjusted for possible overdispersion by including an overdispersion parameter (quasi-likelihood approach)[10]. The type-I error rate was set to α = 0.025 (one-sided). The primary analysis was based on the ITT population. Because it was expected, that most centres recruited only a few patients, the primary analysis did not include centre effects, but centre effects were explored in subsequent sensitivity analyses[11] (see secondary endpoints). If a minimum of five male patients in each treatment group was available a corresponding subgroup analysis of the primary endpoint was conducted. If a sufficient number of patients (per treatment group) with an age ≥70 years was included in this study, the primary endpoint was calculated for this subgroup in addition.[12] **SECONDARY (DESCRIPTIVE) ANALYSES** **(1) Efficacy endpoints** The analysis of the secondary efficacy endpoints was of a descriptive nature. Therefore, no adjustment of error probability was performed. The following secondary efficacy endpoints were evaluated for bacterial UTI with confirmed bacterial origin: 1. The number of bacterial UTI recurrences within a period of 12 months starting after finalization of the immunization scheme was analysed analogously to the primary endpoint using the FAS and PP-population. 2. The time interval [days] until occurrence of the first recurrent UTI starting at – V2 (randomization - for the ITT population) – V5 (after the finalization of the immunization scheme - for the FAS and PP population) were calculated by Kaplan-Meier life-table method. The difference between the treatment groups were analysed by the log-rank test. 3. The area under the "number of recurrences versus time" curve for the periods V2-V5, V2-V9 [NxDays] (AUC_{V2-5},AUC_{V2-9} - for the ITT population), V5-V6 (6 weeks), V5-V7 (6 months), V5-V8 (9.5 months) and V5-V9 (12 months) [NxDays] (AUC_{V5-6}, AUC_{V5-7}, AUC_{V5-8} and AUC_{V5-9} – for the FAS and PP population) were evaluated separately for each period by the ANCOVA including "Baseline" and "Duration of period" as covariates and treatment and menopausal status (pre-/postmenopausal) as factors into the model. 4. The analysis of the change in frequency [N] from the UTI recurrences during the first six months period after finalisation of the immunization scheme (V5-V7) to the frequency [N] of recurrences during the period 7-12 months after finalisation of the immunization scheme (V7-V9) was performed separately for each treatment. This was done by the generalized linear model using the Poisson-distribution and testing for the within-factor "Period".

[10] Addition of "*which was (the natural) logarithm of the treatment duration. The analysis was adjusted for possible overdispersion by including an overdispersion parameter (quasi-likelihood approach)*" by Amendment No. 3 (valid since 28 NOV 2014) (see also Appendix 16.1.1)
[11] Addition of "*the primary analysis did not include centre effects, but centre effects were explored in subsequent sensitivity analyses*" by Amendment No. 3 (valid since 28 NOV 2014) (see also Appendix 16.1.1)
[12] Addition of "*If a sufficient number of patients (per treatment group) with an age ≥70 years was included in this study a corresponding safety analysis was conducted for this subgroup in addition"* by Amendment No. 2 (valid since 07 JAN 2013) (see also Appendix 16.1.1)

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Statistical methods (cont.)	This general linear model also adjusted for "Baseline" as covariate and included menopausal status (pre-/postmenopausal) as factor into the model (FAS and PP population). 5. The difference in the percentage of patients with no recurrences – 13.5 starting after randomization (for the ITT population) – 12 months starting after finalisation of the immunization scheme (for the FAS and PP population) between StroVac® and placebo was analysed using the Chi-Square test. <u>Other investigations for evaluation of efficacy</u> 6. Differences between StroVac® and Placebo in the change in Quality of Life during the observed period were analysed for each questionnaire (EUROHIS-QOL, Fatigue (Scale 1 of GBB –24), Symptom burden, Mental consequences, Effects on daily life, Burden experienced – global judgement) by an ANCOVA including treatment and menopausal status (pre-/postmenopausal) as factors and "Baseline QoL at V1" as covariate into the model (ITT, FAS and PP population) 7. Six and 12 months after finalization of the immunization period (V7, V9), patients and investigators had to assess the efficacy of the vaccination using of a 5-point verbal rating scale. The treatment groups were compared for each time point by the Wilcoxon-Mann Whitney test (ITT, FAS and PP). 8. The difference in the percentage of patients classified as responders (treatment responders [%]) by the global investigator and patient's assessment (very good or good) between StroVac® and placebo was analysed using the Chi-Square test (ITT, FAS and PP population). <u>Sensitivity Analysis</u> 1. Patient Characteristics The primary endpoint and the secondary endpoints were analysed for the subgroup(s) of – patients with infection rates above average during the period of 12 months prior to study inclusion – pre- and postmenopausal women – male patients (if a minimum of five male patients in each treatment group were available) – patients with an age ≥70 years (if a sufficient number of patients per treatment group was included in this study) 2. Centre Effects Because it was expected that the number of patients per centre was low, centre effects were only considered for sensitivity analysis using the ITT set. For this sensitivity analysis no subgroup calculations was done and all centres with less than 5 patients were pooled. The sensitivity analysis was performed as follows: – for the ANCOVA analysis, the factor centre was included into the model – for nonparametric calculations (i.e. Mann-Whitney Test) the Van Elteren-test (con-trolling for centres) was used – for categorical analysis (e.g. Chi-Square Test) the Cochran-Mantel-Haenszel test controlling for centres was used – for life-table analysis, centre was added as strata variable into the log-rank Test 3. Different Definitions of UTIs The following at least suspected UTIs:

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Statistical methods (cont.)	(a) clinical cystitis (two or more typical symptoms reported but bacterial origin not confirmed), (b) patient reported UTIs or (c) monosymptomatic bacteriuria (one symptom reported and either positive urinary dipstick test or positive urinary dipslide test) and (a) + (b) + (c) + bacterial UTIs with confirmed bacterial origin were analysed in the same manner as the primary and the secondary endpoints. **(2) <u>Safety endpoints</u>** The analysis of the safety endpoints was of a descriptive nature. Therefore, no adjustment of error probability was needed. The Medical Dictionary for Regulatory Activities (MedDRA) was used to code adverse events. The following secondary safety endpoints were evaluated for the SEP population: 1. Adverse events (preferred terms (PT)) were tabulated for each treatment group by system organ class (SOC) according to MedDRA. The tables divided the AEs into the defined categories of severity and Investigator's causality assessments. AEs were also displayed according to time of onset (within treatment period and after treatment), pattern of occurrence and outcome. This basic display of AEs was used to compare the AE rates between treatment groups. 2. The course of vital signs in time (blood pressure, pulse rate, temperature) before and after vaccination with StroVac® and placebo was displayed descriptively (number of valid values, number of missing values, arithmetic mean, standard deviation, minimum, median, maximum). Also differences V7-V1, V9-V1 and V9-V5 were displayed for each treatment group accordingly. Abnormal values in vital signs were listed separately by treatment group and visit. 3. Laboratory parameters before (V1) and after vaccination with StroVac® and placebo (V5, V9) were displayed descriptively (number of valid values, number of missing values, arithmetic mean, standard deviation, minimum, median, maximum). Abnormal values in laboratory parameters were listed separately by treatment group and visit. 4. After finalization of the immunization period (V5), patients and Investigators had to assess the tolerability of the vaccination using a 5-point verbal rating scale and differences between the treatment groups were analysed by the Wilcoxon-Mann Whitney test. 5. Assessment of safety in the subgroup of patients who had a urinary tract infection during the immunization period. If a minimum of five male patients in each treatment group was available a corresponding safety analysis was conducted. If a sufficient number of patients (per treatment group) with an age ≥70 years was included in this study a corresponding safety analysis was conducted for this subgroup in addition.[13]

[13] Addition of "*If a sufficient number of patients (per treatment group) with an age ≥70 years was included in this study a corresponding safety analysis was conducted for this subgroup in addition"* by Amendment No. 2 (valid since 07 JAN 2013) (see also Appendix 16.1.1)

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Summary conclusions	Of 412 patients screened, 376 patients (98.4% females, 1.6% males) with a mean age of 44.4 years (range: 18 to 80 years) were randomised and dosed. 50% out of 376 dosed patients received either StroVac® or placebo. 337 patients completed the study as planned. 376 patients were included in the statistical analysis of efficacy and safety (SEP: N=376, ITT: N=375, FAS: N=328, PP: N=292).
Efficacy results	• In total 375 patients were included in the efficacy analysis (ITT). At baseline both treatment groups were comparable with respect to the demographic data and mean UTIs in the 12 months prior to enrolment into the study. • An overall reduction of occurrence of $UTIs_{confirmed}$ in mean from 5.4 $UTIs_{confirmed}$ in 12 months prior to study start to 1.3 $UTIs_{confirmed}$ during 13.5 months in the study could be shown. In terms of the primary efficacy variable 1.2 $UTIs_{confirmed}$ in the StroVac® group vs. 1.3 $UTIs_{confirmed}$ in the placebo group occurred during 13.5 month observation period. However no superiority of StroVac® versus placebo could be shown (p-value 0.6324). • Regarding the second efficacy parameter, during the 12 months after finalising the immunisation period a reduction to 1.0 $UTIs_{confirmed}$ (StroVac®) and 1.1 $UTIs_{confirmed}$ (placebo) was detected but statistically not significant (p-value 0.6886). In total 183 patients (48.8 %) had no $UTIs_{confirmed}$ until the end of the study in the ITT. • The first recurrent $UTIs_{confirmed}$ occurred in median 229.0 days (StroVac®) and 315.0 days (placebo) after V2. This difference could not be confirmed statistically (p-value 0.2007). The same situation applied for V5 (323.0 days (StroVac®) vs. 350.0 days (placebo)) and a p-value of 0.3466. The frequency of $UTIs_{confirmed}$ changed not significantly in total from 0.6 (V5 - V7) to 0.4 (V7 - V9). • Of 433 detected germs *Escherichia coli* had the largest proportion with 64.7 % in both treatment groups. Although *Staphylococcus aureus* was verified in 5.3 % of the germs in total, in 9.2 % of 116 isolated species in the StroVac® group this germ was responsible for recurrent $UTIs_{confirmed}$ and thus the second frequent bacterium in patients of the StroVac® group. The analysis of the primary endpoint showed that 38.0 % of the StroVac® patients and 44.7 % of the placebo patients had no $UTI_{confirmed}$ at all during the study. Due to a difference of 6.7 % between both treatment groups in favour of placebo a possible effect of *Staph. aureus* on the number of UTIs was assumed and an additional analysis was performed. After exclusion of UTIs with *Staph. aureus* infections the difference of patients with no $UTI_{confirmed}$ at all during the study between the treatment groups was 1.6 % (50.0 % StroVac® vs. 51.6 % placebo). • Results of the sensitivity analysis and post-hoc evaluation: In 83 patients of the StroVac® group with infection rates above average (6 and more $UTIs_{confirmed}$) during the period of 12 months prior randomisation the occurrence of $UTIs_{confirmed}$ reduced in mean from 6.4 to 1.3 $UTIs_{confirmed}$ during 13.5 months in the study.
Efficacy results (cont.)	• During treatment with placebo the occurrence changed from in mean 6.7 to 1.8 $UTIs_{confirmed}$. • The difference between both treatment groups was statistically not significant (p-value 0.1276). After 12 months of finalisation of the immunisation period the number of $UTIs_{confirmed}$ lowered to 1.1 $UTIs_{confirmed}$ after treatment with StroVac® and to 1.4 $UTIs_{confirmed}$ after treatment with placebo however these differences were also not significant (p-value 0.3375). • Displayed in Text-Table 1 the sensitivity analysis of patients with number of UTIs above average (i.e. ≥6) in the year before randomisation showed considerably lower p-values than in the analysis of $UTI_{confirmed}$ in the primary and secondary endpoints.

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Therefore, an additional post-hoc analysis of patients with infections above average prior to randomisation versus $UTI_{confirmed}$ and UTI_{all} 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 7 or more UTIs prior to inclusion reduced in the StroVac® group to 2.3 UTI_{all} compared to 4.4 UTI_{all} during placebo treatment with significant differences in the ITT (p-value 0.0482).

Text-Table 1: Means of UTIs with the respective p-values for both evaluation periods for the ITT

UTIs prior to inclusion [ITT]	UTI during the study	Time period [months]	Number of UTIs StroVac®	Placebo	p-value
≥5 UTIs [prim. and second. endpoint]	$UTI_{confirmed}$	13.5	1.2	1.3	0.6324
		12	1.0	1.1	0.6886
≥6 UTIs [sensitivity analysis]	$UTI_{confirmed}$	13.5	1.3	1.8	0.1276
		12	1.1	1.4	0.3375
≥6 UTIs [post-hoc analysis]	UTI_{all}	13.5	2.0	2.6	0.1494
		12	2.6	3.4	0.0687
≥7 UTIs [post-hoc analysis]	$UTI_{confirmed}$	13.5	1.3	2.5	0.1091
		12	1.1	2.0	0.1726
≥7 UTIs [post-hoc analysis]	UTI_{all}	13.5	2.3	4.4	**0.0487***
		12	1.7	3.5	0.0793

** significant p-value*

This significance was verified in the FAS and PP (p-value 0.0487 and 0.0286, respectively) (see Text-Table 2). Furthermore a significant difference could also be shown in the period of 12 months in the PP (p-value 0.0469).

For the FAS a mean reduction from 7.3 to 2.3 UTI_{all} in the StroVac® group and in the placebo group from 7.3 to 4.2 UTI_{all} could be seen, verified by a significant p-value of 0.0487.

In the PP the average of 7.3 UTI_{all} prior to study start reduced to 2.2 UTI_{all} after StroVac® treatment and to 3.9 UTI_{all} after placebo treatment. Significance could also be shown (p-value 0.0286). The period of 12 months after finalising the immunisation showed only a significant difference between both treatment groups in the PP (StroVac®: 1.5 UTIs, placebo: 3.0 UTIs, p-value 0.0469).

Efficacy results (cont.)

Text-Table 2: Post-hoc analysis of UTIs above average with the respective p-values for the FAS and PP

UTIs prior to inclusion [FAS]	UTI during the study	Time period [months]	Number of UTIs StroVac®	Placebo	p-value
≥6 UTIs	UTI_{all}	13.5	2.0	2.6	0.1494
		12	2.6	3.4	0.0687
≥7 UTIs	$UTI_{confirmed}$	13.5	1.3	2.3	0.1200
		12	1.1	1.8	0.2023
≥7 UTIs	UTI_{all}	13.5	2.3	4.2	**0.0487***

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		12	2.3	2.8	0.0943

UTIs prior to inclusion [PP]	UTI during the study	Time period [months]	Number of UTIs StroVac®	Placebo	p-value
≥6 UTIs	UTI_{all}	13.5	2.4	3.2	0.0760
		12	1.9	2.5	0.1230
≥7 UTIs	$UTI_{confirmed}$	13.5	1.2	2.3	0.0882
		12	1.1	1.8	0.1948
≥7 UTIs	UTI_{all}	13.5	2.2	3.9	**0.0286***
		12	1.5	2.7	**0.0469***

** significant p-value*

In this subgroup the non-recurrence of any UTI_{all} within the 13.5 months after randomisation in the StroVac® group was almost twice as high as in the placebo group (23.1 % vs. 12.5 %, respectively). Within the 12 months after finalising the immunisation the rate in the StroVac® group was more than twice as high as in the placebo group (46.2 % vs. 18.8 %, respectively).

- The following Text-Table 3 gives an overview of the number of patients in their different types of UTIs and both evaluation periods for the ITT:
  Text-Table 3: Overview of patients in the different categories of UTI (ITT)

UTI*	Time period	No occurrence of a UTI StroVac® [%]	Placebo [%]	Number of patients with respective UTIs [N=375] StroVac® [N]	%	Placebo [N]	%
Acute uncomplicated symptomatic bacterial UTI [$UTI_{confirmed}$]	13.5 months	38.0	44.7	116	62.0	104	55.3
	12 months	46.0	51.6	101	54.0	91	48.4
Monosymptomatic bacteriuria [UTI_{mono}]	13.5 months	92.5	88.8	14	7.5	21	11.2
	12 months	95.2	90.4	9	4.8	18	9.6
Clinical cystitis [UTI_{cyst}]	13.5 months	44.9	49.5	103	55.1	95	50.5
	12 months	56.7	58.5	81	43.3	78	41.5
Patient reported UTI [UTI_{pat}]	13.5 months	85.6	87.2	27	14.4	24	12.8
	12 months	90.9	88.8	17	9.1	21	11.2
All UTI [UTI_{all}]	13.5 months	30.1	33.8	150	80.2	146	77.7
	12 months	28.3	30.3	134	69.7	131	69.7
Patients with ≥7 UTIs [UTI_{all}]	13.5 months	23.1	12.5	20	76.9	28	87.5
	12 months	46.2	18.8	14	53.8	26	81.2

**all not statistically significant*

Efficacy results (cont.)

- About 39.2 % of the women were postmenopausal and the number of $UTIs_{confirmed}$ reduced during 13.5 months in total to in mean 1.5 compared to 1.2 $UTIs_{confirmed}$ for premenopausal women. In the post immunisation period postmenopausal women had in average 1.2 $UTIs_{confirmed}$ and premenopausal women 0.9. The median time until the occurrence of the first UTI after V2 and V5 was longer in premenopausal women (in total 277.0 vs. 211.0 days; 358.8 vs. 341.0 days, respectively).

  During treatment with StroVac® 43.0 % of premenopausal women had no occurrence of a $UTI_{confirmed}$ and 30.1 % of the postmenopausal women.

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Efficacy results (cont.)

In the placebo group more postmenopausal women had no recurrent $UTIs_{confirmed}$ (42.1 % premenopausal vs. 48.6 % postmenopausal). In total 42.5 % premenopausal women were non recurrent and 39.5 % postmenopausal women.

- 8.2 % of the patients were of 70 years and older and in these the number of $UTIs_{confirmed}$ lowered in mean to 1.3 $UTIs_{confirmed}$ during the 13.5 months study duration. In the StroVac® group the median time until the occurrence of the first UTI after V2 was 110.0 days and 239.0 days after V5. In the placebo group 50 % of the patients had no $UTIs_{confirmed}$, neither after V2 nor after V5. In total 41.9 % of the women ≥70 years had no recurrent $UTIs_{confirmed}$.
- The Text-Table 4 below shows the median time until occurrence of the first UTI and their results which were not analysable for $UTIs_{mono}$ and $UTIs_{pat}$ due to the low number of patients in these UTI categories in combination with the respective lower probability of the occurrence of these UTIs. After treatment with placebo $UTIs_{confirmed}$ and $UTIs_{cyst}$ occurred at least 86 days later than after treatment with StroVac®. The difference of the first occurrence of a UTI_{all} between both treatment groups was only 14.5 days in 13.5 months study duration. Almost no difference could be detected in the period of 12 months (3 days).

Text-Table 4: Overview of days until occurrence of the first UTI

UTI*	Time period	Median time until occurrence of the first UTI [days] StroVac®	Median time until occurrence of the first UTI [days] Placebo	Difference [days]	Number of patients with the respective UTI in total
$UTI_{confirmed}$	13.5 months	229.0	315.0	86.0	220
	12 months	323.0	n.a.	At least: 42.0 (365.0-323.0 days)	175
UTI_{mono}	13.5 months	n.a.	n.a.	.	35
	12 months	n.a.	n.a.	.	19
UTI_{cyst}	13.5 months	325.0	n.a.	At least: 85.6 (410.6-325.0 days)	198
	12 months	n.a.	n.a.	.	141
UTI_{pat}	13.5 months	n.a.	n.a.	.	51
	12 months	n.a.	n.a.	.	31
UTI_{all}	13.5 months	69.0	83.5	14.5	296
	12 months	134.0	137.0	3.0	137

**all not statistically significant; n.a. = not applicable (no further UTI in this category occurred)*

- The differences between the AUCs of all UTI categories during 12 and 13.5 months of evaluation were marginal in all 3 analysis sets. Only the AUC of UTI_{all} was smaller in the StroVac® group compared to the placebo group during 12 months after finalisation of the immunisation period (379.9 vs. 422.3 days) but also statistically not significant.
- In the StroVac® group the difference in the frequency of any kind of the UTI categories in the periods V5-V7 and V7-V9 changed only marginally and showed therefore no period effects.
- In the quality of life questionnaires the “symptom burden-score” and “mental consequence-score” showed a reduction of the symptoms from V1 to V9 of around half. The mental consequence-score showed an almost significant difference between the treatment groups (p-value 0.0734) as results reduced from 11.8 to 5.9 [StroVac®] and from 10.8 to 6.4 [placebo].

  A change in the sexual behaviour could be shown as in the StroVac® group at V9 37 patients (19.7 % of 188 patients) less avoided sexual intercourse, in contrast to

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	17 patients (9.0 % of 188 patients) in the placebo group. During treatment with StroVac® 59 patients had an impairment of sexual life till V9, during placebo 51 patients. • At the end of the study (V9) the investigators assessed 73.3 % of the patients in the StroVac® group and 71.8 % of the patients in the placebo group as responder to the treatment. In the patients' opinion 72.2 % of the patients in the StroVac® group and 69.7 % in the placebo group were responders to treatment. • The proportion of patients with use of previous medication in total was almost similar between both treatment groups (96.3 % StroVac® vs. 96.8 % placebo) as well as in patients with intake of *antiinfectives for systemic use* (73.9 % in the StroVac® group vs. 76.1 % in the placebo group) which were expected to be the most common medications due to the inclusion diagnosis of bacterial UTIs. During the study the overall number of patients with intake of concomitant medication remained almost similar (96.3 % StroVac® vs. 96.8 % placebo) and in the patients with use of *antiinfectives for systemic use* as well (75.0 % StroVac® vs. 74.5 % placebo). But the intake of antiinfectives per patient was lower after treatment with StroVac® compared to the placebo group (463 times use of antiinfectives in the StroVac® group vs. 564 times use of antiinfectives in the placebo group). In total, in the StroVac® group 101 antiinfectives were less taken. Evaluating the intake per patient, during treatment with StroVac® the amount of antiinfectives was in average 3.3 per patient (4.3 prior to study inclusion) compared to 4.0 per patients during treatment with placebo (4.3 prior to study inclusion). The most commonly prescribed antiinfectives were fluoroquinolones (45.7 %).
Safety results	The safety was evaluated in two periods: The "within the treatment period" was defined for adverse events (AE) / adverse drug reactions (ADR) with a start date on / after Day 1 (V2, start of immunization) until the last day of the immunization period (V5 – 1 day). The "after the treatment period" started on the first day of the post-immunization period (V5). **Within the treatment period** A total of 619 AEs occurred in 52.7 % of the patients (198 patients of 376 patients). In the StroVac® group 61.2 % (115 of 376 patients) experienced 426 AEs, in the placebo group 44.1 % (83 of 376 patients) 193 AEs. The AEs were mainly documented in the SOC *general disorders and administration site conditions* (in 130 patients (34.6 %) out of 198 patients). 53.7 % of 188 patients had 270 AEs in the StroVac® group (63.4 % out of 426 AEs) and 15.4 % of 188 patients 43 AEs in the placebo group (22.3 % out of 193 AEs). The most frequently reported AE within this SOC was *vaccination site pain* in 37.2% of the StroVac® patients and 5.3 % of the placebo patients, followed by *influenza like illness* (11.7 % vs. 4.8 % patients, respectively).
Safety results (cont.)	Most of the AEs were mild to moderate in intensity (54.9 % and 33.4 % of 619 AEs, respectively) and less frequently severe (11.6 % of 619 AEs). A higher frequency of severe AEs occurred in the StroVac® group (55 AEs vs. 17 AEs, respectively). *Vaccination site pain*, followed *pyrexia* and *influenza like illness* were the most commonly severe AEs, occurring mainly during treatment with StroVac®. AEs considered certainly, probably or possibly drug related by the investigator were experienced by 119 (63.3 %) patients treated with StroVac®, and by 32 (17.0 %) patients receiving placebo. The most common drug-related AEs reported for StroVac® or placebo

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Safety results (cont.)	were *vaccination site pain* (20.7 % 2.7 %), *vaccination site erythema* (4.8 %, 0.0 %) and *vaccination site swelling* (4.3 %, 0.0 %), respectively. By the end of the study, the majority of AEs had resolved (98.7 % of 619 AEs). 37 SAEs occurred in 29 patients (7.7 % of 376). The incidence of SAEs was higher in the StroVac® group (StroVac®: 29 SAEs in 24 patients (12.8 %), placebo: 8 SAEs in 5 patients (2.7 %). According to the study protocol fever >38.5° occurring up to 72 hours after the injection and chills were to be documented as SAEs. 73.0 % of the SAEs (27 out of 37 SAEs) were *pyrexia* and *chills*, and 23 of these 27 SAEs (85.2%) occurred during treatment with StroVac®. Of 28 drug related SAEs, 24 SAEs occurred in 20 patients of the StroVac® group and were *chills* (15x), *pyrexia* (8x) and *vaccination site swelling* (1x). 4 drug-related SAEs occurred in 3 patients of the placebo group and were *chills* (2x) and *pyrexia* (2x). Except *vaccination site swelling*, all drug related SAE resolved within two days. By the end of the study, all patients with SAEs had recovered. **After the treatment period** A total of 471 AEs occurred in 43.9 % of the patients (165 patients of 376 patients). In the StroVac® group 43.1 % (81 of 188 patients) experienced 227 AEs, in the placebo group 44.7 % (84 of 188 patients) 244 AEs. The AEs were mainly documented in the SOC *infections and infestations* (in 76 patients (20.2 %) out of 164 patients). An infection occurred in 20.7 % of 188 patients treated with StroVac® and in 19.7 % of 188 patients of the placebo group. The most frequently reported AE was *nasopharyngitis* in 4.8 % of the StroVac® patients and 4.3 % of the placebo patients, followed by *influenza like illness* (5.3 % vs. 3.7 % patients, respectively). The intensity, causal relationship and the actions which were taken due to the occurrence of the AE were unknown for 2 AEs. For 1 AE also the outcome was unknown. Therefore sum of AEs was 469 and 470, respectively. Most of the AEs were mild to moderate in intensity (27.7 % and 26.1 % of 469 AEs, respectively) and less frequently severe (12.8 % of 468 AEs). In categories *mild* and *moderate* both treatment groups were comparable but a slightly higher frequency of severe AEs was seen in the placebo group (35 AEs vs. 25 AEs, respectively). There was no accumulation of severe AEs in a specific SOC category. For 5 (2.7 %) patients of the StroVac group and 2 patients (1.1 %) of the placebo group a drug related AE was documented By the end of the study, the majority of AEs had resolved (87.9 % of 470 AEs). 31 SAEs occurred in 24 patients (6.4 % of 376). The number of SAEs was comparable in both treatment groups but in less patients of the placebo group had SAEs (StroVac®: 16 SAEs in 15 patients (7.4 %), placebo: 15 SAEs in 10 patients (5.3 %). No SAE was considered as drug related by the investigators. By the end of the study, 3 SAEs had not yet recovered (*musculoskeletal discomfort*, *breast cancer female*, *cardiomyopathy*). **Subgroup analysis of patients with at least one UTI within the treatment period** During the immunisation period 33 patients reported a total of 92 AEs: 18 patients had 60 AEs during treatment with StroVac® and during placebo 15 patients 32 AEs. In the period after the immunisation a total of 68 AEs occurred in 25 patients: 29 AEs in 11 patients (StroVac®) and 39 AEs in 14 patients (placebo). The analysis of the AEs in this subgroup showed similar characteristics as the full SEP. There were no specific safety findings relevant only for this subgroup.

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	Subgroup analysis of patients with an age ≥70 years During the immunisation period 15 patients out of 31 patients with an age ≥70 years reported a total of 54 AEs: 8 patients had 35 AEs during treatment with StroVac® and during placebo 7 patients 19 AEs. In the period after the immunisation a total of 52 AEs occurred in 18 patients: 34 AEs in 10 patients (StroVac®) and 18 AEs in 8 patients (placebo). The analysis of the AEs in this subgroup showed similar characteristics as the full SEP. There were no specific safety findings relevant only for this subgroup. **Safety laboratory** Mean values of the evaluated laboratory parameters in the blood showed no medically relevant changes from baseline visit (V1) to V5 and V9 in both treatment groups. Values judged as clinically significant were mainly glucose values detected in 7 patients with a diabetes mellitus in their medical history. A clinically significant increase of the C-reactive protein was documented for 3 patients but each value was abnormal at one visit only. **Vital signs** Vital signs (systolic and diastolic blood pressure, body temperature) were measured at V1, 5, 7 and 9 additionally at V2 to 4 before and after the injection but showed no clinically relevant changes in mean vital signs in both treatment groups. In one patient [*Pat ID 332-6-SV-SIFP*] a severe SAE *hypertensive crisis* was reported in the period after treatment in the StroVac® group and was judged as not related to the investigational product and recovered within 21 days. **Global judgement of tolerability** The tolerability of treatment with StroVac® was assessed as “very good” and “good” by 87.7 % of the investigators (sum of both categories) and by 79.2 % of the patients. 98.9 % of the investigators rated placebo as “very good” and “good” and 97.9 % of the patients. All patients for whom tolerability of treatment was judged by the investigator or patient as “poor” (0.5 % respectively 1.6 %) or “very poor” (0.0 % respectively 0.3 %) experienced one or more AEs. Statistical testing for differences between the treatment groups was significant in favor of the placebo group.
Conclusion	The study failed to show superiority of StroVac® over placebo in reduction of bacterial symptomatic uncomplicated UTIs [$UTIs_{confirmed}$] over a period of 13.5 months. However, a strong effect of both treatments could be observed, i.e. reduction of $UTIs_{confirmed}$ from in mean 5.4 UTIs in the year prior to inclusion into the study to in mean 1.3 $UTIs_{confirmed}$ (1.2 $UTIs_{confirmed}$ in the StroVac® group vs. 1.3 $UTIs_{confirmed}$ in the placebo group). The placebo effect was 1.5 times higher as expected. It is assumed that the excipients aluminumphosphate and dextran used in the placebo had their own immune effect and may have elevated the placebo response. In addition, in the StroVac® group considerably more UTIs were caused by *Staphylococcus aureus*. Since this germ is not part of the StroVac® vaccine, a specific immune response was not to be expected.
Conclusion (cont.)	The results of the subgroup analysis in patients with 7 or more UTI per year prior to randomization showed that StroVac® reduced the recurrence of $UTIs_{all}$ statistically significant to 2.3 versus 4.4 in placebo group (p-value 0.0487). That means patients with high frequent recurrences in the history had within 13.5 months after StroVac vaccination 2.1 UTIs less compared to placebo patients. This is a clinical relevant difference. Therefore, a study design with inclusion of patients with 7 and more UTIs in history and a less strict definition of UTI as defined in the protocol might have resulted in a successful outcome of primary endpoints.

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Name of Active Ingredient: at least 10^9 inactivated germs including E. coli, Morganella morganii, Proteus mirabilis, Klebsiella pneumoniae, and Enteroccocus faecalis		

	A focus was laid in a subgroup analysis of post-menopausal women and patients older than 70 years. They benefit as well as other patients from the immunization with StroVac®. Beside the known, typical local and systemic reactions to the vaccination the immunisation with StroVac® was safe and comparable to placebo treatment regarding the safety profile.
Date of the report	22 FEB 2016 (Final)

Attachment to Amended Synopsis

Pharmalog Project No.: 10404 EudraCT No.: 2010-020882-25 Protocol Code: SU5.6

List of 48 Study Centres (corresponding to „Study Centres“ in Synopsis)			
Centre	**Medical specialist**	**ZIP code**	**City**
1	Urologist	107xx	Berlin
2	Urologist	463xx	Borken
3	Urologist	212xx	Buchholz
4	Urologist	225xx	Hamburg
5	General practitioner	803xx	München
6	Urologist	062xx	Lutherstadt Eisleben
7	Urologist	819xx	München
9	Urologist	910xx	Herzogenaurach
10	Urologist	514xx	Bergisch Gladbach
11	Urologist	410xx	Mönchengladbach
12	Urologist	943xx	Bogen
13	Urologist	202xx	Hamburg
14	Urologist	121xx	Berlin
15	Urologist	790xx	Freiburg
16	Urologist	995xx	Apolda
17	Gynaecologist	812xx	München
18	Urologist	210xx	Hamburg
19	Urologist	353xx	Gießen
20	Urologist	997xx	Nordhausen
21	Urologist	223xx	Hamburg
22	Urologist	041xx	Leipzig
23	Urologist	808xx	München
24	Urologist	732xx	Kirchheim
25	Urologist	463xx	Bocholt
26	Urologist	806xx	Zwickau
27	Urologist	454xx	Mühlheim
28	Urologist	044xx	Markkleeberg
29	Urologist	350xx	Marburg
30	Urologist	227xx	Hamburg
31	Urologist	998xx	Gotha
32	Urologist	041xx	Leipzig
33	General practitioner	803xx	München
34	Urologist	146xx	Nauen
35	Urologist	239xx	Wismar
36	Urologist	192xx	Hagenow
37	Urologist	934xx	Cham
38	Urologist	041x	Leipzig
39	Urologist	131xx	Berlin
40	Urologist	107xx	Berlin
41	Urologist	210xx	Hamburg
42	Urologist	421xx	Wuppertal
43	Internal specialist	049xx	Elsterwerda
44	Urologist	041xx	Leipzig
45	Urologist	406xx	Erkrath
46	Urologist	263xx	Wilhelmshaven
47	Urologist	241xx	Kiel
48	Urologist	470xx	Duisburg
49	Urologist	381xx	Braunschweig