Universitäts Klinikum

Clinical Study Report

Individualized homeopathy to reduce the use of antibiotics in women with recurring uncomplicated urinary tract infections

An investigator initiated, monocentric, randomized, double-blind, parallel-group, placebo-controlled, phase IV clinical trial

Investigational Medicinal Product:
Homeopathic medicinal products

Study Code: IHO-0000-REN-0220-S

EudraCT Number: 2021-002214-14

First Patient First Visit: 02.06.2023 – **Last Patient Last Visit:** 27.01.2025

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Synopsis

1.	**Sponsor:** Klinikum rechts der Isar, Technische Universität München, Ismaninger Str. 22, 81675 München, Germany **Sponsor Delegated Person (SDP):** Prof. Dr. med. Lutz Renders
2.	**Name of Finished Products:** Homeopathic medicinal products
3.	**Name of Active Ingredients:** Homeopathic medicinal products
4.	**Individual Study Table:** (only required for submissions) NAP
5.	**Study Title:** Individualized homeopathy to reduce the use of antibiotics in women with recurring uncomplicated urinary tract infections (iHOM)
	Study Design: A monocentric, randomized, double-blind, parallel-group, placebo-controlled, phase IV clinical trial
	Study (Protocol) Code Number: IHO-0000-REN-0220-S
	Eudra-CT Number: 2021-002214-14
6.	**Investigator:** Prof. Dr. med. Lutz Renders
7.	**Participating Clinical Trial Site:** Abteilung für Nephrologie, TUM Klinikum Rechts der Isar Ismaninger Str. 22 81675 München, Germany
8.	**Publication:** no publication yet
9.	**Study period:** First patient first visit: 02.06.2023; last patient included: 02.08.2024; last patient last visit: 27.01.2025.
	Approvals and Amendments: **First Submission:** Approval: Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM): 16.12.2022; clinical study protocol (CSP) Version 1.0 08.08.2022 Changes requested by the Ethics Committee (EC) to CSP Version 1.0 resulted in submission of CSP Version 2.0 23.11.2022 with consecutive approval by EC 30.11.2022 followed by submission of CSP Version 2.0 to BfArM with consecutive approval 05.01.2023 **Amendments**: the following changes were approved/acknowledged by EC: advertising measures, flyer, new version of ICF (correction of inconsistencies) **Amendment 3:** The following major changes were included: exclusion criterion #4 was reduced from 6 to 3 months before baseline, timelines of clinical trial were extended Approval AM2: BfArM: 27.05.2024; EC: 19.06.2024, CSP Version 3.0, 22.02.2024 **End of recruitment** (due to lack of recruitment): Response to end of recruitment (04.09.2024) was received from EC: 10.09.2024. **Early termination of the clinical trial:** Acknowledgement of end of the clinical trial (30.01.2025) was received from EC: 11.02.2025

10.	**Phase of development:** Phase IV
11.	**Objectives:** **Primary Objective:** The aim of this study is to investigate the efficacy of prophylactic individualized homeopathic treatment, using potencies C200 and/or C1000, as a therapeutic principle. This will be compared to a placebo in terms with regard to the number of urinary tract infections (UTIs) treated with antibiotic agents. **Secondary Objectives:** Additionally, the study will assess the efficacy of the homeopathic treatment strategy in comparison to placebo regarding the total number of UTIs, regardless of the treatment administered. Finally, the study will also evaluate the impact of prophylactic individualized homeopathic treatment on disease-specific quality of life, again in comparison to placebo.
12.	**Background/Methodology:** Lifetime prevalence for recurrent, uncomplicated urinary tract infections (UTIs) is estimated to be around 3% of the female population. UTIs are commonly treated with antibiotics and an increase of the incidence of multi-drug resistant pathogens causing UTIs has been observed. Non-antibiotic treatment options for acute UTIs and a reduction of the frequency of UTIs in patients affected with recurrent infections are warranted. One part of the national and international antibiotic surveillance strategy is to reduce the use of antibiotic agents by delayed prescriptions and alternatives. However, alternative treatment options aiming to decrease the frequency of UTIs treated with antibiotics have shown only limited success rates. The World Health Organization has declared the problem of antibiotic resistance to be a global crisis and the European Union has defined, among other things, the reduction of antibiotic use in its strategies to avoid the development of resistance. Recurrent UTIs are one of the most common infectious diseases contributing to a multiple of multidrug-resistant extra intestinal pathogenic E coli, increasing morbidity and mortality due to many treatment failures and hospital admissions, which leads to increased healthcare costs. There is, therefore, an urgent need to optimize appropriate usage, to minimize the burden of disease for the patients and the health care services, while maintaining treatment safety at the same time. As part of the antibiotic awareness strategy in Germany, it is currently recommended to treat uncomplicated UTIs symptomatically as long as no dangerous course of the disease can be expected, but different treatment options aiming to decrease the frequency UTI treated with antibiotics have shown only limited success rates. Thus, the symptom load of the affected patients as well as prescription rates for antibiotics remain high and treatment options are warranted by patients and physicians. Homeopathy has been shown to result in a reduction of acute infectious episodes for other recurrent infectious diseases and a reduction of the frequency of UTIs with individualized homeopathic treatment (iHOM) has been observed in practice. In this study we therefore aim to test the efficacy of this prophylactic treatment approach as an add-on therapy to the treatment standard in a double-blind, placebo-controlled randomized trial. The clinical trial is registered at the EU Clinical Trials Register and ClinicalTrials.gov (identifier: NCT05545514). **Figure 1** displays main aspects of the trial design including the patient flow.

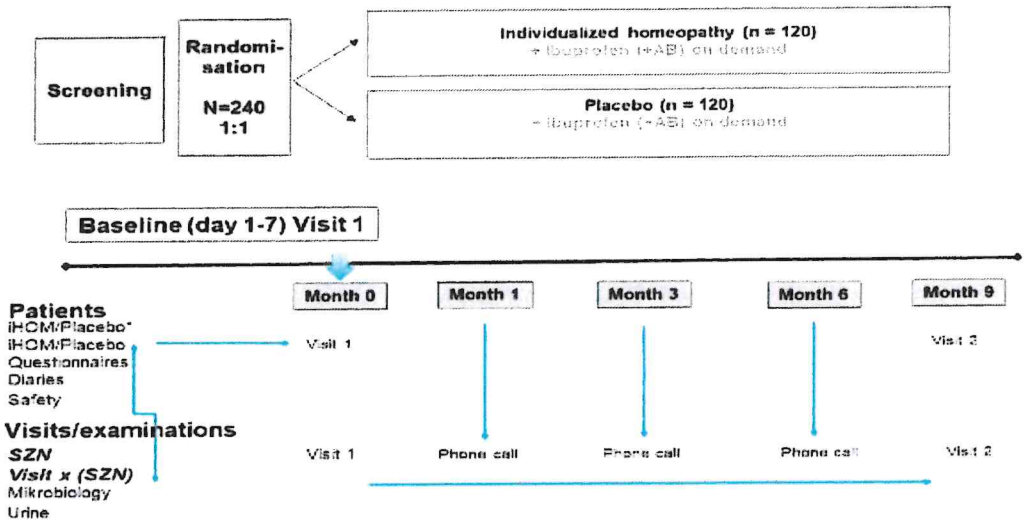


Figure 1: Individualized homeopathy to reduce the use of antibiotics in women with recurring uncomplicated urinary tract infections – study design. Abbreviations: (+AB) = antibiotic treatment if indicated as per avertable dangerous course of disease; iHOM = individualized homeopathy (study medication); * applied once at baseline and repeated, if indicated as per homeopathic treatment principles at further visits (x) and in case of acute symptoms of a urinary tract infection; Visit x = additional visits in case of acute symptoms of a urinary tract infection

13. **Sample size (planned/analysed):**
Planned: To be assessed for eligibility: n = 280 patients
To be allocated and analysed: n = 240 (n = 120 in each study group)
Analysed: Intent-to-Treat (ITT) population: 39 randomized patients who received HMP at least once
Safety population (SP): 39 patients of the ITT population
Per-protocol (PP) population: 22 patients

14. **Patient Population (Diagnosis):**
Women with recurring uncomplicated urinary tract infections
Minimum age: 18 years; maximum age: <65 years
These definitions were applied for all analysis populations, ITT, SP and PP.

Main criteria for inclusion:
1. Females, age 18 < 65 years
2. Signed informed consent
3. Documented recurrent UTI (i.e. ≥ 2 UTI in 6 months and/ or ≥ 3 UTI in 12 months)
4. No change of other prophylactic treatment (e.g. Urovaxom, estrogen) for recurrent UTI for at least three months before baseline
5. No product or dosage change of systemic hormonal treatment (including oral anticonception) for at least three months before baseline
6. Female participants who are not capable of bearing children or who use a method of contraception that is medically approved by the health authority of the respective country.

	Main criteria for exclusion: 1. Individual symptomatology of the patient indicates the prescription of a HMP, which is not available within this clinical trial 2. Pregnancy or breast feeding after pregnancy 3. Women with a complicated urinary tract infection (including infections occurring due to anatomical abnormalities (e.g. an obstruction, renal tract calculi, hydro nephrosis), infections occurring due to an immune compromised state (e.g. HIV, immune suppressive therapy) and recurrent infections despite adequate treatment (multi-drug resistant organisms or atypical organisms)) 4. Surgery of the urinary tract or the pelvic floor 5. Known hypersensitivity against the study medication or the recommended on demand medication (Ibuprofen) 6. Homoeopathic therapy for recurrent UTIs during the last 3 months before baseline 7. Postmenopausal woman WITHOUT previous attempt of a therapy with locally applicated (vaginal) oestrogen 8. Serious acute or chronic organic disease or serious mental disorder, including - diseases requiring immune suppressive therapy - diabetes mellitus type 1 or 2 with an HbA1c > 7% - any acute organic failure - any advanced chronic organic failure (e.g. grade 3 or more) - active cancer - active (=clinically unstable) epileptic, cardiovascular or other organic pathology 9. Patients not able to declare meaningful informed consent on their own (e.g. with legal guardian), or other vulnerable patients (e.g. under arrest) 10. Simultaneous participation in any other clinical trial 11. Employees or family members of the sponsor or investigators
15.	**Test product, dose and mode of administration:** **Experimental intervention**: Homeopathic medical products (HMP): there were 140 predefined HMP at potencies of C200 and C1000 with each HMP in a single-dose container. HMPs were individually selected according to homeopathic treatment principles for sublingual administration of 5 pillules constituting one dose. The HMPs were sucrose capsules impregnated with the specific homeopathic substance. **Control intervention**: placebo pillules in single-dose container Batch-No. (Ch.-B): 221026001, 221116001, 23104001,230105001, 230109001
16.	**Duration of administration:** The maximum duration of administration: 6 months
17.	**Background therapy:** Standard of care **Comparator**: NAP
	Blinding: Double-blind (block wise randomization in a 1:1 ratio stratified by the number of UTIs during the last year (<6, ≥6) and menopausal status (pre, peri, post); randomization lists were created using Rancode 2015.

18.	**Criteria for evaluation:** **Primary endpoint:** Number of UTIs treated with antibiotic agents, measured between baseline and month 9 in both groups. A UTI is defined by the criteria of the German S3-guideline for diagnostic of uncomplicated lower UTI: • Clinical symptoms (either dysuria or increased urinary frequency or increased incontinence or pelvic pain) plus > 10^3 bacteria as monoculture in the urine culture, or • Clinical symptoms plus urine test-strip with an evidence of nitrite and / or leukocyte-esterase and / or blood The criteria for a prescription of an antibiotic agent are: • Fever > 38.0 degree Celsius, and / or • Persistent pain under symptomatic therapy with ibuprofen, not tolerated by the patient, and / or • Clinical suspicion of pyelonephritis **Secondary endpoints:** • Time until the first UTI after the start of the study treatment (regardless of treatment of the first UTI) • The number of UTI treated symptomatically, measured between baseline and month 9 • Subjective symptom load and disease-specific quality of life over the last 3 months, measured at baseline and at month 9 per visual analogue scale (VAS) **Additional descriptive variables:** 1. Individual homeopathic substances and potencies prescribed for recurrent UTI during the study 2. Rescue Medication Score = total number of consumed on demand medication (Ibuprofen) between baseline and month 9, documented by the patient daily in case of an acute UTI 3. Total of UTI with resistant microbes in urine analyses, measured from month 0-9 4. Subjective symptom load and disease-specific quality of life, measured at baseline and at month 9 in one validated questionnaire (ICIQ-FLUTS) over the last 4 weeks 5. Disease-specific quality of life and subjective symptom load over the course of an acute UTI (ACSS-questionnaire), measured continuously in patient diaries 6. Subjective treatment outcome (ORIDL questionnaire), measured at month 9 7. Subjective assessment of general health (SF-12), measured at baseline and at month 9 8. Spectrum of pathogens of documented UTIs, measured between baseline and month 9 9. Number and duration of homeopathic consultations 10. Number of changes of the homeopathic substance and/or potency, measured per patient during the course of the study 11. Number and reasons for individual patients' discontinuation of the study (drop-outs)
	Efficacy: Efficacy assessments follow endpoint analyses.
	Safety assessments: Safety was assessed from baseline until month nine.
19.	**Statistical methods:** Primary intention of the trial was assessment of superiority of homeopathic treatment over placebo. A non-inferiority margin for the primary endpoint of $\Delta = 0.71$ was specified for the rate ratio a priori (before the beginning of the trial) in order to allow assessment of non-inferiority of placebo as compared to homeopathic treatment in the case the primary superiority null hypothesis cannot be rejected. The final analysis of primary and secondary endpoints was intended to be conducted after the end of the follow-up phase of the last patient. Due to early stopping of the trial, the final analysis was conducted using all data available. All statistical analyses were determined and prespecified prior to unblinding in a statistical analysis plan (SAP). An interim analysis was not planned/conducted. The statistician remained blinded until data-base hard-lock.

The statistical test for assessment of the primary hypothesis was conducted two-sided on a significance level of α = 1%. For the rate ratio between the two study groups, a corresponding 99% confidence interval and a 95% confidence interval were estimated based on the regression coefficient and the standard error of the negative binomial regression model.
All other statistical tests were performed and interpreted in an exploratory manner. Tests for the secondary endpoints were performed two-sided on a significance level of α = 5%. For all corresponding effect measures, two-sided 95% confidence intervals were estimated.

Population for analysis
Full analysis set (intention-to-treat): all patients who took the study medication or the corresponding placebo at least once. The primary superiority analysis was conducted in the full analysis set. Patients with an incomplete follow-up were considered until their withdrawal/end of study.
Per Protocol set: all patients who took their allocated medication as indicated and who had a complete follow-up period of nine months. A sensitivity analysis of the primary analysis was conducted using the per protocol population.
Based on the Blinded Data Review Meeting, 22 patients were considered in the Per Protocol Set.
Safety set: all individuals who took at least one dose of the study medication or placebo.

Study groups
Group 1: HMP pillules (verum group)
Group 2: placebo pillules (placebo group)

Primary endpoint analysis: Analysis of the primary endpoint (number of UTIs treated with antibiotic agents within 9 months after baseline visit) was performed following the intention-to-treat (ITT) principle, so each participant was analyzed in the treatment group she was randomized to. The Full Analysis Set used for analysis of the primary endpoint consists of all patients who took the study medication or the corresponding placebo at least once.
A negative binomial regression model with the number of observed events as dependent variable and an indicator for study group (0 = placebo group, 1 = verum group) as independent variable was fitted to the data. Additionally, the observation time was considered as log-transformed offset variable for each patient, which allows inclusion of participants with overall follow-up times shorter than nine months. Due to the small number of patients included caused by early termination of the trial, no further covariates (number of UTIs within the last year before the study, menopausal status) were considered in the model.
For the primary analysis, a significance level of α = 1% was used (two-sided test).
Estimates for mean numbers of UTIs within nine months after study inclusion are presented for both study groups. An estimate for the rate ratio between the groups was derived from the regression coefficient for study group (b_{Gr}) as $\exp(b_{Gr})$ and a 99% and a 95% confidence interval for the rate ratio were obtained correspondingly.
A sensitivity analysis was performed in the Per Protocol set including all patients with complete follow-up who took their allocated medication as indicated.
As the primary null hypothesis (H_0: rate ratio = 1) could not be rejected following the procedure described above, non-inferiority of placebo compared to homeopathic treatment was assessed. The lower bound of the 95% confidence interval for the rate ratio, that was calculated as

$$\text{Lower bound of 95\% CI} = \exp(\hat{b}_{Gr} - z_{0.975} \cdot \widehat{se}_{b_{Gr}}),$$

where $\hat{b}_{Gr}$ and $\widehat{se}_{b_{Gr}}$ are the estimates for the regression coefficient for the group effect (log-rate ratio) and the corresponding estimate for the standard error and $z_{0.975}$ is the 97.5th percentile of the standard normal distribution, were compared to the prespecified non-inferiority margin of Δ = 1 / 1.4 = 0.71. This analysis was performed in the full analysis set based on the intention-to-treat principle and the per protocol set with both analysis sets having equal importance for the interpretation of the results.

	Secondary endpoint analysis: All secondary analyses were performed in an exploratory manner considering all available data without imputation of missing values. For relevant effect measures, 95% confidence intervals were estimated and presented. The distribution of time to first UTI was estimated and visualized using the Kaplan-Meier method considering individual length of follow-up of all participants. A Cox regression model was fitted to the data to compare the study groups (without considering further covariates) and an estimate for the hazard ratio between treatment groups with corresponding 95% confidence interval is presented. Number of symptomatically treated UTIs within nine months after baseline visit were analyzed using a negative binomial regression model as described for the primary endpoint. A rate ratio with corresponding 95% confidence interval was estimated. For comparison of quantitative secondary endpoints and additional descriptive variables between the study groups at fixed follow-up times, mean values, minima and maxima and/or standard deviations are shown. For relevant outcomes, mean differences with corresponding 95% confidence intervals were estimated using linear regression models. For comparison of mean changes, linear regression models with the difference from the time point of interest to the baseline assessment as dependent variable and study group and the corresponding baseline value as independent variables were fitted to the data. All AEs were analyzed on the safety set consisting of all individuals who took at least one dose of the study medication. The overall incidence of non-serious adverse events, SAEs, and related SAEs are tabulated using Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term stratified for treatment group.
20.	**Summary - Conclusions:** **Recruitment** In total, 40 patients were included in the clinical trial (First patient first visit: 02.06.2023; last patient included: 02.08.2024; last patient last visit: 27.01.2025). One of 40 patients was randomized without administration of HMP at least once and was excluded from the ITT analysis set and the safety set (violation of EC #8). Eighteen of 40 patients were excluded from the PP analysis set. Reasons for exclusion were loss to FU, early termination of clinical trial, one patient withdrew informed consent, and one patient with violation of EC #8. 20 patients of the ITT analysis set were included in group 1 (verum group, 51.3%), 19 patients in group 2 (placebo group, 48.7%). The study visit V2 was completed by 13/20 (65.0%) patients in group 1, 9/19 (47.4%) patients in group 2. **Baseline patient characteristics** Only women between 18 and <65 years were included. The mean age was 41.7 (19 to 63) years in group 1 (0 male, 20 female), 39.5 (20 to 61) years in group 2 (0 male, 19 female). The menopausal status in group 1 was pre-menopausal for 11 patients (55.0%), peri-menopausal for 5 patients (25.0%), and post-menopausal for 4 patients (20.0%). In group 2, 12 patients (63.2%) were pre-menopausal, 4 patients (21.1%) were peri-menopausal, and 3 patients (15.8%) were post-menopausal. Mean BMI was 22.9 (18.8 to 30.7) in group 1 and 21.0 (17.7 to 24.8) in group 2. In group 1, number of UTIs last year was <6 for 17 patients (85.0%) and ≥6 for 3 patients (15.0%), in group 2 number of UTIs last year was <6 for 16 patients (84.2%) and ≥6 for 3 patients (15.8%).
	Compliance: Protocol Deviations (PD): Fifty PD were reported in 29 patients (verum group: 31 in 15 patients, placebo group: 19 in 14 patients). Besides the PD (violation of EC #8) which led to the exclusion of one patient from the ITT and PP analyses no further major PD were reported.

	Study medication: Thirty-nine of 40 patients (ITT population) received at least one dose of HMP. 17 patients received HMP but did not reach V2. From these 17 patients, 7 were randomized to group 1, 10 were randomized to group 2. Adherence to intervention: Overall compliance for intervention was good. **Safety Assessments (all patients included)** Annual Safety Reports have been provided to BfArM and EC for the following periods: DSUR 1: 16.12.2022-15.12.2023 DSUR 2: 16.12.2023-15.12.2024 DSUR 3: 16.12.2024-15.12.2025 Adverse Events and one Serious Adverse Event were classified according to CTCAE v5.0 and coded according to MedDRA Version 28.0.
	Safety Results Safety results are reported in the treatment groups of the actual study treatment, regardless of randomization. **Adverse Events (AE)** A total of 119 AE were reported in 34 (87.2 %) of 39 patients as detailed in **Table A1** (in the Appendix). 19 (95.0%) patients experienced 55 AE in group 1, 15 (78.9%) patients experienced 64 AE in group 2. 104 (87.4 %) AE were rated grade 1 (mild), 15 (12.6 %) grade 2 (moderate), 0 (0 %) grade 3 (severe), 0 (0 %) grade 4 (life-threatening) and 0 (0%) grade 5 (death). No relevant differences were observed regarding the AE intensity across groups. One AE was deemed to be related to HMP ("nausea" in a patient from the placebo group). **Serious AE (SAE)** One SAE was reported in group 2 (placebo group). **Suspected Serious Adverse Reactions (SAR)** No SAR was reported. **Suspected Unexpected Serious Adverse Reactions (SUSAR)** No SUSAR was reported.
	Efficacy Results **Primary Endpoint** In the verum group (FAS), 19 UTIs were treated with antibiotic agents during follow-up. In 12 of 20 patients at least one UTI was treated with antibiotic agents (total follow-up time of 159.9 person months). In the placebo group 14 UTIs were treated with antibiotic agents. In 9 of 19 patients at least one UTI was treated with antibiotic agents (136.0 person months). A risk ratio (verum vs. placebo= of 1.16 (99% confidence interval 0.43 to 3.10; 95% confidence interval 0.55 to 2.45; p = 0.699) was observed. Estimated mean numbers of events within nine months obtained from the primary negative binomial model were 1.06 for the verum group and 0.92 for the placebo group. In a sensitivity analysis in the per protocol population of 22 patients with complete follow-up, the estimated risk ratio was 1.12 (95% ci 0.49 to 2.57, p = 0.789). No significant difference between the study groups was observed and non-inferiority of placebo as compared to verum treatment could not be established.

Secondary Endpoints

Time until the first UTI after start of the study treatment: In the verum group, 15 of the 20 patients experienced at least one UTI (irrespective of treatment) during their follow-up, in the placebo group, at least one UTI was observed in 13 of the 19 patients. Median time to the first UTI was 52.5 days (95% confidence interval 36.0 to 125.0 days) after Visit 1 for the verum group and 163 days (95% ci 36.0 to 231.0 days) for the placebo group (hazard ratio (verum vs. placebo): 1.36, 95% ci 0.64 to 2.89, p (logrank test) = 0.431, Figure 2).

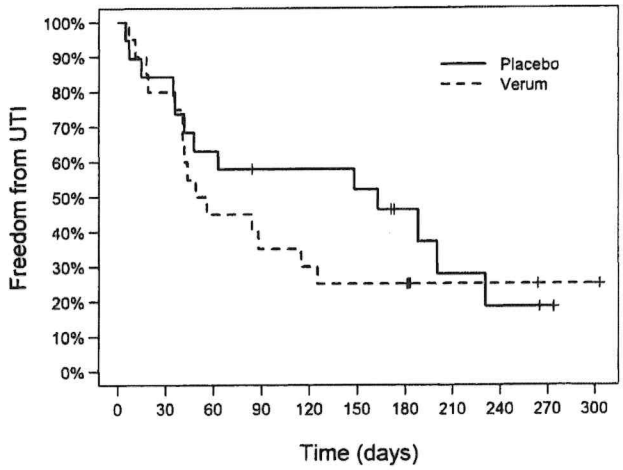


Figure 2 - Kaplan-Meier curves for time to first UTI.

Number of UTI treated symptomatically (i.e. all documented UTIs that were not treated with antibiotics): In the verum group, 12 UTIs were treated only symptomatically, 10 in the placebo group, leading to an estimated risk ratio of 1.02 (95% ci 0.44 to 2.36, p = 0.962).

Subjective symptom load and disease-specific quality of life over the last 3 months: Mean symptom load assessed with a visual analogue scale (high value indicating high well-being) at baseline was 57.1 (10 to 100) in the verum group and 59.4 (20 to 100) in the placebo group. After nine months, the mean value in the verum group (n = 13 patients with valid assessment) increased to 72.3 (20 to 100), in the placebo group (n = 9) to 81.8 (60 to 96). In a linear model considering baseline VAS values, the estimated mean differences between the study groups after nine months was -12.8 (95% confidence interval -28.9 to 3.3, p = 0.114).

Additional descriptive variables

Rescue Medication Score = total number of consumed on demand medication: Overall, use of Ibuprofen was documented by the patients mostly due to UTIs or due to AEs. Mean total intake of Ibuprofen due to UTI was 1210 mg (0 to 8800 mg) in the verum group and 1505 mg (0 to 15200 mg) in the placebo group.

Total of UTI with resistant microbes in urine analyses: Overall, 54 U-Bacterologies were performed (26 in the verum group, 28 in the placebo group). Bacteria were detected in 42 of the 54 urine cultures (77.8%), of which 30 were rated as clinically significant. Multiresitant bacterial infections were detected in the 3 cases, one of which was rated as clinically significant Fosfomycin resistance.

Subjective symptom load and disease-specific quality of life (ICIQ-FLUTS): Mean values of the ICIQ-FLUTS for the different subscales at baseline and at Month 9 are shown in **Table 1**.

		Verum		Placebo	
		n	Mean (Min - Max)	n	Mean (Min - Max)
Filling	**Baseline**	20	4.8 (1 – 12)	19	5.3 (3 - 9)
	9 Months	13	3.6 (0 – 10)	9	2.6 (0 - 6)
Voiding	**Baseline**	20	2.2 (0 – 8)	19	3.0 (0 – 10)
	9 Months	13	1.9 (0 – 6)	9	1.3 (0 – 3)
Incontinence	**Baseline**	20	2.0 (0 – 8)	19	1.7 (0 – 11)
	9 Months	13	1.3 (0 – 6)	9	1.3 (0 – 7)

Table 1: Subscales of the ICIQ-FLUTS

In linear regression models considering baseline values of the corresponding subscales, mean differences between the groups after 9 months of 1.5 (95% ci 0.01 to 3.1, p = 0.049) for Filling, 0.7 (95% ci -0.8 to 2.1, p = 0.352) for Voiding, and 0.3 (95% ci -1.1 to 1.7, p = 0.670) for Incontinence were estimated.

Disease-specific quality of life and subjective symptom load over the course of an acute UTI (ACSS-questionnaire): Results of ACSS-questionnaires are available for up to 50 UTIs. Descriptive summary data showing sum scores for symptom load and disease-specific quality of life on day 1, day 3 and day 7 of an UTI stratified by study group are shown in **Table 2**.

	Verum			Placebo		
	No. of UTIs	Mean ± SD	Min - Max	No. of UTIs	Mean ± SD	Min - Max
Symptom load on Day 1 (sum score)	28	8.9 ± 3.5	0 – 14	21	7.8 ± 3.9	2 – 14
Symptom load on Day 3 (sum score)	28	4.5 ± 4.4	0 – 13	20	5.4 ± 4.1	0 – 15
Symptom load on Day 7 (sum score)	24	1.4 ± 2.6	0 – 11	19	3.6 ± 3.9	0 – 15
Quality of Life on Day 1 (sum score)	29	5.8 ± 2.6	2 – 9	21	4.4 ± 2.2	1 – 9
Quality of Life on Day 3 (sum score)	29	3.4 ± 2.7	0 – 9	20	3.6 ± 2.2	0 – 9
Quality of Life on Day 7 (sum score)	24	1.2 ± 1.7	0 – 6	19	3.0 ± 2.5	0 – 8

Table 2: Descriptive statistics for the ACSS questionnaire (symptom load and disease specific quality of life).

Subjective treatment outcome (ORIDL questionnaire): Data on the subjective treatment outcome based on the ORIDL questionnaire are available for 22 patients (13 from the verum group and 9 from the placebo group). Overall, 15 of the 22 patients reported that for their main complaint, at least a moderate improvement (score >= 2) was experienced (8 from the verum group (61.5%) and 7 from the placebo group (77.8%)). Regarding the problem, 15 patients reported at least a moderate improvement (8 from the verum group (61.5%) and 7 from the placebo group (77.8%)). For overall well-being, 12 patients reported at least a moderate improvement (6 from the verum group (46.2%) and 6 from the placebo group (66.7%)).

Subjective assessment of general health (SF-12): Assessment of general health based on the SF-12 questionnaire was available for all 39 patients (20 in the verum group and 19 in the placebo group) at baseline and for 22 patients (13 verum, 9 placebo) at 9 months. Mean values for the physical score and the mental score and corresponding minima and maxima are shown in **Table 3** for baseline and nine months assessment stratified for study groups.

		Verum		Placebo	
		n	Mean (Min - Max)	n	Mean (Min - Max)
Physical score	**Baseline**	20	47.4 (29.3 – 63.8)	19	46.7 (28.3 – 63.1)
	9 Months	13	46.9 (27.1 – 60.1)	9	54.6 (40.7 – 63.4)
Mental score	**Baseline**	20	43.5 (26.0 – 65.8)	19	45.8 (24.1 – 59.9)
	9 Months	13	46.6 (21.7 – 63.6)	9	48.1 (24.8 – 59.9)

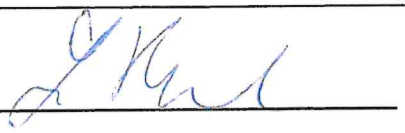
Table 3: Subjective assessment of general health (SF-12)

Spectrum of pathogens of documented UTIs: Bacteria most often detected were Eschericia coli, which was detected in 30 urine cultures, Streptococcus spp. (in 6 cultures), Ureaplasma (in 3 cultures), and Enterococcus spp. (in 2 cultures). Detected once were Proteus mirabilis, other coagulase-negative staphylococci, Lactobacillus jensenii, Staphylococcus epidermidis, Staphylococcus lugdunensis, and gr. negative rods.

Number and duration of homeopathic consultations: Overall, 117 homeopathic consultations were documented over the course of the study (64 in the verum group and 53 in the placebo group). Mean time of the consultations was 47.2 minutes (2 to 150 minutes) in the verum group and 55.9 minutes (6 to 150 minutes) in the placebo group.

Number of changes of the homeopathic substance and/or potency, measured per patient during the course of the study: Overall, 43 changes of the study drug (25 in the verum group, 18 in the placebo group) were documented. Main reason for the change of the study drug was "no reaction/no effect".

Number and reasons for individual patients' discontinuation of the study (drop-outs): Twenty-two of the 40 patients completed the study as planned. One patient did not receive any study medication and did not have any follow-up assessment due to violation of an inclusion criterion. Due to premature termination of the study, 14 patients did not have a follow-up of up to nine months. Two patients were lost to follow-up and one patient withdrew consent during the study.

	Overall Conclusion: The clinical trial recruited 40 patients with UTI. The safety profile was in accordance with administration of HMP in this patient population and did not show any relationship to our study groups (one AE was deemed to be related to HMP ("nausea" in a patient from the placebo group), one SAE was reported in the placebo group). In conclusion, no relevant differences could be shown with respect to the primary and the secondary endpoints between administration of HMP or placebo. This clinical trial provides no evidence that administration of HMP is superior to administration of placebo.
21.	**Date of report:** **Date:** 26.01.2026 **Signature:**  SDP: Prof. Dr. med. Lutz Renders

APPENDIX

	Exposed to placebo N=19			Exposed to verum N=20		
		Subjects affected			Subjects affected	
System Organ Class Preferred Term	*Events*	*n*	*(%)*	*Events*	*n*	*(%)*
OVERALL	64	15	78.9	55	19	95.0
Cardiac disorders	1	1	5.3	0	0	0.0
Arrhythmia	1	1	5.3	0	0	0.0
Gastrointestinal disorders	9	6	31.6	6	4	20.0
Constipation	1	1	5.3	0	0	0.0
Diarrhoea	4	2	10.5	2	1	5.0
Dyspepsia	1	1	5.3	0	0	0.0
Nausea	2	2	10.5	3	3	15.0
Toothache	0	0	0.0	1	1	5.0
Vomiting	1	1	5.3	0	0	0.0
General disorders and administration site conditions	1	1	5.3	0	0	0.0
Pyrexia	1	1	5.3	0	0	0.0
Immune system disorders	1	1	5.3	2	2	10.0
Mite allergy	0	0	0.0	1	1	5.0
Seasonal allergy	1	1	5.3	1	1	5.0
Infections and infestations	32	11	57.9	27	14	70.0
Bronchitis	1	1	5.3	0	0	0.0
COVID-19	3	3	15.8	2	2	10.0
Conjunctivitis	2	1	5.3	0	0	0.0
Gastrointestinal infection	0	0	0.0	1	1	5.0
Genital herpes	0	0	0.0	4	1	5.0
Gingivitis	1	1	5.3	0	0	0.0
Infectious mononucleosis	0	0	0.0	1	1	5.0
Influenza	1	1	5.3	0	0	0.0
Nasopharyngitis	19	10	52.6	15	10	50.0
Norovirus infection	1	1	5.3	0	0	0.0
Oral herpes	2	1	5.3	3	2	10.0
Sinusitis	1	1	5.3	1	1	5.0
Streptococcal infection	1	1	5.3	0	0	0.0
Injury, poisoning and procedural complications	2	2	10.5	0	0	0.0
Joint dislocation	1	1	5.3	0	0	0.0

	Exposed to placebo N=19			*Exposed to verum N=20*		
		Subjects affected			*Subjects affected*	
System Organ Class Preferred Term	*Events*	*n*	*(%)*	*Events*	*n*	*(%)*
Ligament rupture	1	1	5.3	0	0	0.0
Investigations	0	0	0.0	1	1	5.0
Blood iron decreased	0	0	0.0	1	1	5.0
Metabolism and nutrition disorders	0	0	0.0	2	1	5.0
Iron deficiency	0	0	0.0	1	1	5.0
Vitamin D deficiency	0	0	0.0	1	1	5.0
Musculoskeletal and connective tissue disorders	1	1	5.3	7	4	20.0
Arthralgia	1	1	5.3	0	0	0.0
Back pain	0	0	0.0	3	2	10.0
Exostosis	0	0	0.0	1	1	5.0
Muscle spasms	0	0	0.0	1	1	5.0
Plantar fasciitis	0	0	0.0	1	1	5.0
Rotator cuff syndrome	0	0	0.0	1	1	5.0
Nervous system disorders	13	6	31.6	9	5	25.0
Dizziness	0	0	0.0	1	1	5.0
Headache	9	5	26.3	7	4	20.0
Migraine	3	1	5.3	1	1	5.0
Syncope	1	1	5.3	0	0	0.0
Reproductive system and breast disorders	2	2	10.5	0	0	0.0
Dyspareunia	1	1	5.3	0	0	0.0
Vaginal discharge	1	1	5.3	0	0	0.0
Respiratory, thoracic and mediastinal disorders	1	1	5.3	1	1	5.0
Cough	1	1	5.3	1	1	5.0
Surgical and medical procedures	1	1	5.3	0	0	0.0
Tooth extraction	1	1	5.3	0	0	0.0

Table A1: Adverse Events