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# Non-Antibiotic Herbal Therapy (BNO 1045) versus Antibiotic Therapy (Fosfomycin Trometamol) for the Treatment of Acute Lower Uncomplicated Urinary Tract Infections in Women: A Double-Blind, Parallel-Group, Randomized, Multicentre, Non-Inferiority Phase III Trial

Florian M. Wagenlehner[a] Dimitri Abramov-Sommariva[b] Martina Höller[b]
Hubert Steindl[b] Kurt G. Naber[c]

[a]Clinic for Urology, Pediatric Urology and Andrology, Justus-Liebig University, Giessen, Germany; [b]Bionorica SE, Neumarkt, Germany; [c]Technical University of Munich, Straubing, Germany



**Keywords**
Urinary tract infection · Symptomatic treatment · Herbal treatment · Antibiotics

**Abstract**
***Introduction:*** This randomized, controlled, Phase III non-inferiority clinical trial aimed to determine whether herbal therapy with Canephron® N (BNO 1045) is non-inferior to fosfomycin trometamol (FT) in treating acute lower uncomplicated urinary tract infections (uUTIs). ***Materials and Methods:*** Women aged 18–70 years with typical symptoms of newly diagnosed acute lower uUTIs were randomized to BNO 1045 ($n$ = 325) or FT ($n$ = 334), with corresponding matched placebo. The primary endpoint was the proportion of patients who received additional antibiotics (ABs) to treat uUTIs between Days 1 and 38 ±3. ***Results:*** Between Days 1 and 38, 238 (83.5%) patients in the BNO 1045 group and 272 (89.8%) patients in the FT group received no additional ABs. At a 15% non-inferiority margin, BNO 1045 was non-inferior to FT in treating uUTIs (non-AB rate difference: –6.26%; 95% CI –11.99 to –0.53%; 2-sided $p$ = 0.0014). Adverse event rates were similar between groups, with higher rates of gastrointestinal disorders in the FT group and pyelonephritis in the BNO 1045 group. During the trial, no patient died or discontinued due to a treatment-related adverse event. ***Conclusions:*** BNO 1045 has the potential to reduce outpatient use of ABs for uUTIs and thus may have a significant impact on antimicrobial stewardship strategies. Trial registration: NCT02639520, EudraCT number 2013-004529-99.



## Introduction

Urinary tract infections (UTIs) are among the most prevalent infectious diseases encountered in general practice [1, 2] and of these, 80% are classified as uncomplicated UTIs (uUTIs) [3]. Current guidelines recommend the use of antibiotics (ABs) as the first choice of treatment for the acute phase of uUTIs [4].

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E-Mail karger@karger.com
www.karger.com/uin



Prof. Florian M. Wagenlehner
Clinic for Urology, Pediatric Urology and Andrology
Justus-Liebig University
Rudolf-Buchheim-Strasse 7, DE–35392 Giessen (Germany)
E-Mail Florian.Wagenlehner@chiru.med.uni-giessen.de

However, frequent use of ABs can cause collateral damage to the microbiome [5] and increase the risk of AB resistance [6].

Approximately 80% of uUTIs in otherwise healthy women are caused by *Escherichia coli* (*E. coli*) [2]. Global figures suggest that *E. coli* now has a resistance rate above 25% for the majority of common ABs, with rates of up to 45.5% for ciprofloxacin, 48.2% for trimethoprim/ sulfamethoxazole and 50.4% for aminopenicillin in nosocomial UTIs [7].

In order to combat the overuse of ABs and thus the rising rates of antimicrobial resistance, it is important to establish whether there are efficacious substitutes for ABs in the treatment of uUTIs. Previous studies have compared the efficacy of alternatives such as the non-steroidal anti-inflammatory drugs (NSAIDs) ibuprofen [8, 9] and diclofenac [10] with ABs, and have shown promising efficacy results. However, non-inferiority remains to be established.

Herbal preparations are another potential alternative to ABs for the treatment of uUTIs. Stange et al. [11] recently reported the results of a clinical study comparing a herbal combination of horseradish root and nasturtium herb (Angocin®) with AB (co-trimoxazole) for the treatment of acute uUTIs in men and women. Although non-inferiority was not proven between the 2 treatments, the results provided an insight into the potential of herbal alternatives to ABs.

Canephron® N (BNO 1045) is approved as a herbal medicinal product in 28 countries, including Germany and Ukraine. BNO 1045 is a coated tablet containing centaury powder (*Centaurii herba*), lovage root powder (*Levistici radix*) and rosemary leaf powder (*Rosmarini folium*). Pharmacological data for BNO 1045 are well documented in a number of in vivo and in vitro experimental models, indicating that it combines anti-inflammatory [12, 13], spasmolytic [14], anti-adhesive [12] and anti-nociceptive [15] activities with diuretic properties [16]. Unlike ABs such as fosfomycin, which result in considerable changes to the composition of the microbiome, BNO 1045 has been shown to largely preserve the gut microbiota [17]. This is particularly notable, given the implications of recent research into the urinary microbiota, where asymptomatic bacteriuria appears to play an important protective role against UTIs, and could be used as a preventative treatment strategy in recurrent infections [18].

The safety and efficacy of BNO 1045 have been shown in a previous non-randomized, multicentre, open-label pilot trial in patients with acute lower uUTIs [19]. In this pilot trial, 71.2% of patients had a clinical response to treatment with BNO 1045 monotherapy, and the treatment was generally well tolerated.

The objectives of the present clinical trial were to demonstrate non-inferiority of BNO 1045 versus AB therapy, as measured by the proportion of patients who received an additional AB treatment for acute lower uUTIs during the trial, and to assess the safety and tolerability of BNO 1045 in patients with acute lower uUTIs. Fosfomycin (as fosfomycin trometamol [FT]) was chosen as the AB comparator due to its position as a first-line treatment choice in the current European Association of Urology (EAU) Guidelines (at a single oral dose of 3 g) [4].

## Methods

*Trial Design*

This was a double-blind, controlled, double-dummy, parallel-group, randomized, multicentre, multinational Phase III non-inferiority trial, conducted in 51 centres in Europe: 16 in Germany, 22 in Ukraine and 13 in Poland (EudraCT number 2013-004529-99, Clinicaltrials.gov number NCT02639520). The trial was approved by all relevant competent authorities and ethics commissions.

*Patients*

Eligible patients were women aged 18–70 years with a sum-score of ≥6 for the 3 main uUTI symptoms (dysuria, pollakisuria and urgency) reported on the Acute Cystitis Symptom Score (ACSS) typical domain at Day 1, in combination with a positive leukocyte esterase test showing leukocyturia. Patients must have developed symptoms within 6 days prior to Day 1, were willing to refrain from taking concomitant medications and products prohibited by the trial protocol, and were surgically sterile, postmenopausal or willing to use highly effective contraceptive methods for the duration of the clinical trial. Patients were excluded if they demonstrated any signs or symptoms indicative of complicated UTIs, pyelonephritis and/or vulvo-vaginitis at Day 1, had any conditions that might lead to complicated infections, or had a history of recurrent infection of the urinary tract. All patients provided written informed consent to participate. A full list of inclusion and exclusion criteria can be found in the online supplementary material, pages 5 and 6 (for all online suppl. material, see www.karger.com/doi/10.1159/000493368).

*Randomization and Masking*

Patients were randomly allocated 1:1 to either BNO 1045 and FT-matched placebo, or FT and BNO 1045-matched placebo. The randomization sequence was computer-generated and grouped into blocks; numbers were blocked, and block size was not revealed to investigators. The task of preparation and checking of the randomization list was executed on a validated computerized system. Allocated treatment groups were unknown to both patients and the investigators.

*Procedures*

A contract research organization was responsible for the overall management of the trial, while the principal investigator at each centre was responsible for recruitment. Patients were informed of recommendations for treatment intake as part of the informed consent process.

Patients in the FT group were given 5.631 g FT (equivalent to 3 g of fosfomycin) as granules dissolved in 100–200 mL water and ingested immediately, which was administered as a single directly observed treatment on Day 1. Patients in the BNO 1045 group were given coated tablets, each containing powdered centaury herb (*Centaurii herba*) 18 mg, lovage root (*Levistici radix*) 18 mg and rosemary leaves (*Rosmarini folium*) 18 mg. BNO 1045 was administered orally as 2 coated tablets, 3 times a day, before or after meals for 7 days. The herbal powders used in the investigational medicinal product (IMP) came from a single manufacturing batch, and were derived from plants grown and cultivated under defined and controlled conditions and to stringent quality standards.

Treatment started on Day 1 and lasted a further 7 days until Day 8 (online suppl. material, page 2). Follow-up was 30 days after the last treatment date (Day 38), to determine whether uUTI had recurred. A list of measurements taken at each stage is listed in the online supplementary material, page 3. The investigators completed all data-collection forms.

The only concomitant symptomatic treatment permitted was paracetamol.

*Outcomes*

The primary objective of the clinical trial was to demonstrate the non-inferiority of BNO 1045 for 7 days of treatment versus a single dose of FT in women with acute lower uUTIs, as measured by the proportion of patients who received an additional AB for acute lower uUTIs during the trial.

The primary efficacy endpoint was the AB-rate, defined as the proportion of patients who received additional AB for the treatment of acute lower UTIs between Days 1 and 38 ± 3. Secondary efficacy endpoints included ACSS questionnaire assessments at Days 4, 8 and 38, and bacteriuria and leukocyturia based on urine culture test (midstream sample) at each on-site visit. A full list of secondary endpoints can be found in the online supplementary material, page 4.

The ACSS questionnaire is a simple and standardized self-reporting questionnaire for the diagnosis of acute uncomplicated cystitis assessing typical and differential symptoms, quality of life (QoL) and possible changes after therapy [20, 21]. Two versions of the questionnaire were used in this clinical trial; Part A on Day 1 for baseline assessment and Part B for all subsequent visits on Days 4, 8 and 38.

Part A included 18 questions organized into typical symptoms ($n = 6$) of lower uUTIs (ACSS-typical), symptoms ($n = 4$) for differential diagnosis (ACSS-differential), questions ($n = 3$) on QoL (ACSS-QoL) and any additional conditions ($n = 5$) that may affect therapy (ACSS-additional). These questions were all assessed on a 4-point Likert scale, where 0 = no symptoms, 1 = mild, 2 = moderate, and 3 = severe symptoms, apart from ACSS-additional, which used yes/no questions.

Part B included all sections of Part A with an additional section assessing changes in UTI symptoms at a successive visit compared to Day 1, rated on a 5-point scale where 0 = all symptoms resolved, 1 = majority of symptoms resolved, 2 = some symptoms remaining, 3 = all symptoms remain and 4 = my condition is declining.

Each patient used an ACSS version validated in their own language (German, Polish, Ukrainian or Russian; www.acss.world).

Safety endpoints evaluated in this trial included treatment-emergent adverse events (TEAEs); safety laboratory parameters (blood and urine) at Days 8 and 38; investigators' and patients' overall assessments of tolerability at Days 8 and 38; and physical examination and vital signs at Days 1, 4, 8 and 38.

The number and proportion of patients who took paracetamol within 24 h before a visit were recorded and summarized by visit and the treatment group.

*Sample Size and Analysis Approach*

The per-protocol set (PPS) included all patients from the full analysis set (FAS) who had no major protocol deviations. The primary analysis was based on the PPS. The calculation of sample size and power was based on the following assumptions and parameters of the trial design:

- Rate of additional use of antibiotics below 10% in the FT group
- Rate of additional use of antibiotics below 15% in the BNO 1045 group
- A non-inferiority margin of 15%
- A multiple 1-sided significance level (family-wise error rate) of 2.5%
- Equal and balanced distribution of patients across investigational sites, no centre effects and no centre by treatment interaction
- Up to 20% of patients with major protocol violations who cannot be included in the primary analysis in the PP population.

The safety analysis set included all patients treated at least once with the IMP. The FAS included the same patients as the safety analysis set but excluded potentially unblinded patients. Physicians could request microbiological reports at any time based on clinical need; if this occurred, patients were unblinded.

A sample size of 322 randomized patients per treatment group (258 patients in the PPS) was planned, to ensure at least 90% power for demonstrating non-inferiority of BNO 1045 versus FT in the use of additional ABs, by means of Farrington and Manning test for differences.

*Statistical Analysis*

The primary aim of the trial was to investigate alternatives to AB treatment for acute lower uUTIs, and the trial was designed as a comparison between 2 different modes of action: symptomatic treatment of the host with BNO 1045 and treatment of bacteria with FT. Therefore, a non-inferiority margin of 15% was justified instead of the 10% that is usually applied. In accordance with the EAU Guidelines [4], lower uUTIs can be considered a benign infection and hence there was no enhanced risk to patients when not treated with ABs.

The Farrington and Manning test was used to compute the differences in proportions and to assess the primary efficacy endpoint, with a 1-sided significance level of $\alpha = 0.025$ for assessment of non-inferiority. A 2-sided 95% CI was computed. This test was also performed on the FAS to test the robustness of the results in the PPS.

Differences between treatment groups in the ACSS analysis were assessed using the Wilcoxon-Mann-Whitney test (for test-

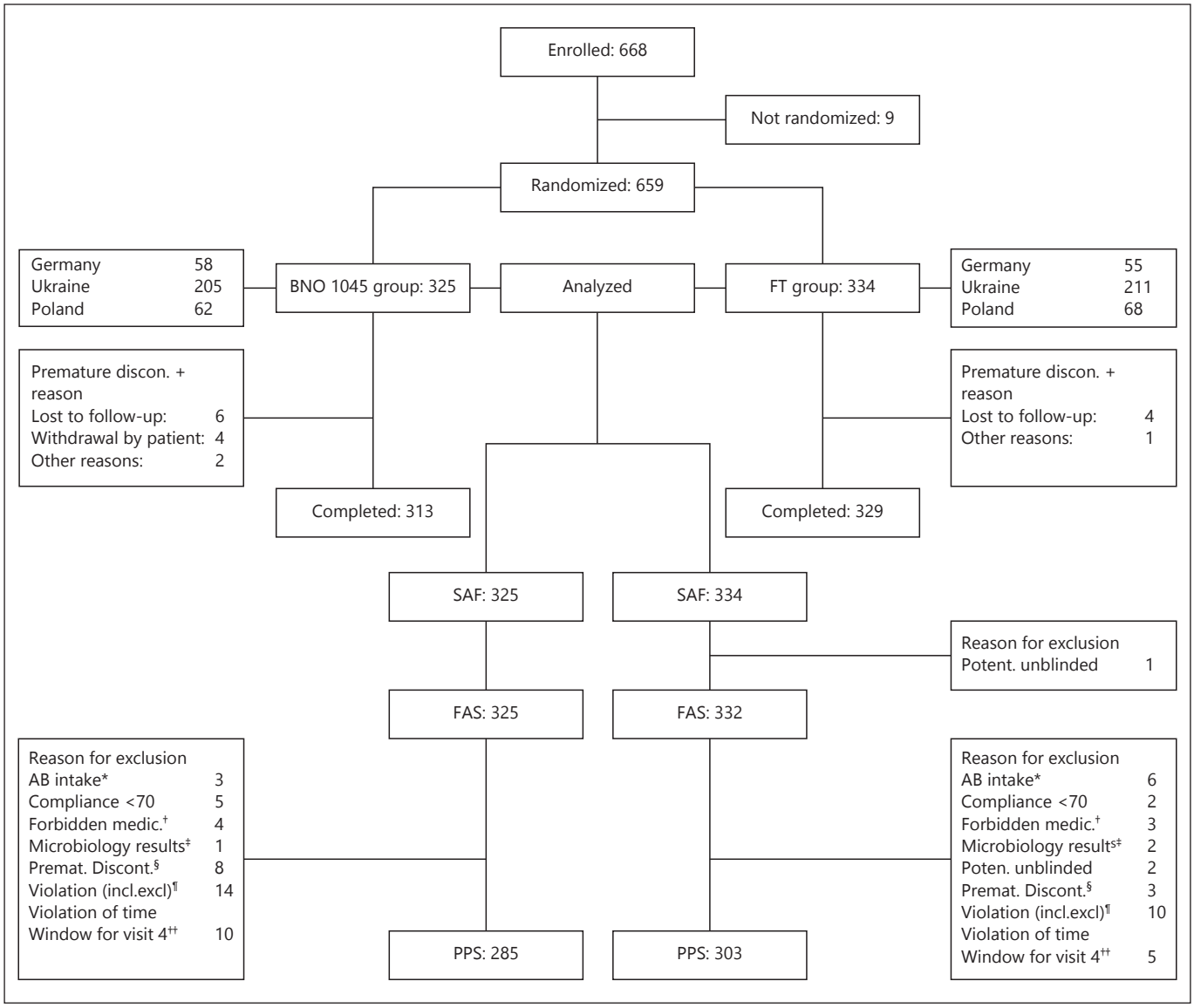


**Fig. 1.** Disposition of patients. * Additional AB intake with possible influence on uUTIs; † Forbidden medicine intake; ‡ Microbiology results requested (possible unblinding); § Premature discontinuation and no documentation of uUTIs relevant AB intake; ¶ Violation of inclusion/exclusion criteria; †† Violation of time window for V4. AB, antibiotic; FAS, full analysis set; FT, fosfomycin trometamol; PPS, per protocol set; SAF, safety analysis set.

ing sample distribution) and Hodges-Lehmann CIs (for a median-unbiased estimate of the population median). Bacterial count was evaluated categorically (colony-forming units [CFU] per mL of urine of $<10^3$, $10^3$, $10^4$, $10^5$, $10^6$ or $>10^6$) and comparisons between treatment groups were made using chi-square test. Comparisons of the proportion of patients who took paracetamol between treatment groups were also made using the chi-square test.

The statistical analysis for this trial did not account for multiple testing, as all secondary endpoints were analysed under the assumption that these endpoints were of an exploratory nature.

## Results

Between 10 February 2016 and 05 May 2017, a total of 668 patients were enrolled, and 659 were randomized; 325 were randomized to treatment with BNO 1045 and FT-matched placebo, and 334 were randomized to treatment with FT and BNO 1045-matched placebo (Fig. 1). Nine patients not fulfilling all inclusion criteria or with at least 1 exclusion criterion were not randomized and were not treated.

**Table 1.** Patient characteristics in the PPS, measured on Day 1

| Characteristic | Category | BNO 1045 (*N* = 285) | FT (*N* = 303)* | Total (*N* = 588) |
|---|---|---|---|---|
| Age, years | Mean (SD) | 43.7 (15.57) | 45.0 (16.41) | 44.3 (16.00) |
| | Median (range) | 42.0 (18–70) | 46.0 (18–74) | 44.0 (18–74) |
| Race, *n* (%) | Caucasian | 281 (98.6) | 299 (98.7) | 580 (98.6) |
| | Other† | 4 (1.4) | 4 (1.3) | 8 (1.4) |
| Weight, kg | *n* | 285 | 303 | 588 |
| | Mean (SD) | 68.9 (15.27) | 68.3 (14.45) | 68.6 (14.85) |
| | Median (range) | 67.4 (41–147) | 65.0 (43–126) | 66.0 (41–147) |
| Height, cm | *n* | 285 | 303 | 588 |
| | Mean (SD) | 165.2 (6.87) | 164.7 (6.11) | 165.0 (6.49) |
| | Median (range) | 165.0 (142–184) | 165.0 (149–187) | 165.0 (142–187) |
| Smoking status, *n* (%) | Smoker | 28 (9.8) | 38 (12.5) | 66 (11.2) |
| | Non-smoker | 238 (83.5) | 246 (81.2) | 484 (82.3) |
| | Ex-smoker | 19 (6.7) | 19 (6.3) | 38 (6.5) |
| Urine culture test, CFU/mL, % | $<10^3$ | 63 (20.9) | 78 (27.3) | 141 (24.0) |
| | $10^3$ | 92 (30.5) | 86 (30.2) | 178 (30.3) |
| | $10^4$ | 35 (11.6) | 29 (10.2) | 64 (10.9) |
| | $10^5$ | 37 (12.2) | 30 (10.5) | 67 (11.4) |
| | $10^6$ | 54 (17.9) | 47 (16.5) | 101 (17.2) |
| | $>10^6$ | 21 (7.0) | 15 (5.3) | 36 (6.1) |
| Menopausal status, *n* (%) | Pre-menopausal | 191 (67.0) | 192 (63.4) | 383 (65.1) |
| | Post-menopausal | 94 (33.0) | 111 (36.6) | 205 (34.9) |
| Sexual activity, *n* (%) | Not active | 95 (33.3) | 107 (35.3) | 202 (34.4) |
| | Active | 190 (66.7) | 195 (64.4) | 385 (65.5) |
| | Missing | 0 | 1 (0.3) | 1 (0.2) |
| Childbearing potential | Yes | 173 (60.7) | 180 (59.4) | 353 (60.0) |
| | No | 112 (39.3) | 123 (40.6) | 235 (40.0) |

* (*n* = 302) for urine culture test results.
† Grouped into one category for data protection reasons.
FT, fosfomycin trometamol; *N*, number of patients in treatment group; *n*, number of patients with data; %, percentage based on *N*; PPS, per-protocol set.

Table 1 shows the characteristics of participants in the PPS measured on Day 1. Most patients were Caucasian (98.6%) and non-smokers (82.3%). The mean age was 44.3 years, mean weight was 68.6 kg, and the mean height was 165.0 cm. The majority of patients were premenopausal (65.1%), with child-bearing potential (60.0%) and were sexually active (65.5%). Approximately 25% of the patients had typical symptoms of acute lower uUTIs and pyuria (see inclusion criteria), but their urine cultures had $<10^3$ CFU/mL on Day 1.

The majority of patients did not take an additional AB between Days 1 and 38 in the BNO 1045 group (*n* = 238; 83.5%) and the FT group (*n* = 272; 89.8%; Fig. 2). The estimated differences between treatment groups in the PPS were within the non-inferiority margin of 15% (difference in non-AB rate: –6.26%; 95% CI –11.99 to –0.53%; 2-sided $p = 0.0014$). The robustness of the results was confirmed by analysing the non-inferiority of BNO 1045 to FT in the FAS (difference in non-AB rate: –8.25%; 95% CI –13.82 to –2.68%; 2-sided $p = 0.0088$). A sensitivity analysis of the FAS did not show substantial influence of the missing values in the PPS, providing further support for the statistical significance of the primary endpoint.

A further sensitivity analysis of the PPS, using a logistic regression model with patients' status of AB intake (yes/no) as a dependent variable, age as a covariate, and treatment, sexual activity and treatment with hormones as factors, revealed no impact of these factors on the primary endpoint ($p > 0.05$).

The AB-rates were comparable across the different reasons for additional AB intake during the clinical trial (persistent or worsening symptoms: BNO 1045: 66.0% and FT: 67.7%; recurrent symptoms: BNO 1045: 23.4%

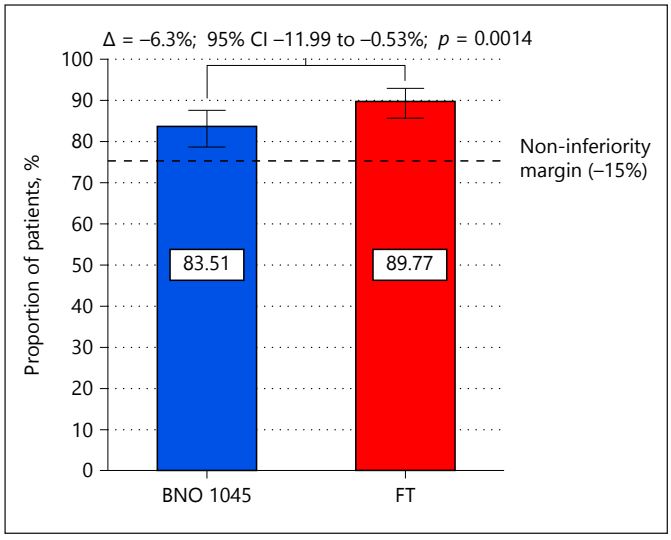


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**Fig. 2.** Non-inferiority of BNO 1045 vs FT (non-AB rate) in the PPS. Percentages are the proportion of patients within each respective treatment group who did not take AB between Day 1 and 38 ± 3. Error bars represent the 95% CIs. Comparison of the non-AB rates between treatments was performed by means of Farrington and Manning test statistics, with 2-sided 95% confidence limits and 2-sided *p* values for the difference in non-AB rates between the groups. FT, fosfomycin trometamol.

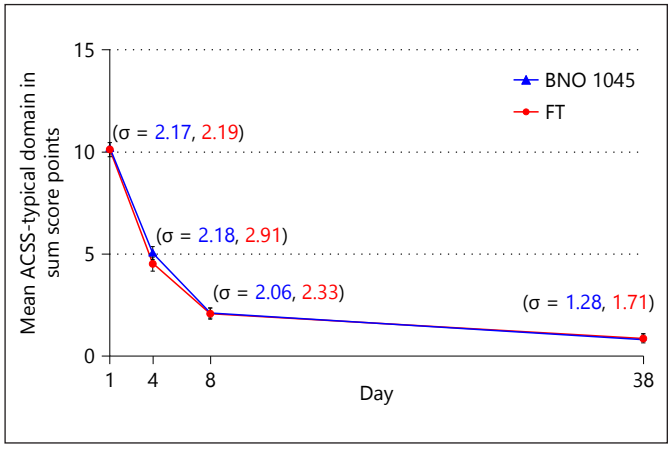


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**Fig. 3.** Comparison of mean sum-scores of the ACSS-typical domain between Days 1 and 38 ± 3 (FAS). Datapoints are mean ACSS-typical domain sum-scores for each respective treatment group at each timepoint. Error bars represent Hodges-Lehman confidence intervals. Numbers in parenthesis are the standard deviations (σ) for BNO 1045 and FT sum-scores respectively. ACSS, Acute Cystitis Symptom Score; FAS, full analysis set; FT, fosfomycin trometamol.

and FT: 25.8%; no symptoms reported: BNO 1045: 10.6% and FT: 6.5%).

Mean sum-scores of the ACSS-typical domain in the FAS were comparable between groups on Day 1 (BNO 1045: 10.2; FT: 10.1), and substantially decreased at Day 4 (BNO 1045: 5.1, FT: 4.5), by the end of treatment (BNO 1045: 2.1; FT: 2.1) and the end of follow-up (BNO 1045: 0.8; FT: 0.9; Fig. 3). A Hodges-Lehmann test comparison of mean ACSS-typical sum-scores between groups indicated that the decrease was slightly higher in the FT group at Day 4 ($p = 0.0166$) but comparable at the end of treatment and the end of follow-up periods ($p > 0.05$).

Overall, ACSS questionnaire results indicated a trend towards decreasing lower uUTI symptom severity over time and increasing QoL, according to the use of a 4-point Likert scale, with BNO 1045. These results were comparable to a decrease in lower uUTI symptom severity and increasing QoL seen in patients treated with FT (Fig. 4).

The proportion of patients in the FAS without significant bacteriuria ($<10^3$ CFU/mL) increased from Day 1 to end of treatment in both groups (BNO 1045: from 25.5% [$n = 83$] to 31.1% [$n = 101$]; FT: from 21.4% [$n = 71$] to 36.7% [$n = 122$]). The difference between groups in the incidence of bacteriuria at end of treatment appeared to be in favour of FT treatment ($p = 0.028$). Leukocyturia was reported to decrease from Day 1 to approximately one third of patients in the FAS population at Day 8 (BNO 1045: from 100.0% [$n = 325$] to 37.2% [$n = 121$]; FT: from 100.0% [$n = 332$] to 34.9% [$n = 116$]). There were no significant differences between the groups with respect to the frequency of leukocyturia at Day 8.

More than 95% of the patients in both treatment groups (FAS) did not take paracetamol within 24 h prior to any of the trial visits, with no difference between the groups ($p > 0.05$).

Overall, 92 (14.0%) patients experienced at least 1 TEAE during the clinical trial. Numbers were similar between groups (BNO 1045: 49 [15.1%] patients; FT: 43 [12.9%] patients; Table 2).

The most commonly reported TEAEs were gastrointestinal disorders, which were reported with a higher frequency in the FT group (22 patients) than in the BNO 1045 group (13 patients). Three serious TEAEs were reported by 2 patients during the trial; 1 patient in the FT group experienced exacerbation of chronic pancreatitis and femoral neck fracture, and 1 patient in the BNO 1045 group experienced pyelonephritis of moderate intensity. None of the serious TEAEs were considered by the investigator to be related to the IMP.

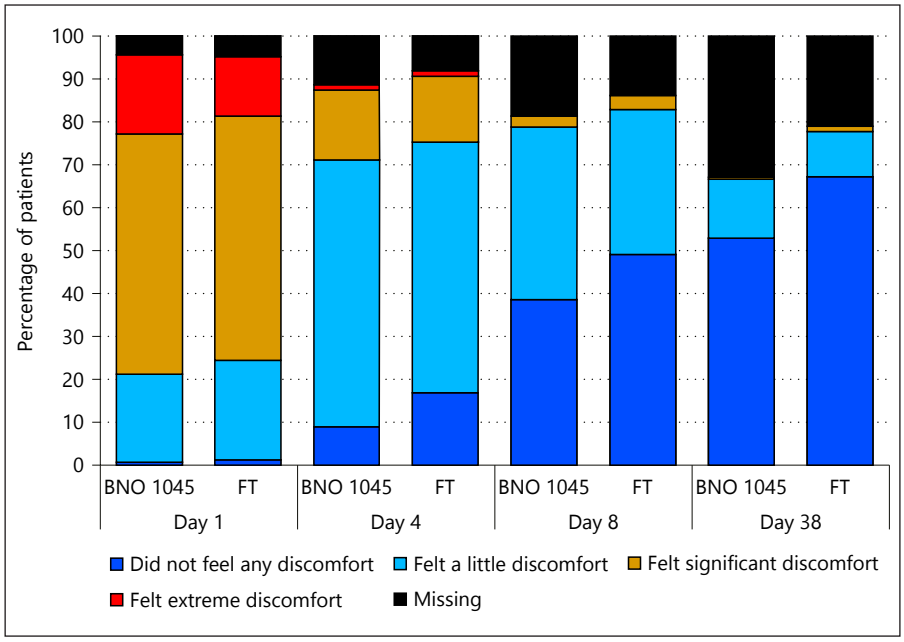


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**Fig. 4.** ACSS-QoL, discomfort because of symptoms in past 24 h (FAS). ACSS-QoL, Acute Cystitis Symptom Score-Quality of Life; FAS, full analysis set; FT, fosfomycin trometamol.

The overall incidence of pyelonephritis was low; nevertheless, a higher number of patients reported pyelonephritis in the BNO 1045 group ($n$ = 5, 4 of mild and 1 of moderate intensity) than in the FT group ($n$ = 1, mild intensity). In the BNO 1045 group, 3 of the 5 pyelonephritis events occurred on the same day (1 event), or 1 day after enrolment (2 events), indicating that pyelonephritis may have already been developing without different diagnostic signs on Day 1.

No patient discontinued the clinical trial due to a TEAE and no patient died during the trial.

## Discussion

This clinical trial of a large cohort of women with acute lower uUTIs demonstrates non-inferiority of a herbal medicine versus an AB for the treatment of acute lower uUTIs. Symptomatic treatment with BNO 1045 was non-inferior to AB treatment with FT in terms of prevention of additional intake of ABs for the treatment of acute lower uUTIs in women. These data makes a compelling case for replacing AB prescription with symptomatic treatment with BNO 1045 for the treatment of lower uUTIs and encourages further research in the area of herbal alternatives to ABs in lower uUTIs.

Current EAU practice guidelines [4] recommend the use of ABs as first choice for the treatment of UTIs. Given that UTIs are among the most prevalent infectious diseases seen in general practice [1, 2], this recommendation may represent a significant contribution to the growing global problem of ABs resistance.

On this basis, it is paramount that potential alternative strategies are identified. Previous studies have suggested that overall AB use could be greatly reduced by initial symptomatic treatment of lower uUTIs with NSAIDs [9, 10], even though symptomatic treatment with these agents is clinically inferior to ABs. Nevertheless, these results were compelling enough for the German Clinical Guidelines [22] to encourage the use of non-AB symptomatic treatment in cases of acute lower uUTIs with mild-to-moderate symptoms.

Indeed, Kronenberg et al. [10] have suggested that a combination approach of symptomatic treatment with the option of deferred selective AB treatment could substantially reduce overall AB use. As 83.5% of patients treated with BNO 1045 did not require further ABs for treatment of lower uUTIs, the use of this herbal alternative could reduce the outpatient demand for ABs for the treatment of lower uUTIs by over 80% (Fig. 2).

The results of the primary hypothesis tested in the PPS were supported by the analysis in the FAS, a subset that also included the results of the worse-case scenario of imputed values for the intake of additional ABs between Days 1 and 38. The shown non-inferiority between treatments did not appear to be influenced by the patients' age, sexual activity, or treatment with hormones.

**Table 2.** TEAEs by MedDRA system organ class in the SAF (occurrence >1 patient in either treatment group)

| System organ class preferred term | BNO 1045 group (*N* = 325) | | FT group (*N* = 334) | | Total (*N* =659) | |
|---|---|---|---|---|---|---|
| | *n*1 | *n*2 (%) | *n*1 | *n*2 (%) | *n*1 | *n*2 (%) |
| All TEAEs | 68 | 49 (15.1) | 64 | 43 (12.9) | 132 | 92 (14.0) |
| Blood and lymphatic system disorders | 3 | 2 (0.6) | 0 | 0 | 3 | 2 (0.3) |
| Ear and labyrinth disorders | 0 | 0 | 2 | 2 (0.6) | 2 | 2 (0.3) |
| Gastrointestinal disorders | 14 | 13 (4.0) | 27 | 22 (6.6) | 41 | 35 (5.3) |
| Abdominal pain | 0 | 0 | 4 | 4 (1.2) | 4 | 4 (0.6) |
| Abdominal pain (lower) | 2 | 2 (0.6) | 0 | 0 | 2 | 2 (0.3) |
| Abdominal pain (upper) | 1 | 1 (0.3) | 2 | 2 (0.6) | 3 | 3 (0.5) |
| Diarrhoea | 3 | 3 (0.9) | 11 | 10 (3.0) | 14 | 13 (2.0) |
| Nausea | 2 | 2 (0.6) | 4 | 4 (1.2) | 6 | 6 (0.9) |
| Vomiting | 2 | 2 (0.6) | 1 | 1 (0.3) | 3 | 3 (0.5) |
| General disorders and administration site conditions | 2 | 2 (0.6) | 1 | 1 (0.3) | 3 | 3 (0.5) |
| Infections and infestations | 17 | 17 (5.2) | 17 | 16 (4.8) | 34 | 33 (5.0) |
| Laryngitis | 0 | 0 | 2 | 2 (0.6) | 2 | 2 (0.3) |
| Pyelonephritis | 3 | 3 (0.9) | 1 | 1 (0.3) | 4 | 4 (0.6) |
| Pyelonephritis (acute) | 2 | 2 (0.6) | 0 | 0 | 2 | 2 (0.3) |
| Respiratory tract infection | 2 | 2 (0.6) | 0 | 0 | 2 | 2 (0.3) |
| Respiratory tract infection (viral) | 1 | 1 (0.3) | 2 | 2 (0.6) | 3 | 3 (0.5) |
| Upper respiratory tract infection (viral) | 5 | 5 (1.5) | 8 | 8 (2.4) | 13 | 13 (2.0) |
| Investigations | 8 | 6 (1.8) | 3 | 1 (0.3) | 11 | 7 (1.1) |
| C-reactive protein increased | 3 | 3 (0.9) | 0 | 0 | 3 | 3 (0.5) |
| Gamma-glutamyl transferase increased | 2 | 2 (0.6) | 1 | 1 (0.3) | 3 | 3 (0.5) |
| Metabolism and nutrition disorders | 2 | 2 (0.6) | 2 | 2 (0.6) | 4 | 4 (0.6) |
| Hyperglycaemia | 2 | 2 (0.6) | 0 | 0 | 2 | 2 (0.3) |
| Musculoskeletal and connective tissue disorders | 4 | 3 (0.9) | 3 | 3 (0.9) | 7 | 6 (0.9) |
| Nervous system disorders | 8 | 7 (2.2) | 3 | 3 (0.9) | 11 | 10 (1.5) |
| Dysgeusia | 2 | 2 (0.6) | 0 | 0 | 2 | 2 (0.3) |
| Headache | 5 | 4 (1.2) | 2 | 2 (0.6) | 7 | 6 (0.9) |
| Renal and urinary disorders | 3 | 3 (0.9) | 2 | 2 (0.6) | 5 | 5 (0.8) |
| Glycosuria | 2 | 2 (0.6) | 0 | 0 | 2 | 2 (0.3) |
| Reproductive system and breast disorders | 5 | 5 (1.5) | 1 | 1 (0.3) | 6 | 6 (0.9) |
| Vaginal discharge | 2 | 2 (0.6) | 0 | 0 | 2 | 2 (0.3) |

FT, fosfomycin trometamol; MedDRA, Medical Dictionary for Regulatory Activities; *N*, number of patients in treatment group; *n*1, number of adverse events; *n*2, number of patients with at least one adverse event; %, percentage of patients with respective TEAE based on *N*; SAF, safety analysis set; TEAE, treatment-emergent adverse event.

The clinical benefit of both treatments on reduction of the main ACSS-typical symptoms was observed after 3 days of treatment (at Day 4), though with a higher average reduction in patients treated with FT versus BNO 1045 ($p$ = 0.0166). These results corroborate those shown in Kronenberg et al. [10], where symptoms took longer to resolve with an NSAID (4 days) than with AB treatment (2 days). Nevertheless, in the present clinical trial, there was a clear trend overall towards a substantial reduction in lower uUTIs symptom severity and increase in QoL at the end of the 7-day treatment period, indicating that the overall effect of BNO 1045 was comparable to FT in this population.

BNO 1045 was generally well tolerated; there were no marked differences in adverse events or safety signals between BNO 1045 and FT treatment groups other than a lower number of gastrointestinal disorders reported in the BNO 1045 group (4.0%) compared with the FT group (6.6%), and a non-significant higher number of pyelonephritis cases were reported in the BNO 1045 group (1.5%) compared with the FT group (0.3%). The higher rate of pyelonephritis is not unexpected, given that the baseline risk in lower uUTIs appears to be between 1 and 2% in placebo-controlled trials [23, 24]. Indeed, higher rates of pyelonephritis have been previous-

ly reported for ibuprofen (2.1%) versus AB (0.4%) [8], and for diclofenac (4.5%) versus AB (0.0%) [10]. Therefore, it would be reasonable to infer that treatment with BNO 1045 compared to AB does not present an elevated risk to the patient, particularly given that symptoms indicative of upper UTIs would necessitate AB therapy. However, further studies should seek to provide further evidence on the incidence of pyelonephritis with BNO 1045.

Our trial did have some limitations, including the fact that urine cultures were negative in approximately 1 quarter of patients. There are 2 possible reasons for this finding. First, the detection limit of $10^3$ CFU/mL may have missed low numbers of uropathogenic *E. coli* [25, 26]. However, the inclusion of patients with a certain severity of symptoms in this trial may have been justified, given that urinary symptoms and bacteriuria often occur independently of one another [27]. Second, transportation of urine samples in borate tubes from some clinical centres to the central laboratory took longer than 24 h, which may have affected the results [28]. In addition, the study relied on patient self-reporting to determine whether additional antibiotics were taken and patient adherence to the BNO 1045 protocol. Finally, the criteria to qualify for additional antibiotic treatment were defined as deemed necessary by the investigator for patients with worsening of uUTI; these criteria may have varied among investigator sites.

Overall, the present clinical trial lends further support to the viability of symptomatic treatment alternatives of acute lower uUTIs to ABs, and does so in a large patient population by demonstrating non-inferiority of a herbal treatment alternative, which had fewer gastrointestinal side effects such as diarrhoea and abdominal pain compared to ABs. Alongside previous study results [8–10], the current trial may inform treatment choices and encourage wider adoption of AB alternatives, such as BNO 1045, for the treatment of lower uUTIs in routine clinical practice.


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This clinical trial has been registered on clinicaltrials.gov as NCT02639520 and on EudraCT as 2013-004529-99. The trial protocol, informed consent document(s), and any other appropriate trial-related documents were reviewed and approved by an independent Ethics Committee.

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This clinical trial was sponsored by Bionorica SE, Germany, and coordinated by the contract research organization Clinipace Worldwide (CPWW). Employees of Bionorica SE had a role in trial design, data analysis, and data interpretation. Prof. Wagenlehner was responsible for data collection and double-checking of data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Author Contribution

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare funding and support have been provided by Bionorica SE to aid in the conduct of the study. F.M.W. reports personal consulting fees and other fees from Bionorica SE during the conduct of the study; personal fees outside the submitted work from Achaogen, AstraZeneca, Janssen, LeoPharma, MerLion, MSD, OM Pharma/Vifor Pharma, Pfizer, RosenPharma and VenatoRx; and other fees outside the submitted work from Enteris BioPharma, Helperby Therapeutics and Shionogi. K.G.N. reports personal consulting fees from Bionorica SE during the conduct of the study, and personal fees outside the submitted work from Adamed, Apogepha, DaiichiSankyo, Enteris, GSK, Helperby, Hermes, Medice, MerLion, OM Pharma/Vifor, Paratek, Roche, Saxonia and Zambon. DAS, HS and MH are employees of Bionorica SE.

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