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# Acute Cystitis Symptom Score questionnaire for measuring patient-reported outcomes in women with acute uncomplicated cystitis: Clinical validation as part of a phase III trial comparing antibiotic and nonantibiotic therapy

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**Purpose:** The Acute Cystitis Symptom Score (ACSS) used in a clinical trial comparing the phytodrug Canephron®N (BNO 1045) with an antibacterial agent (fosfomycin trometamol [FT]) in the treatment of acute uncomplicated cystitis (AC) in women was evaluated as a patient-reported outcome measure in a *post hoc* analysis.

**Materials and Methods:** This double-blind, randomized, multicenter, phase III noninferiority trial was performed in 51 centers in Europe. The ACSS questionnaire was used to assess severity and course of symptoms.

**Results:** The *post hoc* analysis included 325 patients treated with BNO 1045 and 332 patients treated with FT (total of 657 patients). The mean sum-scores of the ACSS-typical domain were comparable between groups on day 1 (BNO 1045: 10.2; FT: 10.1), and then decreased on day 4 (BNO 1045: 5.1; FT: 4.5), at end of treatment on day 8 (BNO 1045: 2.1; FT: 2.1), and at late follow-up on day 38 (BNO 1045: 0.8; FT: 0.9). Predefined thresholds using the scoring system of the ACSS could be established and validated to define "clinical cure."

**Conclusions:** Evaluating not only antibacterial but also nonantibacterial agents indicated for the treatment of AC in women, clinical criteria for diagnostics, and measures of patient-reported outcomes are more important as main objectives than microbiological criteria. In this *post hoc* evaluation, we showed that the ACSS questionnaire, validated in several languages, has the potential to be used as a suitable instrument for diagnostics and patient-reported outcomes in well-designed, international, clinical studies investigating different treatment modalities of uncomplicated urinary tract infections.

**Keywords:** Canephron; Fosfomycin; Patient reported outcome; Questionnaires; Urinary tract infections



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## INTRODUCTION

Urinary tract infections (UTIs) are among the most prevalent infections in general practice, and of these, 80% are classified as uncomplicated UTIs (uUTIs) [1,2]. Several prospective, randomized, placebo-controlled studies have been performed to compare antibacterial with symptomatic therapy for uncomplicated acute cystitis (AC) in women [3-7]. These results were compelling enough for the updated German Clinical Guidelines [8] to encourage the use of nonantibiotic, symptomatic treatment in selected cases of AC with mild-to-moderate symptoms. In order to test not only antibacterial but also nonantibacterial agents properly, commonly accepted guidelines for well-designed, randomized clinical trials are needed.

For nonantibacterial agents the elimination of bacteriuria cannot be one of the main objectives, especially since it is known that urine from healthy subjects is not sterile [9,10], and asymptomatic bacteriuria may even be protective against the recurrence of UTI [11,12]. For such guidelines, clinical criteria should become the main inclusion and outcome criteria, although microbiological investigations may be included, especially if antibacterial and nonantibacterial approaches are compared directly. Although the clinical diagnosis of uUTI is based mainly on history and typical symptoms, these symptoms are not found exclusively in patients with AC. Therefore, not only the presence but also the severity of these symptoms (scoring) and probably also their impact on quality of life (QoL) are important. In clinical trials, a patient-reported outcome measure can be used to measure the effect of a medical intervention on one or more concepts [13].

The Acute Cystitis Symptom Score (ACSS) questionnaire has proven to be useful for clinically diagnosing AC in women [14-17]. The ACSS is now available, translated, and validated in several languages (www.acss.world). In two smaller and one larger noninterventional study, the ACSS was evaluated as a measure of patient-reported outcomes [18-20]. The ACSS has now been used in a larger prospective phase III trial comparing the outcome of an antibacterial agent (a single oral dose of fosfomycin trometamol [FT]) with that of a herbal treatment (Canephron®N [BNO 1045]; 2 dragées three times daily for 7 days) in women with AC [5]. BNO 1045 has been used for the treatment of AC for over 30 years. The preclinical *in vitro* and *in vivo* data suggest that BNO 1045 has the potential for effective treatment of AC-related inflammation and pain [21]. The clinical efficacy of BNO 1045 has been proven in several studies [22]. With the data of this recent clinical trial [5], additional assessment of the ACSS as a patient-reported outcome measure can be performed and compared with results obtained by the earlier noninterventional studies [18-20].

## MATERIALS AND METHODS

### 1. Trial design

This was a double-blind, controlled, double-dummy, parallel-group, randomized, multicenter, multinational phase III noninferiority trial conducted in 51 centers 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. The trial protocol, informed consent document(s), and any other appropriate trial-related documents were reviewed and approved by independent Ethics Committees. According to national regulatory requirements the trial was approved in Germany by the Central Ethics Committee of the Department of Medicine of Justus Liebig University Giessen (reference number: 150/15) and in Poland by the Central Bioethics Committee at the Lower Silesian Medical Chamber in Wroclaw (reference number 24/05/2016). In Ukraine the trial was approved by the respective local ethics committee of each investigator. Informed consent was obtained from all participants in writing. The informed consent process as well as the trial conduct were in compliance with International Conference on Harmonization-Good Clinical Practice.

### 2. Patients

Eligible patients were women aged 18 to 70 years with a sum score of ≥6 for the three main ACSS-typical symptoms (dysuria, urinary frequency, and urgency) on day 1 in combination with a positive result on an esterase test showing leukocyturia. The study design, inclusion and exclusion criteria, and the patients' characteristics are listed in the Supplementary material [5].

### 3. 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; block size was not revealed to the investigators. Allocated treatment groups were unknown to both patients and the investigators.

### 4. Procedures

Patients in the FT group were given 5.631 g FT (equivalent to 3 g of fosfomycin) and those in the BNO 1045 group

were given 5.631 g placebo as granules dissolved in 100 to 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 18 mg powdered centaury herb (*Centaurii herba*), 18 mg lovage root (*Levistici radix*), and 18 mg rosemary leaves (*Rosmarini folium*) while patients in the FT group received tablets comparable in size, shape, color, and composition that contained placebo. BNO 1045 or BNO 1045 matched placebo tablets were administered orally as 2 coated tablets, 3 times a day, before or after meals for 7 days.

Treatment started on day 1 (visit 1) and lasted for 7 days until day 8 (visit 3). At day 4 (visit 2) an early clinical assessment was performed. Follow-up was 30 days after the last treatment date (day 38; visit 4) to evaluate sustained outcome as a secondary endpoint [23]. The only concomitant symptomatic treatment permitted was paracetamol, which was documented.

## 5. Outcomes

The primary objective of the clinical trial was to demonstrate the noninferiority 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 antibiotic for acute lower uUTIs during the trial until the follow-up visit [5]. Secondary efficacy endpoints included clinical assessment by the ACSS questionnaire, as well as bacteriuria and leukocyturia based on the results of urinalysis and culture (midstream sample) at each on-site visit.

In addition, at the end of treatment (visit 3) and at the end of the follow-up period (visit 4), both the investigator and the patient (by investigator's interview) had to provide an overall assessment of treatment efficacy using the following scores on a 5-point verbal rating scale: very good=0 (symptoms healed, cured compared with the day of the start of treatment); good=1 (symptoms improved compared with the day of the start of treatment); moderate=2 (symptoms unchanged compared with the day of the start of treatment); poor=3 (symptoms deteriorated compared with the day of the start of treatment); and very poor=4 (symptoms clearly deteriorated compared with the day of the start of treatment). This 5-point rating scale questionnaire has been used successfully by Bionorica for several decades within clinical trials to determine the efficacy of different medicinal products in various indications.

## 6. Acute Cystitis Symptom Score (ACSS)

The ACSS questionnaire used in this study consists of two parts that 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 domain), symptoms (n=4) for differential diagnosis (ACSS-differential domain), questions (n=3) on quality of life (ACSS-QoL domain), and any additional conditions (n=5) that may affect therapy (ACSS-additional domain). 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 the ACSS-additional domain, which used yes/no questions.

Part B included all sections of Part A with an additional section assessing changes in UTI symptoms ("dynamics" domain) at a follow-up 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.

## 7. Analysis approach

The dynamics domain of the "follow-up Part B" form of the ACSS and the assessment of overall efficacy by the investigator and patient were considered for evaluation of clinical outcome. For the purpose of dichotomization, items rated 0 and 1 in the dynamics domain and "very good" and "good" by the investigator or patient were merged and classified as "clinical cure." Consequently, the three remaining items were merged to "failure." All analyses were conducted on the full analysis set, which included all patients treated with the investigational medicinal product at least once and were not potentially unblinded.

## 8. Statistical analysis

Continuous and categorical variables were summarized by using ordinary descriptive statistics (n, mean, standard deviation [SD], median, and interquartile range) and frequency counts or percentages as appropriate.

The following different thresholds to define clinical cure were tested using the typical domain and the QoL domain of the ACSS, which were then compared with the dynamics domain of the ACSS ("very much better" plus "much better") and the overall assessments of the patients and the investigators ("very good" plus "good"), representing overall clinical success. Using the guidelines of the U.S. Food and Drug Administration (FDA) [23] and draft guidelines from the European Medicines Agency (EMA) [24], in which the four typical symptoms (FDA) of frequency, urgency, dysuria, and suprapubic pain or the three typi-



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cal symptoms (EMA) of frequency, urgency, and dysuria were mentioned for inclusion criteria were also evaluated by the ACSS scoring system, the following eight thresholds defining "clinical cure" were analyzed: A) typical domain of ACSS ≤5; B) typical domain of ACSS ≤4; C) typical domain of ACSS ≤5, no item >1; D) typical domain of ACSS ≤4, no item >1; E) typical domain of ACSS ≤5, no item >1, and no item of QoL >1; F) typical domain of ACSS ≤4, no item >1, and no item of QoL >1; G) four symptoms (adapted FDA) ≤4, no item >1; H) three symptoms (adapted EMA) ≤3, no item >1.

For all thresholds to define clinical cure, "no visible blood in urine" was required.

The predetermined thresholds were evaluated by the assessment of their relations with the overall outcome as reported by the patients in the dynamics domain of the ACSS and the assessment of overall efficacy by the investigator and the patient, respectively.

Diagnostic values such as sensitivity, specificity, Youden's index, positive and negative predictive values, positive and negative likelihood ratios, and the diagnostic odds ratio were calculated, and 95% confidence intervals (CIs) were calculated where appropriate.

Comparisons of the two treatment groups, who fulfilled the predetermined thresholds, were made using Fisher's exact test, differences in the sum score of the typical domain of the ACSS were assessed using the Wilcoxon–Mann–Whitney test. The distribution of the severity of typical symptoms, QoL, dynamics, and assessment of overall efficacy by investigator and patient was compared by using the chi-square test. A p-value of less than 0.05 was considered statistically significant. All analyses were considered *post hoc* without adjustment for multiplicity. SAS 9.4 (SAS Institute Inc., Cary, NC, USA; 2010) was used for statistical analysis and graphical presentations of results. Validation of the results was performed by an independent statistician.

## RESULTS

Between 10 February 2016 and 5 May 2017, a total of 668 patients were enrolled in 51 centers in Europe (16 in Germany, 22 in Ukraine, and 13 in Poland), and 659 patients were randomly assigned; 325 were randomly assigned to treatment with BNO 1045 and FT-matched placebo, and 334 were randomly assigned to treatment with FT and BNO 1045-matched placebo [5].

As reported earlier in the per-protocol set, between days 1 and 38, 238 patients (83.5%) in the BNO 1045 group and 272 patients (89.8%) in the FT group received no additional antibiotics [5]. At a 15% noninferiority margin, BNO 1045 was noninferior to FT in treating uUTIs (nonantibiotic rate difference: -6.26%; 95% CI, -11.99 to -0.53%; 2-sided p=0.0014). Adverse event rates were similar between the groups. The rate of gastrointestinal disorders was higher in the FT group (22 cases in the FT group versus 13 in the BNO 1045 group) and there were 5 cases (4 of mild and 1 of moderate intensity) of pyelonephritis in the BNO 1045 group compared with 1 case (mild intensity) in the FT group. More than 95% of the patients in both treatment groups (full analysis set) did not take paracetamol within 24 hours of any the trial visits, with no significant difference between the groups (p>0.05).

The current analysis was performed with data from patients of the full analysis set, who were treated with the investigational medicinal product at least once and were not potentially unblinded, consisting of 325 patients treated with BNO 1045 and 332 patients treated with FT (total, 657; Germany, 112; Poland, 129; Ukraine, 416) [5]. The mean sum-scores (SD) of the ACSS-typical domain in the full analysis set were comparable between groups on day 1 (BNO 1045: 10.2±2.17; FT: 10.1±2.19), and substantially decreased at day 4 (BNO 1045: 5.1±2.81; FT: 4.5±2.91), and by the end of treatment (BNO 1045: 2.1±2.06; FT: 2.1±2.33) and the end of follow-up (BNO 1045: 0.8±1.28; FT: 0.9±1.71) (Supplementary Table 1). Fig. 1 shows the distributions of the sum-scores of the typical domain between the two treatment groups illustrated as boxplots. Wilcoxon–Mann–Whitney test comparison of mean ACSS-typical sum-scores between the 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 at the end of the follow-up periods (p>0.05). Therefore, it was considered justified to validate the ACSS as a patient-reported outcome measure to analyze the combined ACSS data of

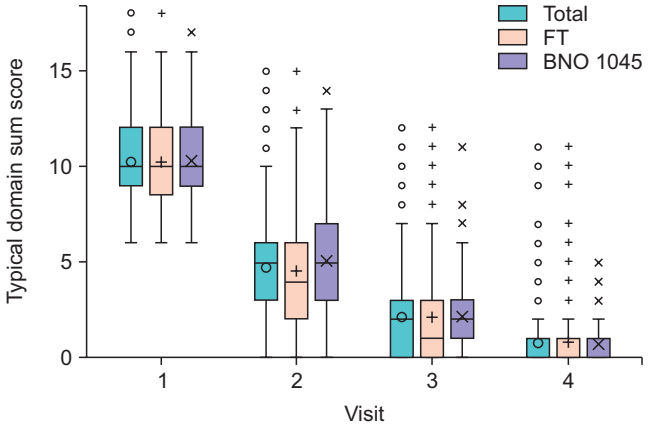


**Fig. 1.** Boxplots of Acute Cystitis Symptom Score typical domain sum score by visit and treatment in the full analysis set. FT, fosfomycin trometamol.

both groups (BNO 1045 and FT) together at the follow-up visits.

## 1. ACSS as a patient-reported outcome measure

The following parts of the ACSS were considered for validation: the questions (n=6) related to typical symptoms (ACSS-typical), the questions (n=3) on QoL (ACSS-QoL), and the questions (n=6) on changes in UTI symptoms (ACSS-dynamics) at a follow-up visit. The results were compared with the overall assessment by the patients and investigators to evaluate the efficacy of treatment with the investigational medicinal product.

Fig. 2 shows the severity of the individual typical symptoms of the ACSS at visits 1 to 4. At visit 1, most of the patients reported the five typical symptoms: frequent urination (99.8%), urgent urination (99.2%), dysuria (98.6%), incomplete bladder emptying (89.5%), and suprapubic pain (83.6%), but only 11.8% also complained about visible blood in urine, which is pathognomonic for hemorrhagic cystitis. In this trial the number of patients with visible blood in urine was rather small and almost not present at the follow-up visits. The other five symptoms showed distinct and somewhat parallel reductions in severity (Supplementary Table 2).

Fig. 3 shows the severity of the three categories of the QoL domain. At visit 1 most of the patients complained about some discomfort (99.0%) and interference with everyday activities or work (96.5%) or some impact on social activities (93.5%). The number of patients with a moderate to severe degree (together) of symptoms decreased for the three QoL categories distinctly from visit 1 to 4 (Supplementary

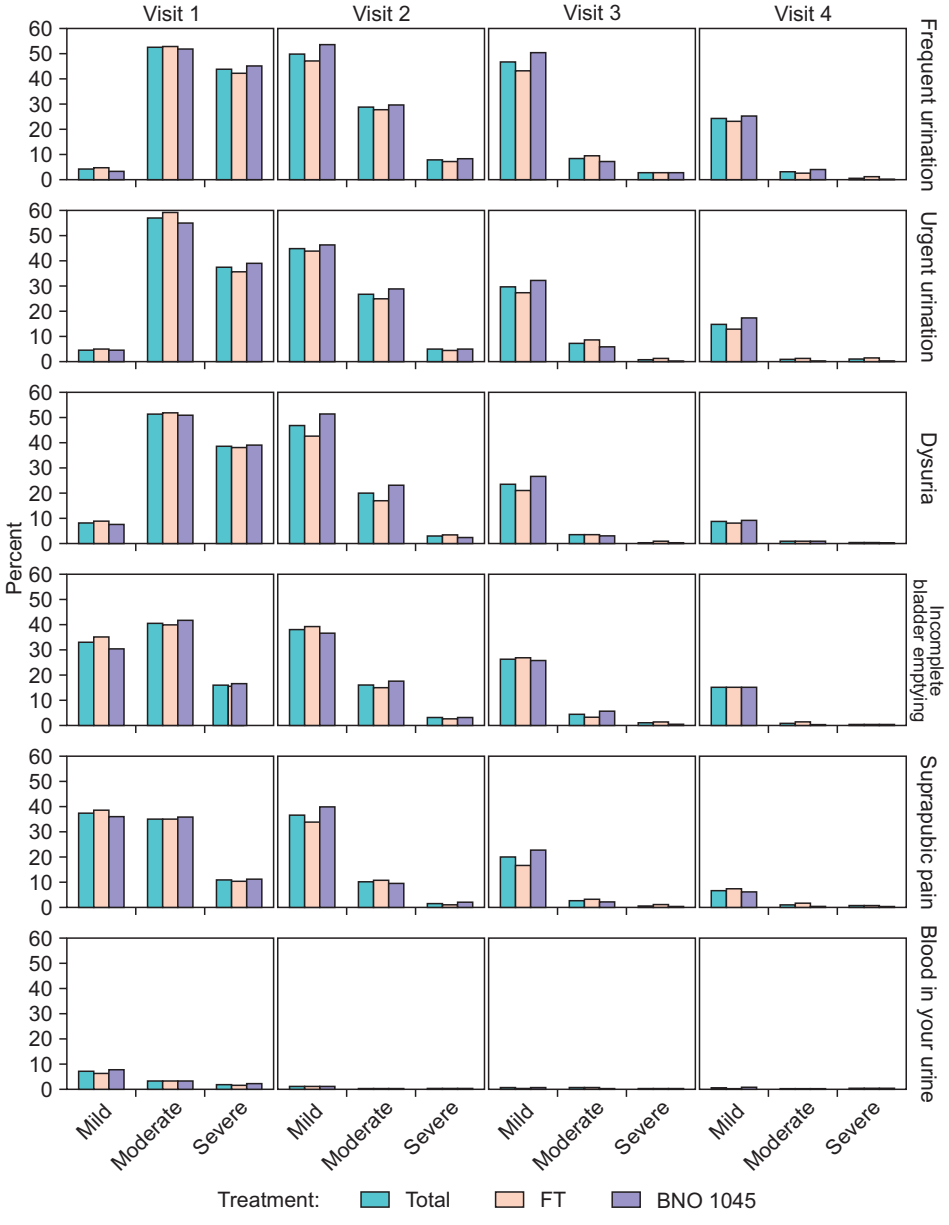


**Fig. 2.** Typical symptoms of the Acute Cystitis Symptom Score by visit and treatment in the full analysis set. FT, fosfomycin trometamol.



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Table 2).

Fig. 4 shows the results of the overall assessment by the patients and investigators to evaluate the efficacy of treatment. According to the dynamics domain of the ACSS, at visits 2, 3, and 4, the percentages of patients who rated the change in their condition as only a little better, no change, or worse were 58.0%, 21.6%, and 12.3%, respectively. According to the overall assessment by the investigator at visits 3 and 4, the percentages rating the changes as only moderate, poor, or very poor were 14.7% and 8.5%, respectively, and the corresponding percentages for the patients were 16.7% and 9.1% (Supplementary Table 2).

In Table 1 the percentages of patients achieving clinical cure for the different thresholds are presented. When comparing thresholds C (ACSS), G (adapted FDA), and H (adapted EMA), clinical cure was found in 45.2%, 47.6%, and 50.1% of patients at visit 2; in 81.5%, 83.2%, and 84.1% of patients at visit 3; and in 95.0%, 95.2%, and 95.6% of the patients at visit 4.

In Supplementary Table 3 the relations between ACSS thresholds A-F and the overall clinical assessment by the investigator and the patient or the dynamics domain (ACSS) are calculated for sensitivity (95% CI), specificity (95% CI), Youdens Index, positive and negative predictive values (95% CI), positive and negative likelihood ratios, and diagnostic odds ratio for visits 3 and 4; the corresponding ROC curves are shown in Supplementary Figs. 1–6.

Further informative data are shown for the typical symptoms domain (Supplementary Table 4), the QoL domain (Supplementary Table 5), and the dynamics of the ACSS and for the assessment of overall efficacy by investigator and patient (Supplementary Table 6) by visit and treatment in the full analysis set.

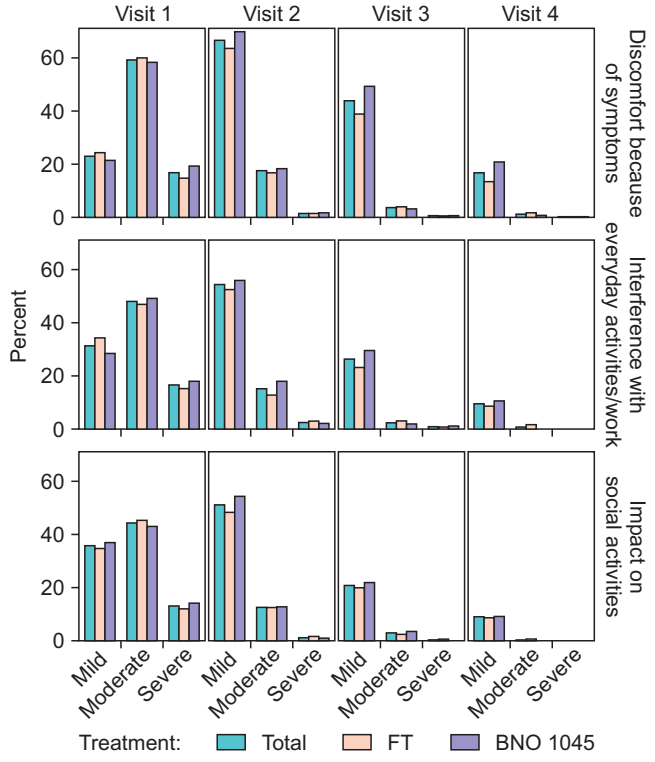


**Fig. 3.** Quality of life of Acute Cystitis Symptom Score by visit and treatment in the full analysis set. FT, fosfomycin trometamol.

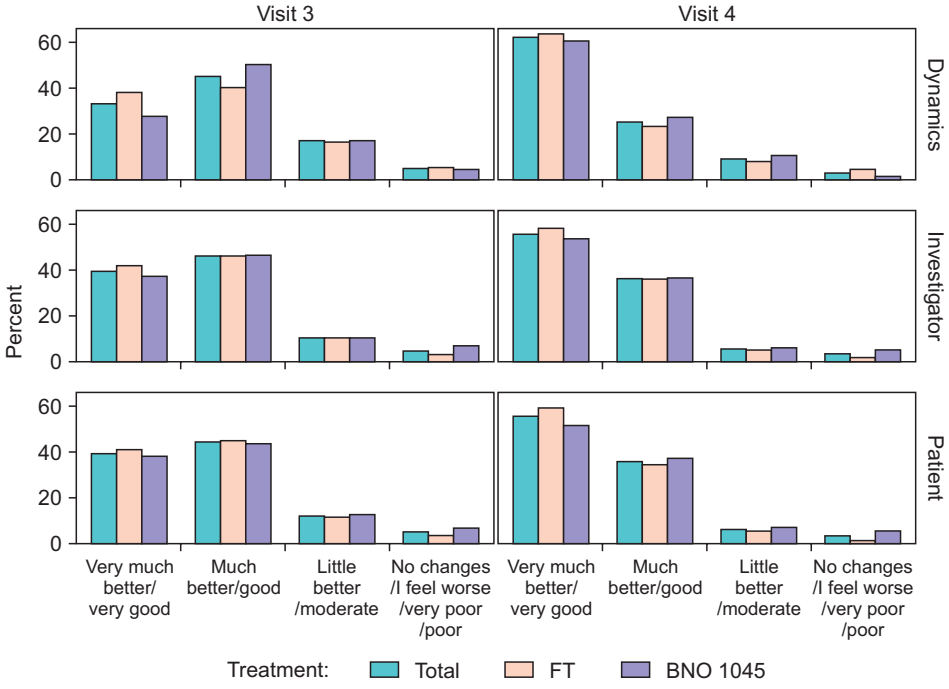


**Fig. 4.** Assessment of overall clinical efficacy using the dynamics domain of the Acute Cystitis Symptom Score and the assessment of overall clinical efficacy by the investigator (physician) and patient by visit and treatment in the full analysis set. FT, fosfomycin trometamol.

**Table 1.** Thresholds to define clinical cure by use of different criteria based on the Acute Cystitis Symptom Score by visit and treatment in the full analysis set

| ACSS Criterion | BNO 1045 | | FT | | Total | | |
|---|---|---|---|---|---|---|---|
| | (n, 100%) | Criterion fulfilled (%) | (n, 100%) | Criterion fulfilled (%) | (n, 100%) | Criterion fulfilled (%) | p-value[a] |
| Visit 2 | | | | | | | |
| A) Typical domain ≤5+condition 1 | 288 | 59.4 | 305 | 64.9 | 593 | 62.2 | 0.1756 |
| B) Typical domain ≤4+condition 1 | 288 | 43.4 | 305 | 54.4 | 593 | 49.1 | 0.0085 |
| C) Typical domain ≤5+condition 2 | 288 | 42.4 | 305 | 47.9 | 593 | 45.2 | 0.1872 |
| D) Typical domain ≤4+condition 2 | 288 | 36.5 | 305 | 44.6 | 593 | 40.6 | 0.0452 |
| E) Typical domain ≤5+condition 3 | 288 | 39.6 | 305 | 43.9 | 593 | 41.8 | 0.3176 |
| F) Typical domain ≤4+condition 3 | 288 | 35.4 | 305 | 41.0 | 593 | 38.3 | 0.1766 |
| G) FDA symptoms ≤4+condition 2 | 288 | 44.1 | 305 | 50.8 | 593 | 47.6 | 0.1180 |
| H) EMA symptoms ≤3+condition 2 | 288 | 45.8 | 305 | 54.1 | 593 | 50.1 | 0.0487 |
| Visit 3 | | | | | | | |
| A) Typical domain ≤5+condition 1 | 265 | 91.3 | 287 | 89.5 | 552 | 90.4 | 0.5635 |
| B) Typical domain ≤4+condition 1 | 265 | 84.2 | 287 | 85.7 | 552 | 85.0 | 0.6348 |
| C) Typical domain ≤5+condition 2 | 265 | 82.6 | 287 | 80.5 | 552 | 81.5 | 0.5833 |
| D) Typical domain ≤4+condition 2 | 265 | 80.0 | 287 | 78.7 | 552 | 79.3 | 0.7528 |
| E) Typical domain ≤5+condition 3 | 265 | 81.9 | 287 | 79.1 | 552 | 80.4 | 0.4526 |
| F) Typical domain ≤4+condition 3 | 265 | 79.2 | 287 | 77.4 | 552 | 78.3 | 0.6070 |
| G) FDA symptoms ≤4+condition 2 | 265 | 84.9 | 287 | 81.5 | 552 | 83.2 | 0.3073 |
| H) EMA symptoms ≤3+condition 2 | 265 | 85.7 | 287 | 82.6 | 552 | 84.1 | 0.3529 |
| Visit 4 | | | | | | | |
| A) Typical domain ≤5+condition 1 | 218 | 99.5 | 262 | 97.3 | 480 | 98.3 | 0.0772 |
| B) Typical domain ≤4+condition 1 | 218 | 96.8 | 262 | 94.3 | 480 | 95.4 | 0.2729 |
| C) Typical domain ≤5+condition 2 | 218 | 95.0 | 262 | 95.0 | 480 | 95.0 | 1.0000 |
| D) Typical domain ≤4+condition 2 | 218 | 93.1 | 262 | 93.1 | 480 | 93.1 | 1.0000 |
| E) Typical domain ≤5+condition 3 | 218 | 95.0 | 262 | 95.0 | 480 | 95.0 | 1.0000 |
| F) Typical domain ≤4+condition 3 | 218 | 93.1 | 262 | 93.1 | 480 | 93.1 | 1.0000 |
| G) FDA symptoms ≤4+condition 2 | 218 | 95.0 | 262 | 95.4 | 480 | 95.2 | 0.8331 |
| H) EMA symptoms ≤3+condition 2 | 218 | 95.0 | 262 | 96.2 | 480 | 95.6 | 0.6550 |

ACSS, Acute Cystitis Symptom Score; FT, fosfomycin trometamol; FDA, U.S. Food and Drug Administration; EMA, European Medicines Agency. Condition 1: visible blood in urine=0, condition 2: visible blood in urine=0 and no item >1, condition 3: visible blood in urine=0 and no item >1 and no item of quality of life >1. FDA symptoms: frequency, urgency, dysuria, and suprapubic pain. EMA symptoms: frequency, urgency, and dysuria.
[a]:Fisher's exact test.

## DISCUSSION

Current guidelines still recommend the use of antibiotics as the first choice of treatment for the acute phase of uUTIs [25]. However, frequent use of antibiotics can cause collateral damage to the microbiome [26] and increase the risk for antimicrobial resistance [27]. In order to combat the overuse of antibiotics and thus the rising rates of antimicrobial resistance, it is important to establish whether there are efficacious substitutes for antibiotics in the treatment of uUTIs. Commonly accepted guidelines for well-designed clinical studies are needed to test both antibacterial and nonantibacterial investigational medicinal products, indicated for the treatment of AC, for which clinical criteria for diagnostics and outcome need to be established as main objectives.

Questionnaires are commonly used to assess clinical criteria for diagnostics and outcome, such as the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) for the treatment of patients with chronic prostatitis [28]. For the diagnosis and treatment of uUTI in women, the UTI Symptom Assessment (UTISA) questionnaire was described by Clayson et al. [29], which also uses a scoring system of UTI symptoms and QoL assessment but does not include questions for differential diagnosis concerning pyelonephritis, fluor vaginalis, or sexual transmitted diseases, which can imitate so-called typical urinary symptoms, or questions concerning additional conditions like pregnancy, menopause, and diabetes mellitus.


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Since the ACSS questionnaire was used in this double-blind, controlled, double-dummy, parallel-group, randomized, multicenter, multinational phase III noninferiority trial in the treatment of AC, comparing a phytodrug (BNO 1045) with an antibacterial agent (FT) [5], its suitability as a patient-reported outcome measure could be validated and compared with the results of an earlier noninterventional study [20] in which the same clinical thresholds defining clinical cure could be tested.

The overall results of the three systems (ACSS, FDA, EMA) were fairly comparable if "clinical cure" was defined such that none of the symptoms reported by the patient had to be present at a severity degree of more than mild (lowest severity category), which corresponds to the thresholds of C (ACSS), G (adapted FDA), and H (adapted EMA) (Table 1). It should be noted; however, that the so-called typical symptoms mentioned in the FDA (4 symptoms) and EMA (3 symptoms) guidelines are unfortunately not obliged to be used by such a scoring system. In our opinion, this becomes necessary if a nonantibiotic approach is included in such a clinical study. Accordingly, therefore, clinical criteria such as patient-reported outcomes need to be considered as a primary endpoint. To achieve complete elimination of all symptoms does not seem realistic, because as discussed earlier, these symptoms may be typical for AC but are not found exclusively in female patients with AC. Besides symptom severity, the patient could also be asked about symptoms of discomfort (bothersomeness) and impact on daily and social activities (QoL domain), as is considered necessary for the patient-reported outcome measure by Holm et al [30]. Assessment of discomfort or QoL is not included in the guidelines of the FDA or EMA but can be performed by using the ACSS and the UTISA questionnaire. Unfortunately, we could not test the overall clinical assessments proposed in the guidelines of the FDA and EMA [23,24] in relation to the predetermined thresholds defining a clinical cure.

For the first time, the ACSS questionnaire was included in a double-blind, controlled, double-dummy, parallel-group, randomized, multicenter, multinational phase III noninferiority clinical trial for the treatment of AC in female patients comparing a phytodrug with an antibacterial agent. Our study showed that the ACSS questionnaire, validated in several languages, has the potential to be used as a suitable instrument for diagnostics and as a patient-reported outcome measure in well-designed prospective clinical studies investigating different treatment modalities of uUTI. The overall results confirmed the results obtained in the earlier, larger noninterventional study [20].

## CONCLUSIONS

To combat the overuse of antibiotics, nonantibacterial alternatives should be evaluated in the treatment of AC in female patients. In this case, elimination of bacteriuria may not be suitable as the main objective. Clinical criteria become more important for diagnostics and outcome measures. The ACSS questionnaire, which is validated in several languages, has the potential to be used as a suitable instrument for diagnostics and as a patient-reported outcome measure in well-designed, international, and multilingual clinical studies investigating different treatment modalities of uUTI.

## CONFLICTS OF INTEREST

Dr Jakhongir F. Alidjanov reports on fees from Bionorica SE and OM-Pharma/Vifor for his consultancy work.

Dr Andre Overesch, Dr Dimitri Abramov-Sommariva, Dr Martina Hoeller, and Dr Hubert Steindl are employees of Bionorica SE, Neumarkt, Germany.

Dr Florian M. Wagenlehner reports personal fees and other from Bionorica, during the conduct of the study; personal fees and other from Achaogen, personal fees from AstraZeneca, personal fees and other from Bionorica, other from Enteris BioPharma, other from Helperby Therapeutics, personal fees from Janssen, personal fees from LeoPharma, personal fees from MerLion, personal fees from MSD, personal fees and other from OM Pharma/Vifor Pharma, personal fees from Pfizer, personal fees from RosenPharma, personal fees and other from Shionogi, personal fees from VenatoRx, personal fees from GSK, other from Deutsches Zentrum für Infektionsforschung (DZIF) (Giessen-Marburg-Langen site), outside the submitted work.

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Research conception and design: all authors. Data acquisition: Andre Overesch, Dimitri Abramov-Sommariva, Martina Hoeller, and Hubert Steindl. Statistical analysis: Jakhongir F. Alidjanov, Andre Overesch, and Hubert Steindl. Data analysis and interpretation: all authors. Drafting of the manuscript: Jakhongir F. Alidjanov, Andre Overesch, Martina Hoeller, and Kurt G. Naber. Critical revision of the manuscript: all authors. Administrative, technical, or material support: Dimitri Abramov-Sommariva and Martina Hoeller. Supervision: Dimitri Abramov-Sommariva, Hubert Steindl, Florian M. Wagenlehner, and Kurt G. Naber. Approval of the final manuscript: all authors.

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## SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4111/icu.20200060.

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