Investigator's brochure

FOsfomycin Randomised controlled trial for E.coli Complicated urinary tract infections as Alternative Stepdown Treatment (FORECAST)

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1. SUMMARY

Urinary tract infections (UTI) are the most common bacterial infections seeking antibiotic treatment in the western world. The resistance rate of bacteria causing UTI for currently used oral antibiotic options is worrisome, i.e.beta-lactams, ciprofloxacin or trimethoprim-sulfamethoxazole. If no antibiotic options are available, patients need to receive the entire course intravenously, either in the hospital or provided at home by specialized personnel. The demand for alternative antibiotic options is urgent.

The FORECAST trial is a multicentre randomised double-blinded, double dummy trial. It aims to provide evidence for the efficacy and safety of the use of fosfomycin-trometamol as a stepdown treatment of complicated UTI (cUTI) in hospitalised patients after empiric adequate antibiotic treatment. After fulfilling entry criteria, patients will be allocated between the study medication, oral fosfomycin 3000mg every 24 hours or the current standard of care, oral ciprofloxacin 500mg every 12 hours. Patients will be treated for a total antibiotic duration of 10 days, including intravenous antibiotics. Ciprofloxacin, is chosen as 'standard of care' as it has the best safety and effectivity profile for this indication and it is the most prescribed antibiotic for this indication and. A double-dummy model is used as it is impossible to equalize ciprofloxacin and fosfomycin with regard to aspect. Therefore blinding is only possible if both are substituted by placebo's (see table 1).

Fosfomycin is registered worldwide for the oral use of uncomplicated UTI as an on-time gift therapy (fosfomycin-trometamol 3 gram). Fosfomycin is used in much higher dosages (up to 24 gram/24 hours) as a last-line intravenous option for soft tissue infections and sepsis (Fomicyt). The use of fosfomycin for both indications is considered safe; only few serious adverse events are described in human and tolerability is good. In animal studies, fosfomycin has only minor side effects, but no serious adverse events, acute nor chronic, and no hazardous effects have been found concerning fertility, teratology, mutagenicity or carcinogenicity. The pharmacodynamic, pharmacokinetic properties and the low resistance rates of common UTI causing Escherichia *coli*, makes fosfomycin-trometamol an attractive candidate for the stepdown treatment of E.coli AF-UTI.

Overall, the risk for patients to participate in the FORECAST trial is considered low. The efficacy and safety will be closely monitored throughout the trial.

2. INTRODUCTION

This investigator brochure provides information about the medicinal products that are used in the FORECAST trial.

Complicated UTI (cUTI) infections are a frequent reason for admittance to the emergency ward and hospitalization (1). If a patient is hospitalised for the treatment of acute febrile UTI, usually antibiotics are empirically administered intravenously. If the patient shows clinical improvement and the criteria for a safe intravenous-to-oral antibiotic switch are fulfilled, a switch can be made to oral antibiotics and the patient could be discharged subsequently. The Dutch guidelines advice a total antibiotic therapy for cUTI of 10-14 days, with the exception of a 7-day treatment with fluorquinolones for uncomplicated pyelonephritis in women (1,2). Only few oral antibiotic options are available for this stepdown treatment, as sufficient levels in affected body compartments have to be achieved and the pathogen must be susceptible. Often used oral antibiotics for this indication are amoxicillin, amoxicillin + clavulanic acid, ciprofloxacin and trimethoprim-sulfamethoxazole (1). However, the level of antibiotic resistance of common pathogens of cUTI for these antibiotics is worrisome, which gives rise to the search of alternative antibiotic options (3).

The rationale to use fosfomycin-trometamol as a stepdown therapy for cUTI is based on several arguments. First, fosfomycin-trometamol has been used for the treatment of uncomplicated UTI where it is non-inferior to nitrofurantoin and trimethoprim and has good clinical (90%) and bacterial (78%) cure rates and little side effects (5.3%) (4) (5).The summary of product characteristics of Monuril 3000 (fosfomycin-trometamol 3000mg) could be found on the Dutch website of the ‘college ter beoordeling van geneesmiddelen’ (6). Second, the pharmacokinetic characteristics of fosfomycin-trometamol favor the use as a stepdown therapy for E. coli cUTI, reaching moderate concentrations in serum, and high concentrations in urine and bladder wall (7–9). Third, in vitro microbiological activity was demonstrated in gram-negative-bacteria as well as in gram-positive-bacteria. The resistance rate of pathogens causing UTI for fosfomycin is low, especially for E.coli, even for Extended Spectrum Beta Lactamases (ESBL’s) producing bacteria (3). Fourth, the existing literature reports a good clinical efficacy of fosfomycin-trometamol as an initial and stepdown treatment for cUTI, which is promising for its use as a stepdown treatment (10–12). Fifth, the safety profile of fosfomycin is considered good, when used as a single oral gift of fosfomycin-trometamol and for the intravenous administration of high dosages of fosfomycin-disodium (13,14). Finally, the participants in the FORECAST trial are not critically ill, as patients are empirically treated with adequate intravenous antibiotics and strict requirements are applied

in order to stepdown to one of the treatment arms. Usually, patients will be hospitalised for at least 24 hours after the first administration of stepdown therapy in order to evaluate the clinical response and tolerability, except for non-ill vital patients.

In the FORECAST trial, fosfomycin-trometamol 3000mg is prescribed for a new indication, cUTI, and dosed every 24 hours for a total antibiotic therapy (iv+oral) of 10 days and a maximum use of 8 days. This requires additional information, which is provided in this investigators brochure. Ciprofloxacin, dosed 500mg every 12 hours, is a registered regimen for the stepdown treatment of cUTI and implemented in Dutch and international guidelines (1,5). The efficacy and safety has been thoroughly evaluated and is described in the summary of product characteristics and the IMPD (15). Therefore the investigators brochure will shortly evaluate the efficacy and development of resistance of ciprofloxacin.

Fosfomycin-trometamol and its placebo will be manufactured by Basic Pharma BV according to good manufacturing practice (GMP). Ciprofloxacin and its placebo will be manufactured by Basic Pharma BV. Basic Pharma BV is responsible for the labeling of all medicines and the storage and the delivery to the UMC Utrecht. Basic Pharma BV is responsible for the storage and transport to the pharmacy departments of the participating centres. The data-management of the UMC Utrecht, ResearchOnline, is responsible for the randomisation proces.

Duration (hours) ↓	**Study population**		**Control population**	
12 H	Sachet Fosfomycin sachet 3g	Placebo tablet	Placebo sachet 3g	Ciprofloxacin tablet 500mg
12 H		Placebo tablet		Ciprofloxacin sachet 500mg

Table 1: medications applied to participants

3. FOSFOMYCIN-TROMETAMOL

Fosfomycin is an old antibiotic agent, discovered in 1969 (27). It is a phosphoenolpyruvate (PEP) analogue that is produced by Streptomyces spp.. It has a bactericidal action, primarily by inhibiting bacterial cell wall (peptidoglycan) synthesis (13). In the Netherlands, Fosfomycin is orally available as fosfomycin-trometamol (Monuril). Fosfomycin-trometamol is identical to fosfomycin-tromethamine. Fosfomycin-trometamol is a phosphoric acid derivative of fosfomycin, available in a single dose sachet containing white granules. One sachet contains 5.63 g of fosfomycin-trometamol, corresponding with 3000mg fosfomycin(6).

3.1 Physical, Chemical, and Pharmaceutical Properties and Formulation

A detailed description can be found in the IMPD. The SMP of Monuril provides more information (6)

3.2 Nonclinical studies

In animal studies, fosfomycin-trometamol is well absorbed, distributed to highly perfused organs and predominantly excreted as an unchanged drug in the urine. Fosfomycin has little side effects in animal studies, acute nor chronic and no hazardous effects have been found concerning fertility, teratology, mutagenicity or carcinogenicity (6). In vitro microbiological activity was demonstrated in gram-negative bacteria as well as in some gram-positive bacteria. The resistance rate of the common pathogens causing UTI for fosfomycin is very low, especially for E.coli (1% for inpatient isolates in 2015 in the Netherlands) (3), but even for ESBL’s producing bacteria (5,17–19).

Further manufacturing information could be found in the IMPD.

3.3 Effects in humans

3.3.1 Pharmacokinetics and product metabolism in humans

The oral bioavailability of fosfomycin-trometamol ranges between 34 and 58% (19) (20). Following oral administration, fosfomycin-trometamol is converted to the free acid, fosfomycin, which is rapidly absorbed. Absorption occurs in the small intestine; co-administration with food reduces drug absorption (21), therefore it is advised to take it on an empty stomach, at least 2-3 hours after a meal. Age does not seem to effect absorption (22). The degree of binding of the fosfomycin molecules to protein is negligible (23). Information about the apparent volume of distribution is conflicting (40-136 liters) (24). Fosfomycin is cleared non-metabolized in urine by glomerular filtration (for 97%) and in lesser extent (the remaining 3%) by fecal excretion (9,20). Fosfomycin is actively eliminated through hemodialysis (25). Gross renal impairment significantly modifies the pharmacokinetics of fosfomycin-trometamol, leading to significantly higher C_{max} in uremic patients than in healthy individuals. Dose adjustments are not recommended for endogenous creatinine clearances of >30 ml/min per 1.73 m2. Age does not affect fosfomycin clearance independent from glomerular function (22). There is no pharmacokinetic modification for hepatic impairment (26).

Following the administration of 3gram of fosfomycin-trometamol in 12 healthy individuals in fasting state, the maximum drug concentration (C_{max}) was 21.8mg/L (SD ±4.8), the time to C_{max} was 2.0 hours and the plasma elimination half time ($T_{1/2}$) was 4.5 hours with an area under the curve of 145mg/L·hours (SD±40) (9). Another article reports mean C_{max} from 22 to 32 mg/L after one single dose of 3gram fosfomycin-trometamol, reached between 2-2,5 hours and a $T_{1/2}$ of 5.7 hours with an area under the curve of 145 to 228mg/h/l (26). Following a single 3gram dose fosfomycin-trometamol, peak urine concentrations are reached within 4 hours with high urine and bladder tissue concentrations (>128mg/L) for 1 to 2 days (27). In a case report, with a patient with ESBL prostatitis, for which long-term fosfomycin-trometamol was prescribed (3 gram every 24 hours for 12 weeks) adequate plasma levels were found (mean 5.3 µg/mL); dosing fosfomycin 3gram twice a day was poorly tolerated (8). In a prospective study, 26 healthy males who required TURP, received 3 gram of oral fosfomycin-trometamol before the procedure. Mean plasma, urine and prostate levels were respectively 11.4 mg/L after 565 minutes, 571mg/L after 593 minutes and 6.5 µg/g after 603 minutes with a prostate/plasma ratio of 0.67 (28). Following a single dose of 3gram fosfomycin-trometamol, sufficient intra-prostatic concentrations in uninflamed prostatic tissue is achieved (8).

Pharmacodynamics and pharmacokinetics have been described in critical ill patients for intravenous fosfomycin. This shows good tissue penetration, which is not affected by illness. Parker et all. tested fosfomycin concentrations in 515 plasma samples of 12 critically ill patients, who received 6 gram of fosfomycin every 6 hours. Plasma fosfomycin concentrations transcended the MIC's for the causative pathogens (29), however pharmacokinetics were dependent of creatinine clearance (29). Severe inflammation has no clinical relevant effect on the ability of fosfomycin to penetrate into inflamed lung tissue (30). In critically ill patients, fosfomycin concentrations in muscle interstitium and plasma exceeded the MICs for clinical relevant pathogens (31). Limited peritoneal fluid penetration was found following intravenous administration (32).

3.3.2 Efficacy.

Fosfomycin has evident antimicrobial properties. Information about resistance pattern of urine cultures among inpatient departments could be found in the Nethmap 2016 report (3). In the FORECAST study, susceptibility to fosfomycin is already established before randomisation. The effectiveness of fosfomycin-trometamol as a single dose for the treatment of an asymptomatic UTI is evident (33), therefore it is adviced in the Dutch guideline for general practitioners https://www.nhg.org/standaarden/volledig/nhg-standaard-urineweginfecties). It is registered by the Food and Drug Administration (FDA) and disclosed in international guidelines (5). Several immune-modulatory effects have been described in vitro and in vivo (27).

The efficacy of oral fosfomycin-trometamol as prescribed in the FORECAST trial has never been evaluated. The following articles are summarized as they could provide indirect evidence for the efficacy of fosfomycin in the FORECAST trial. These articles mainly focus on the treatment of ESBL producing bacteria, cUTI, chronic prostatitis and the use of fosfomycin as a prophylactic agent for endo-urological interventions.

A systematic review was performed in 2010 in order to evaluate in vitro susceptibility rates and clinical effectiveness of oral fosfomycin-trometamol for the treatment of MDR-Enterobacteriaceae. In vitro, MDR-Enterobacteriaceae were highly susceptible for Fosfomycin (>90%). Oral fosfomycin-trometamol for complicated and uncomplicated UTI with MDR-Enterobacteriaceae, was highly effective (93.8%), but unfortunately only two studies were conducted (34). In a small prospective observational study that investigated patients with complicated lower UTI due to ESBL producing E.coli, oral fosfomycin-trometamol, without pre-treatment with intravenous antibiotics, was compared to carbapenem. Fosfomycin-trometamol 3gram was given every 48 hours for three doses and compared with

14 days of intravenous carbapenem treatment. The clinical and microbiological responses after 7-9 days after the end of treatment were not significantly different, resp. 95% and 80% in the Carbapenem group and 77.7% and 59.3% in the fosfomycin group (11). Veve et all retrospectively found that oral fosfomycin-trometamol (average 6 days, dosed every 24, 48, 72 hours or as a single dose) was non-inferior to intravenous ertapenem (1 gram daily, average 10 days) in matched patients treated at home for ESBL UTI regarding the 30 days revisit/readmission rate (10). In a prospective uncontrolled open-label multicentre study in China, Qiao et all evaluated the clinical and microbiological efficacy and safety of three doses of 3 g oral fosfomycin-tromethamine administered orally every 48 hours to 361 patients with uncomplicated or complicated lower urinary tract infections. The clinical efficacy rate for complicated lower UTI was 62.7% (42/69), the microbiological efficacy was 83.87% (26/31) (35). A recent retrospective assessed the use of oral fosfomycin in complicated or MDR UTI in 57 patients in the United States; 44 had a complicated UTI. Most patients received 1 dose of 3 gram fosfomycin. The small proportion that was clinically (24/44) or microbiologically (16/44) evaluable, had good success rates, respectively 95.8% and 75% (12). Fifty-two patients with uncomplicated and complicated UTI with ESBL were evaluated retrospectively in Turkey. All isolates were resistant for ciprofloxacin and co-trimoxazol and susceptible for fosfomycin and carbapenem. Patients received 3gram fosfomycin-trometamol every 48 hours for 3 gifts. The clinical and microbiology rate was resp. 94.3% and 78.5%, which was similar in patients with or without a cUTI (36). Another retrospective review evaluated the clinical outcomes of 760 patients that received oral fosfomycin in a tertiary care hospital in the United States. The overall clinical success was 74.8%-87.5% (the latter defining an indeterminate outcome as success). However, most patients used fosfomycin in a single dose. The presence of an intravenous catheter and recent surgery were associated with clinical failure. Male gender, using immunosuppressive medication, ESBL producing bacteria, presence of urinary catheter or having a cUTI was not significantly associated with clinical failure; however patient numbers were low (37). The efficacy and safety of oral fosfomycin-trometamol for urinary tract infections in hospitalised patients was evaluated in the United Stated. Seventy-one patients were included, many of them had significant comorbidities (diabetes 39%, urological devices 38%, recent urological procedures 10%, immunosuppression 51% or corticosteroid usage 21%). The cure rate was 83%, the recurrence rate with the same pathogen was 3% (38). One case report describes the clinical and microbiological success of long-term oral fosfomycin-trometamol in two patients with a prostatitis caused by an MDR-ESBL(8). One reports the success of oral fosfomycin in the multidrug treatment of persistent K. pneumoniae Carbapenemase bacteraemia (39). Fosfomycin has been tested as prophylactic therapy for endo-urological interventions and

surgical procedures. It was equally effective as ciprofloxacin in preventing prostatitis (40–42).

In most countries, including the Netherlands, the intravenous variant of fosfomycin, Fomicyt, is registered and used in the treatment of adults and children with complicated urinary tract infections, osteomyelitis, nosocomial infections of the lower respiratory tract, bacterial meningitis, or bacteraemia (presumably) associated with one of the above infections (14). It is indicated if usual antibiotics are insufficiently effective or cannot be applied. It is prescribed sporadically, often in a high dosage as a multidrug treatment for ESBL bacteraemia/sepsis. Good clinical results have been reported (39).

3.3.3 Safety

Fosfomycin is contraindicated in patients with known hypersensitivity, but is generally considered safe. The allergic risk is very low (20). Mild and self-limiting gastro-intestinal disturbances, such as diarrhoea, nausea, abdominal pain and dyspepsia are the most common. Headaches, dizziness, upper respiratory tract infections, vaginitis, bacterial and fungal superinfections have been reported. Transient laboratory alterations concerns all blood series (neutropenia, eosinophilia, anaemia, low platelet count, increased liver enzymes, bilirubin), but no renal insufficiency (43).

In a meta-analysis of RCT's comparing oral fosfomycin-trometamol with other antibiotics for the treatment of patients with lower UTI's, no significant difference was observed in the development of adverse events, even among pregnant women (27). In a retrospective study of 760 patients with a pharmacy order for fosfomycin-trometamol in the United States, none of the patients experienced adverse events related to anaphylaxis, skin rash, or Clostridium difficile infection. Fosfomycin was used for a maximum of 3 days, but in most of the cases as a single dose. No deaths were reported as a result of fosfomycin use or the underlying conditions for which fosfomycin was administered (37). In a prospective trial, with the use of fosfomycin-trometamol 3 gram on day 1, 3 and 5 for 361 patients with uncomplicated or complicated UTI in China, no serious adverse events were found. No patients showed abnormal laboratory test results. Diarrhoea was the most frequently reported adverse event, in 18/356 patients (5.06%). Only one patient discontinued the trial due to moderate diarrhoea (0.28%) (35). In a case report, in which a patient used long-term antibiotic treatment for a chronic prostatitis, fosfomycin-trometamol was first dosed 3gram every 12 hours for a period of 5 days, resulting in intolerable gastrointestinal side effects. These side effects cleared promptly after reduction of the dosage to 3g every 24 hours (8).

Fosfomycin was not mutagenic or genotoxic in the Ames test in cultured human cells nor in vivo mouse and Chinese hamsters. It did no effect fertility or reproductive performance in male and female rats (13). Animal reproduction studies have failed to demonstrate a risk in the fetus and there are no adequate and well controlled studies in pregnant women, so it should only be used if clearly indicated (13). It crosses the placental barrier through simple diffusion but does not affect the transport of other nutrients (44). Excretion in human milk is expected due to low molecular weight, although no data is available (13). Absorption of fosfomycin-trometamol is decreased by metoclopramide, with a maximum concentration occurring earlier (1.8 vs 2.1 hours), the clinical consequences are indistinct and metoclopramide is not contra-indicated (6,20). No hard contraindications exist for the administration of fosfomycin with other medications (13). There is limited experience in regard to the overdose of oral fosfomycin. Hypotonia, somnolence, electrolytes disturbances, thrombocytopenia and hypoprothrombinemia have been reported in cases of overdose with parental use of fosfomycin. Treatment should be symptomatic and supportive (13). An overdose is not expected with the relatively low oral dosage in this trial. Information about the development of resistance during fosfomycin therapy is provided in section 5.4.

3.3.4 Marketing experience

In the Netherlands, fosfomycin-trometamol, has been registered as an oral single dose, for an asymptomatic UTI, on 29 march 1990 (6). Before registration, the US performed 3 clinical trials on fosfomycin-tromethamine (=fosfomycin trometamol), demonstrating the safe risk profile and efficacy (13). Fosfomycin has been marketed as fosfomycin-calcium previously, but as a result of low bio-availability, it is not registered in the Netherlands nor internationally (27). Fosfomycin is also registered as an intravenous administration, fosfomycin-disodium (in the Netherlands registered as Fomicyt) for the treatment of cUTI, osteomyelitis, nosocomial infections, lower airway infections, bacterial meningitis and bacteremia in conjunction with one of the above infections. It is only indicated when it is deemed inappropriate to use the common used antibiotics or when these antibiotics failed (14).

3.3.5 Summary of Data and Guidance for the Investigator

In this FORECAST trial we aim to provide evidence for the efficacy and safety of the use of fosfomycin-trometamol as the stepdown treatment of cUTI after an initial adequate intravenous treatment. This is not yet registered for this indication.

The pharmacokinetic and pharmacodynamic profile of oral fosfomycin-trometamol favours its use in the FORECAST trial. Fosfomycin has a acceptable bio-availability and high tissue penetration. The administration of 3 gram of fosfomycin-trometamol lead to sufficient MIC’s in

urine, bladder wall and prostate, high enough to kill in vitro susceptible E. coli. A review of the clinical efficacy and safety of fosfomycin-trometamol in indications that are comparable to this trial, is promising. Serious adverse events of fosfomycin are scarce. The studies that used oral fosfomycin-trometamol 3 gram every 24 hours for more than once reported a moderate tolerability. Prescribing fosfomycin-trometamol 3 gram every 12 hours was not tolerated in a case report. It is unlikely that accumulation of fosfomycin will happen when used 3 gram every 24 hours. Indirect evidence, that has been obtained from the higher dosed intravenous variant of fosfomycin (Fomicyt), shows a good safety profile (14). Fosfomycin had little side effects in animal studies, acute nor chronic, and no hazardous effects have been found concerning fertility, teratology, mutagenicity or carcinogenicity (6).

Patients will be included if the causative pathogen is susceptible for fosfomycin, according to EUCAST breakpoints, which is 32mg/L for oral fosfomycin for Escherichia coli for cystitis (6). Susceptibility to fosfomycin will be measured following EUCAST recommendations. Patients, included in the FORECAST trial, have been pre-treated with adequate intravenous antibiotics for ≥48 hours and fulfil the criteria for safe iv-to oral antibiotic switch. As a result, critically ill patients will not be randomised. Pregnant and lactating women are excluded from the study as too little experience exist for the safety and efficacy in this population. Specific patients groups will be excluded: renal transplant patients, polycystic kidney disease, neutropenia (<500 /µl), paraplegia, long-term indwelling catheters, urostomy, double-J catheter, nephrostomy catheter, suprapubic catheter suspicion/presence of renal abscess, suspicion of septic metastatic foci/endocarditis. As fosfomycin is cleared through glomerular filtration, patients are excluded if they have renal insufficiency (GFR < 30 ml/min/1,73 m3) or renal replacement therapy. Based on literature, no hard contraindications exist for the administration of fosfomycin with other medications.

4 CIPROFLOXACIN

Ciprofloxacin is used as the standard of care in the FORECAST trial. Ciprofloxacin 500mg every 12 hours is already included in the Dutch guideline for cUTI as a stepdown therapy after intravenous antibiotic pre-treatment (1). Ciprofloxacin is a fluorinated quinolone, which has a bactericidal action. It acts by inhibition of bacterial topoisomerase II (DN gyrase) and topoisomerase IV, which are combined for DNA replication, transcription, repair and recombination. Ciprofloxacin is indicated for multiple bacterial infections, including complicated urine tract infection (12). Ciprofloxacin is available in the Netherlands in granules for suspension (50mg/ml and 100mg/ml), tablets (250mg, 500mg and 750mg) and infusate (mg/ml). In this study the tablets that will be used contain 582 mg ciprofloxacin hydrochloride monohydrate, which is equivalent to 500mg ciprofloxacin. The experience with ciprofloxacin is huge, and the safety and efficacy profile are considered good. Therefore this IB will often refer to the summary of product characteristics or the IMPD.

4.1 Physical, Chemical, and Pharmaceutical Properties and Formulation

A detailed description can be found in the attached summary of product characteristics (chapter 6) and the IMPD.

4.2 Nonclinical studies

Information could be found in the summary of product characteristics (6) and the IMPD.

4.3 Effects in humans

4.3.1 Pharmacokinetics and product metabolism in humans

Information could be found in the summary of product characteristics (6), section 5.2.

4.3.2 Efficacy

Information about resistance pattern of urine cultures in inpatient departments could be found in the Nethmap 2016 report (3). In the FORECAST trial, the susceptibility for ciprofloxacin is

an inclusion criteria. More information about the efficacy in specific bacterial infections is found in the summary of product characteristics, section 4.2, 4.5 and 5.1 (6).

Below, the effectiveness and safety of ciprofloxacin for the treatment of cUTI is summarized, cited from the Dutch SWAB guideline for cUTI (1).

The use of ciprofloxacin as a stepdown therapy after an empirical intravenous antibiotic treatment is recommended in the SWAB guideline (1). The following information provides information about the empirical treatment with ciprofloxacin for cUTI and originates from the SWAB guideline (1). The cure rate of ciprofloxacin 500mg every 12 hours for 7-14 days for an acute uncomplicated pyelonephritis in women is high (96-97%), with no significant difference between the 7- or 14 day treatment. On the other hand, a 7 day ciprofloxacin regimen has greater microbiological and clinical cure rates than a 14 day co-trimoxazol regimen for acute uncomplicated pyelonephritis in women. A similar good efficacy of ciprofloxacin 500mg every 12 hours is reported when treated for 7 or 14 days in women with complicated pyelonephritis, however only few subjects were evaluated (n=4). Another population based cohort with acute pyelonephritis in the ambulatory care setting showed that an increased chance of treatment failure was present when the treatment lasted less than 10 days. In men, no difference was found between the treatment of community acquired febrile UTI after treatment of ciprofloxacin 500mg every 12 hours for 2 or 4 weeks.
Recommendations: the guideline advices to treat an acute uncomplicated pyelonephritis in healthy women with ciprofloxacin for 7 days. The treatment of other complicated UTI's should be 10-14 days. The literature on which base a 7-day ciprofloxacin regimen for uncomplicated pyelonephritis in women is recommended is mainly derived from ambulatory patients. This can not be translated directly to our study as participants in the FORECAST trial already necessitate hospitalization and empiric intravenous antibiotics, which implies they are more vulnerable. Therefore, an estimated total antibiotic duration (intravenous + oral) in the FORECAST trial of 10 days is safe.

4.3.3 Safety

The safety profile for fosfomycin is considered good. Specific side-events, contra-indications and interactions are mentioned in the summary of product characteristics (15). Ciprofloxacin could be dosed 500mg every 12 hours for a creatinine clearance (GFR) higher than 30ml/min (https://www.farmacotherapeutischkompas.nl/).

4.3.4 Marketing experience

The use of oral ciprofloxacin 500mg every 12 hours for the treatment of cUTI has been approved globally and implemented in Dutch and international guidelines (1,5). More information about the marketed use of ciprofloxacin in the Netherlands could be found in the IMPD.

4.3.5 Summary of Data and Guidance for the investigator

The favorable safety profile and the high effectivity, make ciprofloxacin a well-established antibiotic treatment for cUTI. It is currently prescribed on a daily basis as 500mg every 12 hours as a stepdown treatment after intravenous antibiotics for cUTI. Ciprofloxacin is chosen as the standard of care for its good safety and efficacy. The susceptibility of the causative pathogen for ciprofloxacin and fosfomycin is established before randomization. More information about the development of resistance during therapy is found in section 5.4.

5 RISK-BENEFIT ANALYSIS

5.1 Safety

Both for fosfomycin as ciprofloxacin the safety profile is considered excellent. Serious adverse events are seldom reported for both medicines. Oral ciprofloxacin 500mg every 12 hours has been used as a 14 day regimen with a good tolerability and safety. Oral fosfomycin-trometamol 3000mg has been used as a one-single dose with a good tolerability and safety. Intravenous-fosfomycin (Fomicyt) is indicated in much higher doses as an last-line intravenous option for soft tissue infections and sepsis with a good tolerability and safety profile. The only concern is the tolerability of fosfomycin-trometamol if used orally every 24 hours, up to 8 days. However a review of existing literature of fosfomycin use for more than a single-dose is reassuring and only describes mild gastro-intestinal complaints.

5.2 Efficacy

The objective of the FORECAST trial is to find evidence for the efficacy and safety of oral fosfomycin-trometamol 3000mg every 24 hours as a stepdown treatment for AF-UTI. Oral ciprofloxacin every 12 hours has been registered for the this indication. The favorable pharmacodynamic and pharmacokinetic profile, together with the good susceptibility for Escherichia *coli*, and the effectivity in cUTI as described in literature make fosfomycin-trometamol an interesting candidate as a stepdown treatment for cUTI. The in- and exclusion criteria are designated to optimize patient safety and efficacy, see table 2. Corresponding with the inclusion criteria for the FORECAST trial, participants are empirically pre-treeated with an adequate intravenous antibiotic. Randomisation takes place if the criteria for safe early iv-to oral switch are fulfilled and if the causative pathogen is susceptible for both ciprofloxacin and fosfomycin. Participants are therefore not critically ill and in vitro susceptibility for both antibiotics is known. Patients with a higher than expected chance of clinical failure with one of the treatment regimens of the FORECAST trial are excluded. In a subset of patients plasma and urine concentrations of fosfomycin will be measured as this has not been done before. This will be described in a different study protocol.

5.3 Risks and discomfort of other study related procedures

Because a double-dummy design is chosen, all participants are asked to take 2 encapsulated tablets and one sachet every 24 hours. On the day of randomization, laboratory values (pregnancy test, creatinine, white blood cell count) are determined, in the case it hasn't been already done by the physician en is nessecary for determining inclusion. We expect that most physicians already performed a pregnancy test during hospitalization in most women in childbearing age. An urine culture will be taken 10-14 days after the end of treatment. All these procedures, except for the intake of placebo are part of the routine clinical practice. Therefore, we expect only minimal risks nor discomfort for participants.

5.4 Antibiotic resistance

According to the Nethmap 2016, the resistance rate for Enterobacteriaceae for the current used oral antibiotics is worrisome. Table 2 described the bacterial resistance rates in urine isolates among out- and inpatient departments (3). The raise of ciprofloxacin use has led to the emergence of fluorquinolone resistance, ESBL producing bacteria and vancomycin resistant enterococci (VRE). Furthermore the direct development of resistance during ciprofloxacin treatment is well known (45,46). This emergence of bacterial resistance, reducing the oral antibiotic options for cUTI was the incentive for the search to alternative antibiotic options.

For fosfomycin, several mechanisms of resistance are described, the most frequently observed acquired chromosomal in vitro mechanisms relate to a acquired decrease of fosfomycin uptake into cells. Resistance can also relate to mutations in the drug's target of action or a plasmid like mutation, katalyzing fosfomycin into an inactive form (27,47). However in clinical studies the development of in vivo resistance during oral fosfomycin therapy for UTI's appears to be considerably lower than expected from in vitro data, possibly because resistance mechanisms are biologically costly, having a negative influence on survival outside the host (47). Furthermore mutations may enable bacterial washout, preventing establishment in the bladder (48).

In the Netherlands, the antibiotic resistance level for fosfomycin in E. coli was <1% in 2015, which is equal to 2012. However, for other enterobacteriaceae the resistance level among clinical isolates for fosfomycin is increasing, for K. pneumoniae a rise of 9% in 5 years (2010 22%, 2015 31 %) and for P. mirabilis a rise of 5% in 5 years (2010 11% 2015 16%) (3).

In Spain, an 50% increase of fosfomycin consumption resulted in an *in vitro* increase of fosfomycin-resistance in urinary cultures of 1.6 to 3.8% (49). The development of resistance

during fosfomycin treatment has been proven in a case report: three patients were treated with fosfomycin for a K. pneumoniae bacteremia; the identified resistant bacteria after therapy were considered the same mutants as the causative bacteria (50). However the development of resistance after a single dose treatment for cystitis could not be found (4). Urine cultures are taken 10-14 days after therapy in order to describe the development of resistance. A substudy, the FORECAST-eco will focus on the development of resistance in the gut microbiome, collecting stool samples of among 50 participants before randomisation, 10-14 days post-end of treatment and 30-35 days end of treatment. The latter because we expect the spontaneous wash-outs of resistant mutants because a loss of fitness (4)

	Outpatient departments			**Inpatient departments**		
Antibiotic	Co-amoxiclav	Ciprofloxacin	Co-trimoxazole	Co-amoxiclav	Ciprofloxacin	Co-trimoxazole
E. coli	20%	16%	28%	21%	13%	25%
K. pneumoniae	10%	6%	14%	11%	6%	13%
P. mirabilis	10%	10%	30%	11%	9%	27%

Table 2: Resistance rates 2015 among urine isolates in inpatient and outpatient departments

6 CONCLUSION

The FORECAST trial aims to provide evidence for the effectiveness, safety and ecological impact of fosfomycin-trometamol as a stepdown treatment in patients with cUTI, compared to the current standard of care, ciprofloxacin.

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