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Methenamine hippurate to prevent recurrent urinary tract infections in older women: protocol for a randomised, placebo-controlled trial (ImpresU)

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ABSTRACT

Introduction Methenamine hippurate is a urinary antiseptic used as preventive treatment for recurrent urinary tract infections (UTIs) in some Scandinavian countries. However, the scientific evidence for the preventive effect and safety for longer-term use is limited. The aim of this study is to assess whether methenamine hippurate can reduce the incidence of UTIs in older women with recurrent UTIs.

Methods and analysis The ImpresU consortium is a collaboration between Norway, Sweden, Poland and the Netherlands. The study is a randomised, controlled, triple-blind phase IV clinical trial. Women ≥70 years with recurrent UTIs are screened for eligibility in a general practice setting. We aim to include 400 women in total, with 100 recruited from each collaborating country. The participants are randomised to treatment with methenamine hippurate 1 g or placebo tablets two times per day for a treatment period of 6 months, followed by a drug-free follow-up period of 6 months. The primary outcome is number of antibiotic treatments for UTIs during the treatment period. The secondary outcomes include number of antibiotic treatments for UTIs during the follow-up period and self-reported symptom of severity and duration of UTI episodes. Differences in complications between the treatment groups are measured as safety outcomes. We also aim to investigate whether strain characteristics or phylogenetic subgroups of Escherichia coli present in the urine culture at inclusion have a modifying effect on the outcomes.

Ethics and dissemination Ethical approvals are obtained in all participating countries. The results will be communicated in peer-reviewed journals and at scientific conferences.

Trial registration number ClinicalTrials.gov Registry (NCT04077580); EudraCT: 2018-002235-15.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first study to examine the preventive effect of methenamine hippurate using a randomised, placebo-controlled clinical trial design with a long-term follow-up.
⇒ The study investigates the effect of a potentially highly relevant non-antibiotic preventive treatment for recurrent urinary tract infections (UTIs).
⇒ Diagnosis and treatment of UTIs are left to the physicians. Individual interpretations of definition of UTI and adherence to guidelines may impact the registration of UTI episodes.

INTRODUCTION

Urinary tract infections (UTIs) are one of the most common bacterial infections in humans. 1 Women are more prone to develop UTIs than men, and the incidence of UTIs peaks in young sexually active women and again in postmenopausal women. 2,3 Approximately half of all women will experience at least one episode of UTI in their lifetime, with half of them experiencing recurrence within 6–12 months. 4,5 The prevalence of UTIs in women over 65 years is almost double the rate seen in the overall female population, 6 and recurrent UTIs in older women are consequently a major driver of antibiotic prescriptions. Repeated antibiotic exposure over decades has altered the susceptibility of uropathogens showing increasing antimicrobial resistance (AMR). AMR is considered by the WHO to be one of the largest threats to global health. 7 Older age, previous UTI and antibiotic exposure are all risk factors for development of AMR. 8–10 Studies have shown that reducing antibiotic prescribing at the level of primary care is associated with decreased local AMR. 11 Both rational prescribing of antibiotics and feasible and appropriate non-antibiotic preventive
measures are important to reduce antibiotic pressure and slow the progression of AMR.12

**Methenamine hippurate**

Methenamine was first used as a urinary antiseptic more than 100 years ago.13 In Norway and Sweden, the combination drug methenamine hippurate has been used as a preventive treatment for recurrent UTIs for nearly 50 years.14 Despite its popularity in the Nordic countries, the drug is hardly used outside of Scandinavia. Methenamine hippurate is absorbed from the gastrointestinal tract and excreted by the kidneys to form methenamine and hippuric acid. Methenamine is hydrolysed to formaldehyde and ammonia in acidic urine. Formaldehyde acts as a bacteriostatic agent, denaturising the enzymes of the bacteria.15 The hippuric acid ensures that the pH in the urine stay acidic, but has limited bacteriostatic effect itself.16 Despite evidence suggesting carcinogenic effect of formaldehyde when inhaled in high dosages, the Scientific Committee on Health and Environmental Risks assessment report on methenamine from 2007 concludes that formation of low-dose formaldehyde from cleavage of methenamine in body compartments should be of no concern with respect to carcinogenicity.17–19 Being an antiseptic, formaldehyde has not yet been shown to cause AMR.20 21 In an era of increasing AMR, methenamine hippurate represents a potentially highly relevant non-antibiotic preventive treatment in women with recurrent UTIs.22

However, non-antibiotic treatment options for UTIs like methenamine hippurate have not yet yielded conclusive evidence of effect.23–25 The lack of conclusive evidence is manifested as an absence of clear official guidelines for initiation and duration of prophylactic treatment with methenamine hippurate.26 Evaluation of treatment duration is especially challenging in the older population, often leading to prolonged or life-long treatment. Recent years’ progression of AMR has led to a growing interest in exploring methenamine hippurate as a preventive alternative for recurrent UTIs. A recent study comparing long-term methenamine hippurate treatment with trimethoprim found similar rates of recurrence and adverse effects in the two groups.27 The current pivotal study in this field, the ALTAR Study, recently demonstrated non-inferiority of methenamine hippurate compared with low-dose prophylactic antibiotics.28 This trial recruited women ≥18 years of age with recurrent UTI from secondary urology and urogynaecology care. The participants were randomised to 12-month treatment with methenamine hippurate or low-dose antibiotics. The study was open-labelled, that is, the participants were aware of their treatment allocation. Although the ALTAR Study demonstrated non-inferiority, methodologically, the gold standard for demonstrating effect of a drug intervention is to compare the effect with no active treatment/placebo. Blinding the study to treatment allocation will further strengthen the outcome by reducing intentional and unintentional bias.29

The vast majority of methenamine hippurate users are older women.30 This is consistent with the gender distribution of UTIs and the increasing burden of UTIs with age. These patients are frequently attended in primary healthcare. Therefore, the ImpresU consortium set out to evaluate the prophylactic effect of methenamine hippurate on recurrent UTI in the patient population known to have the highest disease burden using a triple-blind, randomised, placebo-controlled trial design (RCT).

**Escherichia coli**

*E. coli* is a part of the human gastrointestinal microbiota.31 Uropathogenic *E. coli* from faecal reservoirs are the predominant causative microbes in uncomplicated UTIs.32–34 Strains of *E. coli* can be divided into phylogenetic subgroups (A, B1, B2, C, D, E and F). Subgroup B2 and D are the most prevalent types associated with extraintestinal infections.35–37 The management of UTIs is complicated by increasing prevalence of antibiotic-resistant strains of *E. coli*.38 Persistent or relapsing UTIs are often associated with *E. coli* strains of subtype B2, and recent research indicates that recurrences often are caused by the same strain as the first UTI episode.39 40 Our hypothesis is that the phylogenetic subgroups or other strain characteristics of *E. coli* present in the urine cultures at inclusion could have a modifying role on the preventive effect of methenamine hippurate.

**Unresolved issues and objectives**

To our knowledge, the preventive effect of methenamine hippurate has never been tested against placebo in a large prospective RCT with long-time follow-up among older women in primary care.

**Risk/benefit evaluation**

The benefit of the study is potentially large for older women with recurrent UTIs, resulting in fewer UTI episodes, reduced antibiotic usage and increased quality of life. Subsequent reduction of urinary antibiotic use may contribute to slowing the progression of AMR in the population. Methenamine hippurate is a well-tolerated drug and adverse effects are uncommon and generally mild.13 The risk of the study is considered to be very small, and the possible benefits greatly outweigh the potential risk.

**METHODS**

**Study design and procedures**

This study is a triple-blind, randomised, controlled phase IV trial in women ≥70 years with recurrent UTIs. Recurrent UTIs are defined as ≥2 episodes of antibiotic-treated UTIs during the last 12 months or ≥2 episodes during the last 6 months.41 Antibiotic treatment is defined as receiving any course of urinary antibiotics for a suspected UTI regardless of dose regimen. The participants will be recruited from general practice, and the included patients will be randomised to active intervention (1 g
methenamine hippurate ×2, standard recommended dose13 or control (one placebo tablet two times per day) for 6 months. To evaluate if there is a prolonged effect of treatment, another 6 months of follow-up will be performed. A total of 400 patients will be randomised, approximately 100 patients in each participating country. Study visits and procedures are listed in table 1.

Study assessments
Visit 1: screening, inclusion and randomisation
Eligible patients will be found through a screening procedure of the electronic patient record in the general practitioner (GP) office. Patients living in nursing homes are not included in this study. Signed and dated informed consent will be collected by the research team prior to any study-related activity (online supplemental file 1), and the patient will be enrolled by the researcher with assistance from the GP. Demography, level of care, concomitant medication and relevant medical history will be registered, including risk factors for recurrent UTIs (ie, urinary bladder dysfunction, diabetes mellitus, obesity (body mass index >30), local treatment with oestrogen, sexual activity or abnormality of the urogenital tract), as well as previous diagnosis of urinary tract stones, pyelonephritis and urosepsis. A voided urine specimen will be collected for dipstick analysis of pH, nitrite and leukocyte esterase and subsequently sent for culturing with examination of resistance pattern and urease production.

We will freeze any isolates of E. coli found and send them to the Department of Clinical Microbiology at Sahlgrenska University Hospital in Sweden for analysis of strain characteristics and phylogenetic subgroup.

Telephone follow-up in case of acute UTI episode(s)
Any episodes of acute UTIs during the study period will be handled by regular health services. The participants are instructed (both orally and written, see online supplemental files 1 and 2) to contact the study team on a designated study phone each time they are prescribed a course of antibiotics/waiting for a suspected UTI. The study team will then follow up on the UTI episode by telephone consultations with the participant every 7 days until resolved. We will register UTI symptoms using patient-reported outcome (table 2). We will register the antibiotic prescribed for the episode (name of drug, dosage and duration), results of urine analysis (dipstick and urine culture, if taken) and any complications of the UTI (ie, pyelonephritis, urosepsis or hospital admissions). Relevant serious adverse events (SAEs) will be registered.

Telephone contacts every 30 days during the first 6 months and at the end of study
The study participants will be contacted by telephone every 30 days in the 6-month treatment period, at the end of treatment and at the end of study. Any symptoms/side effects from the trial medication will be recorded, as well as relevant SAEs. Participants will be asked if they have forgotten to contact the study team in case of any UTI-related healthcare contacts. If so, the study team will follow up the episodes retrospectively with registration of relevant data. Compliance with study medication will also be registered.

Study population
There are several inclusion and exclusion criteria (box 1).

Subject enrolment and randomisation
Four sets of 100 random numbers, one set for each participating country, will be created by a member of the research team using Research Randomizer.42 A block randomisation will be performed. Block size will be concealed to prevent functional unblinding. The outcome will be transferred to a separate Excel spreadsheet for each country, and each country will follow their randomisation list strictly sequentially as subjects are eligible for randomisation. If a subject discontinues from the study, the subject number will not be reused, and the subject will not be allowed to re-enter the study. The inclusion will stop when a total of 400 participants are included in the study.

Discontinuation and withdrawal of subjects
Subjects are free to discontinue their participation at any time without prejudice to further treatment. Participants developing SAEs possibly due to methenamine hippurate will discontinue study medication. Alkalisating antacids can potentially reduce the effect of methenamine hippurate and should be avoided. Study participants requiring long-term use of antacids during the first 6 months of study will discontinue study medication. If prophylactic urinary antibiotics are initiated after enrolment and randomisation in the study, the participants will discontinue study medication. Participants developing serious illness, making it impossible for them to continue taking the study tablets or comply with study requirements, will discontinue study medication and/or withdraw from study participation. Other reasons for discontinuing treatment or withdrawing a subject are incorrect enrolment and subjects lost to follow-up. Participants who prematurely discontinue treatment, except for patients withdrawing their consent, will be followed up in the same framework as participants receiving study medication.

Patient and public involvement
The concept and patient information material was presented for a group of users prior to study start to ensure readability and comprehension. Input from participating patients and clinicians early in the study will be used to adapt and improve study implementation.

STUDY TREATMENTS
Identity of investigational medicinal products
Investigational medicinal products (IMPs) will be purchased from the pharmaceutical company Mylan. The IMP and corresponding placebo will be sent to Kragerø Tablet factory for packing and labelling according to the
### Table 1  Study visits and procedures

<table>
<thead>
<tr>
<th>Time point</th>
<th>Study period</th>
<th>Enrolment</th>
<th>Allocation</th>
<th>Treatment period</th>
<th>Follow-up period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Screening</td>
<td>Baseline</td>
<td>At time of UTI</td>
<td>Follow-up UTI*</td>
</tr>
<tr>
<td>Eligibility screen</td>
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<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Informed consent</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demography</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical history</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical examination</td>
<td>X†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant medication</td>
<td>X‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Randomisation</td>
<td>X</td>
<td></td>
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<tr>
<td>CRF completion</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Dispensing of trial drugs</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interventions</td>
<td>Methenamine hippurate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compliance</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Midstream urine dipstick/culture</td>
<td>X</td>
<td>X§</td>
<td></td>
<td>X§</td>
<td>X§</td>
</tr>
<tr>
<td>Assessments</td>
<td>UTI record</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
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<td>Patient-reported outcome</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Adverse event assessment</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Standard Protocol Items: Recommendations for Interventional Trials figure for the ImpresU clinical trial.

*Every episode of acute UTI both in intervention period and follow-up period will be followed with registrations every 7 days until the patient is restored.
†If needed to determine eligibility or complete baseline data.
‡After baseline visit, concomitant medication will only be registered in case of serious adverse event (SAE).
§If taken by the GP.
¶In case of SAE present and not resolved by day 360, this will be followed until resolution.
CRF, case report form; GP, general practitioner; IMP, investigational medicinal product; UTI, urinary tract infection.
randomisation list. Kragerø Tablet factory will deliver the IMPs to a designated pharmacy in each country, which in turn will distribute to participating sites. The IMPs will be handed out consecutively to participants for 6 months’ use. Boxes with active substance consist of tablets with methenamine hippurate 1 g. Boxes with placebo will contain tablets with the equivalent dose of lactose. The placebo tablets will have identical shape, size and markings as the methenamine tablets. The boxes will have identical labelling with corresponding labels for each participating country in local language. Only the participants’ study ID on the label will be linked to the randomisation list, revealing the content of the IMPs.

**Storage and handling**

One pharmacy/medical distributor will be responsible for delivering the IMPs to the relevant sites in each country. The medication will be stored at each site in a locked cupboard in a secure access room together with the sealed code envelopes. IMPs will be stored with a controlled temperature not exceeding 30°C. A member of the research team will collect and count any remaining IMPs by the end of the treatment period to report treatment compliance. Any unused IMPs will be sent to the designated pharmacy for drug count and destruction.

**Blinding**

Participants, GPs meeting patients, pharmacists dispensing drugs, the investigators and persons involved in statistical analysis will not be aware of group allocation until all statistical analyses are done (triple blind).

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**Table 2** Patient-reported outcome form used at every UTI episode in the ImpresU clinical trial

<table>
<thead>
<tr>
<th>Patient-reported outcome</th>
<th>Yes □ No □</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Degree of pain at urination (scale 0–6)*</td>
<td></td>
</tr>
<tr>
<td>2. Urgency (scale 0–6)*</td>
<td></td>
</tr>
<tr>
<td>3. Frequent urination (scale 0–6)*</td>
<td></td>
</tr>
<tr>
<td>4. Visible blood in urine?</td>
<td>Yes □ No □</td>
</tr>
<tr>
<td>5. Abdominal pain not related to urination</td>
<td>Yes □ No □</td>
</tr>
<tr>
<td>6. Has the patient had fever? (&gt;38° rectal OR &gt;37.5 axillae OR &gt;37.8 tympanic)</td>
<td>Yes □ No □</td>
</tr>
<tr>
<td>7. Side effect of study drug? If yes, what side effect:</td>
<td>Yes □ No □</td>
</tr>
<tr>
<td>8. Feeling unwell?</td>
<td>Yes □ No □</td>
</tr>
<tr>
<td>9. Flank pain?</td>
<td>Yes □ No □</td>
</tr>
<tr>
<td>10. Other symptom(s):</td>
<td></td>
</tr>
<tr>
<td>11. I feel restored</td>
<td>Yes □ No □</td>
</tr>
</tbody>
</table>

*State the degree of the problem on a scale from 0-6 where: 0 = normal/no problem, 1 = little problem, 2 = some problem, 3 = moderate problem, 4 = large problem, 5 = bad, 6 = as bad as it can be UTI, urinary tract infection.

**Box 1** Inclusion/exclusion criteria in the ImpresU clinical trial

**Inclusion criteria**

⇒ Woman.
⇒ Age ≥70 years.
⇒ Recurrent urinary tract infections (UTIs) (≥3 episodes of antibiotic-treated acute cystitis the last 12 months or ≥2 episodes the last 6 months).
⇒ Able and willing to comply with all trial requirements.
⇒ Able and willing to give informed consent.

**Exclusion criteria**

⇒ Intake of methenamine hippurate within the last 12 months.
⇒ Allergy for methenamine hippurate.
⇒ Current antibiotic prophylaxis for UTI.
⇒ Urinary catheter (chronic indwelling catheters as well as intermittent urinary catheterisation).
⇒ Known severe chronic renal failure or estimated creatinine glomerular filtration rate <30 mL/min (known—registered in general practitioners’ clinical records).
⇒ A known condition or treatment associated with significant impaired immunity (eg, long-term oral steroids, chemotherapy or immune disorder).
⇒ Known severe hepatic impairment.
⇒ Severe dehydration.
⇒ Any previous episode of gout (urate).
⇒ Need for long-term use of antacids such as magnesium hydroxide, magnesium carbonate, aluminium hydroxide.
⇒ Life expectancy estimated by a clinician to be less than 6 months.
⇒ Involvement in, including completion of, follow-up procedures, in another clinical trial of an investigational medicinal product in the last 90 days.
⇒ Incontinence too severe to be able to provide a voided urine specimen.
⇒ Participation in ImpresU Work Package 2.*
⇒ Significant known abnormal renal tract anatomy/physiology (ie, single kidney, persistent urinary tract stone disease, severe vesicoureteral reflux) or neuropathic bladder disorders.
⇒ Lactose intolerance.

*An antibiotic stewardship intervention to improve antibiotic prescribing for UTIs in frail older adults.

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**Breaking the blinding in an emergency situation**

The study code should only be broken for valid medical or safety reasons. There will be one sealed opaque envelope for each medication ID available at the study sites, revealing the identity of the IMP. On patient/physician information cards, there will be a telephone number provided by the sponsor to be used in emergency situations. The coordinating centre (or the sponsor) provides the treating physician with treatment allocation details, and the treating physician deals with the participant’s medical emergency accordingly.

**Study objectives and variables**

The primary objective of this study is to investigate if methenamine hippurate reduces the need for antibiotic use due to recurrent UTIs (table 3). The remaining objectives...
are considered secondary. Pyelonephritis, hospitalisation and death will be registered as safety endpoints.

Handling, storage and destruction of biological samples

At inclusion, a urine specimen will be collected for culture and dipstick urinalysis. After analysis, the urine specimen will be destroyed. However, we will freeze isolates from the inclusion urine culture. Bacteria are not regarded human material and do not need biobank registration. The study team will order copies of medical records from acute UTI episodes including laboratory urinalysis results.

SAFETY

Methenamine hippurate is a well-tolerated drug, and the adverse effects are generally mild. Anticipated adverse drug reactions in the study include gastric irritation, irritation of the bladder, nausea and vomiting (all uncommon), diarrhoea and abdominal pain (incidence unknown). Skin and subcutaneous disorders like rash and pruritus are both registered as uncommon. Participants developing clinically significant dehydration or receiving a course of sulfonamide antibiotics will pause IMP due to the theoretical increased risk of crystalluria. The participants will continue with study treatment when dehydration is clinically resolved and/or the sulfonamide antibiotic treatment is completed.

Adverse events

As methenamine hippurate has been in clinical use for decades, non-SAEs will not be recorded for the purpose of this study—except in the Netherlands, where the Medical Ethical Committee required registration of all adverse events (AEs). It will be left to the investigator’s clinical judgement to decide whether a symptom or side effect is of sufficient severity to require the participant’s removal from treatment. A participant may also voluntarily discontinue treatment due to intolerable symptoms or side effects.

Serious adverse event

All SAEs that are life-threatening or result in death will be reported. SAEs requiring inpatient hospitalisation or prolongation of existing hospitalisation, and SAEs resulting in persistent or significant disability/incapacity will only be reported if relationship with IMP cannot be excluded or the SAE is a complication of a UTI. SAEs requiring inpatient hospitalisation or prolongation of existing hospitalisation, and SAEs resulting in persistent or significant disability/incapacity will only be reported if relationship with IMP cannot be excluded or the SAE is a complication of a UTI. SAEs representing expected events in a frail older population will not be reported. If relationship with IMP cannot be

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Outcome measures/variables/ endpoints</th>
<th>Time point(s) of evaluation of this outcome measure (if applicable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary objective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>To investigate if methenamine hippurate reduces the need for antibiotic use due to recurrent UTIs (measured as number of antibiotic courses).</td>
<td>Number of UTI antibiotic treatments during the 6 months of treatment. If the participant receives &gt;1 antibiotic course for UTI without symptom relief, it is regarded as one episode and counted as one antibiotic treatment. If there has been an asymptomatic period of at least 14 days in between two UTI antibiotic courses, this is regarded as a new antibiotic treatment.</td>
</tr>
<tr>
<td>Secondary objectives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2a</td>
<td>To investigate if methenamine hippurate will have a prolonged effect on antibiotic usage even after discontinuation.</td>
<td>Number of UTI antibiotic treatments during the 6 months following completion of treatment. If the participant receives &gt;1 antibiotic course for UTI without symptom relief, it is regarded as one episode and counted as one antibiotic treatment. If there has been an asymptomatic period of at least 14 days in between two UTI antibiotic courses, this is regarded as a new antibiotic treatment.</td>
</tr>
<tr>
<td>2b</td>
<td>To investigate if methenamine hippurate reduces the incidence of UTIs.</td>
<td>Number of UTIs (acute symptoms specific/to the urinary tract) during the 6 months of treatment. If the participant has had &gt;1 UTI episode without symptom relief, it is regarded as one episode. If there has been an asymptomatic period of at least 14 days in between two UTI episodes, this is regarded as a new episode.</td>
</tr>
<tr>
<td>2c</td>
<td>To investigate if methenamine hippurate can reduce severity of UTI symptoms.</td>
<td>Registration of symptom severity when initiating treatment for UTI.</td>
</tr>
<tr>
<td>2d</td>
<td>To investigate if methenamine hippurate can reduce duration of UTI episodes.</td>
<td>Registration of number of days of symptoms during UTI episodes.</td>
</tr>
<tr>
<td>2e</td>
<td>To investigate if number of complications such as pyelonephritis and hospital admission for UTIs differ between methenamine hippurate and placebo.</td>
<td>Registration of number of pyelonephritis and hospital admission for UTI.</td>
</tr>
<tr>
<td>2f</td>
<td>To investigate if strain characteristics/phylogenetic subgroups of Escherichia coli found at inclusion are an effect modifier in all the above outcomes.</td>
<td>See above</td>
</tr>
</tbody>
</table>

UTIs, urinary tract infections.
excluded, these SAEs are possibly, probably or definitely related to the trial medication. These AEs will be reported as SAR (serious adverse drug reaction) if expected and included in Summary of Product Characteristics (SmPC) or as SUSAR (suspected unexpected serious adverse reaction) if unexpected and not included in SmPC (figure 1). SAEs will be registered throughout the whole study period. In case of a SAE not resolved by the end of the study, this SAE will be followed until resolution.

Premature termination of the study

A data safety monitoring committee (a statistician and two external researchers with experience in clinical trials and UTIs in primary care) will meet every 6 months to ensure data safety. The difference between groups in SAEs deemed to be linked to methenamine hippurate will be continuously monitored. The study will be terminated if there is a significant difference between the two trial arms regarding SAE, SAR and SUSAR probably or definitely related to the trial medication or UTI. This will be evaluated by comparing the two groups without breaking the code. The code will be broken if the difference between groups is statistically significant (p<0.05). The study will be prematurely terminated if the statistical difference is to the disadvantage of active IMPs. SAE, SAR and SUSAR possibly related to the trial medication or UTI will be registered but not used for decision-making.

STATISTICS

Sample size calculation

The sample size calculation is made for the primary objective described in table 1. We assume these selected older women will have an average of two courses of antibiotics for suspected UTIs every 6 months. We assume a 25% reduction of antibiotic prescriptions during the first 6 months after the introduction of methenamine hippurate based on a consensus in the research group that a smaller effect would be less clinically relevant. This means that the intervention group would have an average of 1.5 prescriptions while the control group is assumed to remain around 2.0. We assume the SD in each group to be 1.5. This will result in an effect size of 0.33 (small effect). We assume the level of significance being 0.05, the power to be 0.80 and that a two-tailed test is explored. We use Student’s t-test as the statistical analysis but also calculate for Mann-Whitney test (if the outcome variable is not normally distributed). The planned statistical method will be multivariable linear regression. Student’s t-test and Mann-Whitney test are used as surrogate methods to estimate sample size. Under the assumptions given above, an effective sample size of 286 patients (143+143) is required if t-test can be used. However, if Mann-Whitney test is required, we need 298 (149+149) patients. To achieve an effective sample size of at least 298, after considering a 25% loss to follow-up, we aim to include 400 patients.

STATISTICAL ANALYSIS

We will adjust all analyses for confounding variables obtained at visit 1 (box 2).

Primary and secondary statistical analyses and management of missing data

The primary statistical analysis is intention to treat. Patients who have completed only a part of the first 6 months will contribute data up until they leave the study. Their data will be recalculated as if they had participated in all 6 months. Patients leaving during the second 6-month period will also contribute with data as above. Patients leaving the study before the second 6-month period commences will have their value for this period set to be the median value for both groups. A complete case analysis and a per-protocol analysis will also be made as secondary analysis and reported.

DATA MANAGEMENT

Recording and management of data

We will use the electronic data capture system Research Online (RO) for data collection. RO meets all requirements according to Good Clinical Practice for electronic data entry with respect to safeguarding data integrity and data security regulations. Web-based case report forms are implemented into the system to facilitate data collection. Participants will be identified by a unique trial-specific number. All source data will be stored at the coordinating centres for a minimum period of 15 years after termination of the trial. After the data of the last subject are entered, a clean file will be produced for further analysis and publication, and the database will close. Direct access to the data will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

Study sponsor

University of Oslo, Norway.

Monitoring

A study monitor will be appointed by the sponsor to monitor the study in all four countries. The quality control will have a risk-based approach. The monitor will have regular contacts with the coordinating centres and sites, and the extent of monitoring will be defined in a separate monitoring plan. Authorised representatives of the sponsor or regulatory authorities may perform audits or inspections, including source data verification.

DISCUSSION

AMR in urinary pathogens is on the rise. With increasing life expectancy and current antibiotic use, this trend will continue unless appropriate prescribing and feasible and effective non-antibiotic preventive measures are
Figure 1  Safety reporting flow chart for the ImpresU clinical trial. *A follow-up report should be submitted in writing within 48 hours. **Follow-up information to be provided in further 8 days. AE, adverse event; PI, principal investigator; SAE, serious adverse event; SAR, serious adverse drug reaction; SUSAR, suspected unexpected serious adverse reaction; UTI, urinary tract infection.
implemented. If methenamine hippurate is safe and effective in reducing UTI episodes in older women with frequent UTIs, it could potentially change the management of recurrent UTIs outside Scandinavia. Less use of urinary antibiotics will reduce antibiotic pressure and potentially slow the progression of AMR. If methenamine hippurate is not effective, the result will still be beneficial as many women can avoid unnecessary medication.

This study also sets out to unravel whether methenamine hippurate, if proven effective, has a prolonged effect even after discontinuation of a 6-month treatment period. If so, this will guide the preparation of more precise guidelines for prophylactic use of this drug.

Including only women ≥70 years experiencing the highest number of UTIs in the 12 months preceding inclusion increases the chance of a spontaneous reduction in episodes in the following 12 months—regardless of any intervention.\(^\text{45}\) As a result, we expect a decrease in the number of UTIs in both the placebo and intervention groups in the intervention period. However, the RCT design compensates for the possible effect of regression to the mean.

Management of acute UTIs is handled by regular health services in this study. With four European countries participating, the guidelines differ slightly. The individual interpretation of diagnosis and treatment guidelines will probably also differ on a physician level. In case of acute UTIs, patient symptoms will be

Table 4 Study objectives and statistical analysis in the ImpresU clinical trial

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Statistical analysis</th>
<th>Time point(s) of evaluation of this outcome measure (if applicable)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary objective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 The primary objective of this study is to investigate if methenamine hippurate reduces the need for antibiotic use due to recurrent UTI (measured as number of antibiotic courses).</td>
<td>Standard linear regression will be used where the number of UTI antibiotic treatments will be the dependent variable. Group allocation together with the confounding variables above will be independent variables. The dependent variable will be transformed using a rank transformation in case it is not normally distributed. A p value will be delivered, but no useful effect size if a rank transformation is used.</td>
<td>After 6 months of treatment</td>
</tr>
<tr>
<td>Secondary objectives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2a To investigate if methenamine hippurate will have a prolonged effect on antibiotic usage even after discontinuation.</td>
<td>Will be analysed using the same statistical approach as objective 1.</td>
<td>Six months after completing (12 months after commencing) treatment</td>
</tr>
<tr>
<td>2b To investigate if methenamine hippurate reduces the incidence of UTI.</td>
<td>Will be analysed using the same statistical approach as objective 1. UTIs will be the dependent variable.</td>
<td>After 6 months of treatment</td>
</tr>
<tr>
<td>2c To investigate if methenamine hippurate can reduce severity of UTI symptoms.</td>
<td>The outcome variable is measured at first day of UTI using a 6-grade ordinal scale. The median value of all UTIs will be used if the patient has more than one episode of UTI. The dependent variable will be transformed using a rank transformation and analysed with linear regression using the same covariates as when analysing objective 1.</td>
<td>After 6 months of treatment</td>
</tr>
<tr>
<td>2d To investigate if methenamine hippurate can reduce duration of UTI episodes.</td>
<td>Will be analysed using the same statistical approach as objective 1. Number of days with symptoms will be the dependent variable. The dependent variable will be transformed using a rank transformation in case it is not normally distributed. A p value will be delivered, but no useful effect size if a rank transformation is used.</td>
<td>After 6 months of treatment</td>
</tr>
<tr>
<td>2e To investigate if the number of complications such as pyelonephritis and hospital admission for UTI differ between methenamine hippurate and placebo.</td>
<td>Will be analysed using the same statistical approach as objective 1. Number of severe events such as pyelonephritis or hospital admission will be the dependent variable. The dependent variable will be transformed using a rank transformation in case it is not normally distributed. A p value will be delivered, but no useful effect size if a rank transformation is used.</td>
<td>Six and 12 months after commencing treatment</td>
</tr>
<tr>
<td>2f To investigate if strain characteristics/phylogenetic subgroups of Escherichia coli found at inclusion are an effect modifier in all the above outcomes.</td>
<td>Phylogenetic subtype of pure cultures of E. coli in the inclusion urine culture will be analysed in a separate statistical analysis if the number of cultures available for typing is at least 60. All statistics above will be repeated adding phylotype as an extra independent variable. Purely descriptive statistics will be presented if the number is less than 60.</td>
<td>See above</td>
</tr>
</tbody>
</table>
reported directly from the patient, making the data prone to recall bias. In cases where the study team is notified of a UTI the same day, the patient symptoms are recorded in real time minimising bias. However, missed UTIs discovered at monthly follow-up or when checking the patient records at end of study will be recorded retrospectively.

Ethics and dissemination

All participants will receive standard medical care in case of a UTI. The participants will receive written information with contact details to the principal investigator, the study team and a study telephone manned at all hours during the study period. A data monitor committee will ensure data safety. The risk of the study is considered very small, and our risk/benefit analysis concludes that the possible benefits of this study greatly outweigh the potential risk. The study protocol has been approved by the Norwegian Medicines Agency (NoMA, 18/16028-15), the Regional Committee for Medical and Health Research Ethics, Norway (REK south-east, 2018/2502 A), the Swedish Medical Product Agency (5.1-2019-103684, 5.1-2021-35901, 5.1-2021-64842 and 5.1-2021-92970), the Swedish Ethical Review Authority (2019-02749, 2020-00360 and 2021-03992), Committee of Bioethics of the Medical University of Lodz, Poland (RNN/311/19/KE), Office for Registration of Medicinal Products, Medical Devices and Biocidal, Poland (UR/DBL/D/417/2021), Centrale Commissie Mensgebonden Onderzoek, the Netherlands (NL71512.041.19.) and Medical Ethical Review Committee, METC Utrecht, the Netherlands (20/032).

Substantial amendments will be communicated to relevant competent authorities. Within 1 year after the end of the study, the sponsor will submit a study report with the results of the study to the accredited competent authority. In addition, the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

Insurance

The Norwegian study subjects are covered by ‘Legemiddelansvarsforsikringen’. The Swedish study subjects are covered by the ‘Swedish Pharmaceutical Insurance’, LFF Service. The Dutch study subjects are covered by CNA Insurance Company (Europe). The Polish study subjects are covered by Towarzystwo Ubezpieczeń i Reasekuracji ‘WARTA’.

Trial status

Subject enrolment started in December 2019 and will be completed by end of June 2022. All follow-ups are expected to be completed by the end of June 2023.

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Contributors ML, P-DS, CMPMH, TJMV and MG-C conceptualised the ImprEsU Project and obtained funding. ML, P-DS, RG, SRH-O and ESA drafted the protocol for the RCT. SH, NG, CA, WGG, HAMK, TNP, AK, MG-C, CMPMH and TJMV revised the protocol. SRH-O drafted the manuscript. All authors critically revised the article draft and approved the final manuscript.

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Disclaimer The funders will have no role in study design, data collection, management, analysis and interpretation, nor in writing and submission of reports for publication.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

Request to participate in drug trial

Version 3

ImpresU - can Methenamine reduce episodes of urinary tract infections (UTI) in women over 70 with recurrent UTI?

This is a request for you to participate in a research project testing the drug methenamine hippurate. Methenamine disinfects the urinary tract and is not regarded as an antibiotic. Methenamine is the most commonly used drug for preventive treatment of urinary tract infections in Norway. The aim of the study is to determine whether methenamine has a preventive effect and leads to fewer infections in women over the age of 70 with frequent urinary tract infections. Your General practitioner (GP) has, through a computer program searching his/her medical records, found that you are a patient frequently suffering from urinary tract infections. Based on these finding, he/she has contacted you to require your participation in a study testing a preventive drug for urinary tract infections.

The study is conducted by the (Insert national research group/university), and the sponsor of the study, The University of Oslo.

What does the project entail?

In this study, we wish to investigate whether methenamine has a preventive effect on urinary tract infections in women over the age of 70. In order to do so, we will be testing methenamine against placebo over a period of six months. In the Norwegian part of the study, 100 patients will be participating. One half of the patients will get methenamine, while the other half will get placebo tablets. The study is blinded, which means that neither your doctor nor the research team will know whether you get methenamine or a placebo. This information is sealed and only to be revealed if a situation where it is important to know whether you are getting the active drug or not occurs. The medicine is free of charge, and you will be given medication for six months of treatment. After the treatment period, we wish to continue the follow up for an additional six months in order to investigate whether methenamine has a prolonged preventive effect even after the treatment is completed.

At the first meeting, a representative from the research team will give you information on the study, and you will get the opportunity to ask any questions you might have. If you wish to participate, we will get your GP to help us determine whether you are an eligible
candidate for the study. By signing this declaration, you consent for the research team getting access to relevant information in your medical records through your GP. We will also be asking you for a urine sample during this meeting.

If you are getting symptoms of a urinary tract infection within the study period, we ask you to contact your GP in the normal manner for an evaluation of treatment. At this consultation, a urinary sample will be taken. We also ask you to contact the research team on the same day using the listed number. After this, our study nurse will contact you once a week until your infection has cleared. During these calls we will register symptoms and the degree of symptoms, what kind of treatment you receive and the duration of the treatment. Any side effects or complications due to the study medicine will also be recorded. Our study nurse will call you once a month throughout the treatment period the first six months of the study to check up on you and to see how you are doing.

If you get a urinary tract infection and your doctor is not available, we ask you to contact other health care institutions to get an evaluation of treatment and thereafter call the research team on the listed number. By signing this declaration, you give your consent for the research team to collect relevant data from your medical records at the health care institution you received your treatment if necessary.

**POSSIBLE ADVANTAGES AND DISADVANTAGES AND SERIOUS SIDE EFFECTS**

Methenamine has been used for nearly 50 years without a documented effect. It is important to clarify whether methenamine actually can reduce the number of episodes in women with frequent urinary tract infections. If so, more patients can benefit from an effective preventive treatment. This will lead to a reduction in antibiotic prescriptions for urinary tract infections, and contribute to reduce the development of antibiotic resistance in the future, as well as saving patients from the unnecessary side effects of antibiotics.

If methenamine does not show a preventive effect on frequent urinary tract infections, this will cause many women not to be prescribed unnecessary medicine.

Since methenamine has been used on a large scale in this country, the drug has a well-documented safety profile with few and mild side effects. We do not know of any serious side effects linked to the use of methenamine. The most common side effects that can occur are all less common (more than 1 of 1000, less than 1 of 100) and include stomach disorders such as nausea/vomiting, stomach irritation, upset stomach and rash/itching and irritation of the bladder. A rare side effect (more than 1 of 10 000, less than 1 of 1000) is microscopic (not visible) blood in the urine.

The treatment of every episode of a urinary tract infection is determined by your doctor in the normal manner. Participation in the study will therefore not result in any other treatment for your urinary tract infection than you would otherwise have.
VOLUNTARY PARTICIPATION AND POSSIBILITY TO WITHDRAW CONSENT

It is voluntary to participate in the project. If you wish to participate, you have to sign the consent form on the last page. You can, whenever you like and without stating a reason, withdraw your consent without any consequences for further treatment.

If you consent to participate in the study, you have the right to gain access to the information registered on you and have the information corrected should there be any mistakes in your information. You also have the right to gain insight into the security measures taken in the processing of your data. If you wish to withdraw from the study, there will not be registered any more information on you, but data already collected will not be deleted.

If you wish to withdraw your consent or have questions about the project, you can contact (Insert contact information for Principal Investigator).

WHAT HAPPENS TO THE COLLECTED DATA ON YOU?

The tests will be done in the same manner as any other tests taken in your GP's office, and are requisitioned by your doctor. We will not collect biological material, and are only interested in the results from the tests your doctor required.

The results we will require are from urinary dipsticks, ph and culture. If there is growth of bacteria in your urine culture, the bacteria will be investigated further, but your urine sample will be destroyed in the usual manner.

The tests taken, and the information registered on you, are only to be used as described in the purpose of the project.

All the data on you is processed without a name or a national identification number, or any other recognizable information. A code will link you to your information through a list of names.

It is only (insert all persons that have access to the national list) who have access to this list. The list will be securely stored at the research center.

This study is a cooperation project between Norway, Sweden, the Netherlands and Poland. The study will take place simultaneously in the four participating countries. After coding, the data on you will be gathered in a database in the Netherlands where final analyzes will take place. The data from all the participating countries will be analyzed collectively and are later to be published in international journals.

By participating in the project, you consent to the information being transferred to other countries as a part of a research and publishing collaboration. The project leader will make sure that your data is taken care of in a safely manner.
The code that links you to your personal identifiable information is not transferred.
Your collected data is to be deleted 15 years after the project has ended.
It will not be possible to identify you in the results of the published study.

APPROVAL
(Insert name of Competent Authority) has evaluated the project and given their approval (Insert study reference number).

According to the new personal data act, the data controller institution, (Insert name of university and name of Principal Investigator), have a personal responsibility to ensure that the handling of your information has a legal basis. This project has the legal basis in the EUs General Data Protection Regulation, article 5, article 6 1a and article 9 2a, and your consent.

You have the right to complain about the processing of your information to the Data Protection Authority.

CONTACT INFORMATION
If you have any questions about this project, please contact (Insert name and contact information for coordination researcher).

You can contact the Data Protection Official at the institution if you have questions about the processing of your personal data in the project. At the (insert university), questions about data protection are addressed to (insert contact information).

WHAT INFORMATION ABOUT YOU WILL BE REGISTERED?
• Relevant past medical history to determine if you are eligible to participate in the study.
• Year of birth and residency
• Certain other health information important for the evaluation of the results of the study. We will be collecting this information from your GP, your medical records and from you directly.
• During the first meeting, we will take a urine sample and register the results of this test.
• With every episode of a urinary tract infection, we will register symptoms and the degree of the symptoms, what treatment you receive and the duration of the treatment. The results of the urine test taken by your doctor with every episode will also be registered. In every case of a urinary tract infection, we will follow up to register the course of the infection until the infection has cleared. Any side effects or complications due to the study medicine will also be recorded. Our study nurse will call you once a month throughout the study to check up on you and to see how you are doing.
• If you receive treatment for a urinary tract infection from other health professionals than your GP, it may be necessary to collect information from their medical records as well in order to obtain the information listed above.

• Representatives from The University of Oslo (the sponsor of the study), The Norwegian Medicines Agency and control authorities, both domestic and abroad, can gain access to study information from relevant parts of your medical record. The purpose of this is to ensure that the registered study information match the information in your medical record. Everyone with access to your medical record have a duty of confidentiality.

**FINANCE**

The study is funded by (Insert source of funding); the sponsor of the study is The University of Oslo.

**INSURANCE**

You are insured in accordance to the product liability law in (Insert national insurance company).

**INFORMATION ABOUT THE OUTCOME OF THE STUDY**

The participants in the study have the right to get information about the outcome of the study if desirable.
I CONSENT TO PARTICIPATE IN THE STUDY AND THAT MY PERSONAL INFORMATION CAN BE USED AS DESCRIBED.

(Signature of participant, date)

CONFIRMATION OF GIVEN INFORMATION

I confirm to have given information about the project

(Signature, role in the project, date)

*Note: The model consent form will be adapted according to rules and regulations from the competent authorities in each participating country.
Date/start medication: ______

Patient study ID: ______

**PATIENT INFORMATION**

- The study medication is taken 1 tablet twice daily for 6 months. The total study period is 12 months.
- In case of a urinary tract infection: contact your doctor.
- Bring a urine sample to the doctor’s appointment.
- After the doctor’s appointment, contact: (study phone)
- The study team will call you once a week until the infection has cleared.
- The study team will also call you once a month in the 6 months of medication to check how you are doing.

**SHOW THIS CARD IF YOU ARE IN CONTACT WITH HEALTH CARE PERSONNEL OTHER THAN YOUR GP**

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**HEALTH CARE PERSONNEL**

- The study lasts for 12 months from start of medication.
- The first 6 months, the patient will receive: **Methenamine hippurate 1g x 2 OR placebo 1 tbl x 2**
- In case of a UTI, we ask that symptoms are recorded and that a copy of the relevant EPJ note and results of dipstick/culture, if taken, are sent to the patients’ GP.
- Methenamine hippurate has few and mild side-effects.
- In case of a serious adverse event, contact (study phone)
- If the patient is starting long-term treatment with antacids (Your generic names®) while receiving study medication, the patient has to be excluded from the study.
- The study medication has to be temporarily paused in the case of severe dehydration or treatment with sulphonamide antibiotics (your generic names®) until rehydrated/end of sulphonamide treatment.