CLINICAL STUDY PROTOCOL

The effect of methenamine hippurate to reduce antibiotic prescribing due to new episodes of urinary tract infections (UTI) in elderly women with recurrent UTI – a triple-blinded, randomized placebo-controlled phase IV study

Study Code:	ImpresU WP3 (**Im**proving rational **pres**cribing for **U**TI in frail elderly Work Package 3)
EudraCT Number:	2018-002235-15
Version Number:	Version 11.1
Date:	7th July 2021
Sponsor:	University of Oslo
Principal investigator(s):	Sigurd Høye

SYNOPSIS

Title: The effect of methenamine hippurate to reduce antibiotic prescribing due to new episodes of urinary tract infections (UTI) in elderly women with recurrent UTI – a triple-blinded, randomized placebo-controlled phase IV study

EudraCT Number: 2018-002235-15

Indication: Recurrent UTI in elderly women is a major driver of antibiotic prescription.

Rational for conducting the study: There is a need for a large well-conducted randomised controlled trial (RCT) to clarify both the safety and preventive effect of methenamine hippurate for longer term use.

Primary objective: The primary objective of this study is to investigate if taking methenamine hippurate reduce the need for antibiotic usage due to recurrent UTI (measured as the number of courses of antibiotics).

Secondary objectives:

- to investigate if methenamine hippurate will have a prolonged effect on antibiotic usage even after discontinuation
- to investigate if taking methenamine hippurate reduces the incidence of UTI
- to investigate if methenamine hippurate can reduce severity of UTI symptoms
- to investigate if methenamine hippurate can reduce duration of UTI episodes
- to investigate if number of complications such as pyelonephritis and hospital admission for UTI differ between methenamine hippurate and placebo
- To investigate if phylogenetic subgroups of E. Coli found at inclusion is an effect modifier in the above outcomes.

Study design: Blinded randomised controlled phase IV trial where patients are randomised to active intervention (methenamine hippurate) or controls (placebo).

Study population: Women aged ≥70 years with recurrent UTIs in community dwellings.

Number of patients: 400.

Inclusion criteria:

- woman
- age ≥70 years
- recurrent UTIs defined as ≥3 episodes of antibiotic treated acute cystitis (acute symptoms specific/related to the urinary tract) during the last twelve months or ≥2 episodes during the last 6 months
- able and willing to comply with all trial requirements
- able and willing to give informed consent

Exclusion criteria:

- the patient has taken methenamine hippurate within the last 12 months
- the patient is allergic to methenamine hippurate
- the patient is having current antibiotic prophylaxis for UTI
- the patient has a urinary catheter (chronic indwelling catheters as well as intermittent urinary catheterisation)
- the patient has known severe chronic renal failure or estimated creatinine glomerular filtration rate ≤30 ml/min (known = registered in GP clinical records)
- the patient has a known condition or treatment associated with significant impaired immunity (e.g. long-term oral steroids, chemotherapy, or immune disorder) (known = registered in GP clinical records)
- the patient has a known severe hepatic impairment (known = registered in GP clinical records)
- the patient is suffering from severe dehydration
- the patient has gout
- the patient has a need for long term use of antacids such as magnesium hydroxide, magnesium carbonate, aluminium hydroxide
- the patient has a life expectancy estimated by a clinician to be less than six months
- the patient has been involved in, including completion of, follow-up procedures, in another clinical trial of an investigational medicinal product in the last 90 days
- the patient suffers from incontinence too severe to be able to provide a voided urine specimen
- the patient is participating in ImpresU Work Package 2
- the patient is suffering from significant known abnormal renal tract anatomy/physiology (i.e. single kidney, persistent urinary tract stone disease, severe vesicoureteral reflux) or neuropathic bladder disorders
- lactose intolerance.

Premature termination of the study
The difference between groups in SAEs deemed to be linked to possible treatment with methenamine hippurate will be continuously monitored without breaking the code. The study will be terminated in case there are significantly more SAEs within one of the groups during the trial.

Investigational product, dosage and administration: Methenamine hippurate 1 gram or placebo per os morning and evening day 1-180.

Primary outcome variables and examinations: Number of UTI courses during day 2-180

Study period: 1 November 2019 to 31 December 2022.

SIGNATURE PAGE

I confirm that I have read and understood this protocol and that I will work according to the protocol. By my signature, I agree to personally supervise the conduct of this study in my affiliation and to ensure its conduct in compliance with the protocol, informed consent, IRB/EC procedures, the Declaration of Helsinki, ICH Good Clinical Practices guideline, the current EU directive Good Clinical Practice and local regulations governing the conduct of clinical studies.

I will accept the monitors overseeing of the study.
I will promptly submit the protocol to applicable ethical committee.

Signature Chief Principal Investigator — 07.07.2021 (Date (day-month-year))

Sigurd Høye
Printed name of Chief Investigator

Signature Sponsor — 07.07.2021 (Date (day-month-year))

Mette Brekke University of Oslo
Printed name of Sponsor

Signature Principal Investigator Sweden — 08-07-2021 (Date (day-month-year))

Pär-Daniel Sundvall
Printed name of Principal Investigator Sweden

Signature Principal Investigator the Netherlands

19-8-21
Date (day-month-year)

Theo Verheij
Printed name of Principal Investigator the Netherlands

Signature Principal Investigator Poland

07.07.2021
Date (day-month-year)

Maciek Godycki-Cwirko
Printed name of Principal Investigator Poland

CONTACT DETAILS

Role	Name	Address	Phone	Fax	E-mail
Sponsor	University of Oslo	PO Box 1130, Blindern, 0318 Oslo, Norway		+47 22850650	Mette.brekke@medisin.uio.no
Chief Investigator	Sigurd Høye	PO Box 1130, Blindern, 0318 Oslo, Norway	+47 22844603	+47 22850650	Sigurd.hoye@medisin.uio.no
Principal Investigator Sweden	Pär-Daniel Sundvall	Research and Development Primary Health Care, Region Västra Götaland, Research and Development Centre Södra Älvsborg Sweden, Sven Eriksonsplatsen 4, SE-503 38 Borås	+46 722506196		par-daniel.sundvall@vgregion.se
Principal Investigator the Netherlands	Theo Verheij	Universitair Medisch Centrum Utrecht, Julius Center, Heidelberglaan100, 3584CX, Utrecht, the Netherlands,			T.J.M.Verheij@umcutrecht.nl

Principal Investigator Poland	Maciek Godycki-Cwirko	Medical University of Lodz, Centre for Family and community Medicine, Ulica Kopcinskiego 20, 90-153 Lodz,	Phone +48 42 679 55 46, Fax +48 42 678 6041		maciej.godycki-cwirko@umed.lodz.pl

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
ADR	Adverse Drug Reaction
AE	Adverse Event
AMR	Antimicrobial Resistance
CA	Competent Authority
EC	Ethics Committee
(e)CRF	(electronic) Case Report Form
EDC	Electronic Data Capture
GCP	Good Clinical Practice
GP	General Practitioner
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
ImpresU	**Im**proving rational **pres**cribing for **U**TI in frail elderly
ISF	Investigator Study File
OOH	Out Of Hours Service
PI	Principal Investigator
PRO	Patient Reported Outcome (PRO)
RCT	Randomised Controlled Trial
RO	Research Online
SAE	Serious Adverse Event
SAR	Serious Adverse drug Reaction
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reactions
UTI	Urinary Tract Infection
WP	Work Package

1. INTRODUCTION

1.1. Background

Recurrent urinary tract infection (UTI) in elderly women is a major driver of antibiotic prescription (1-9). Hence, the question of feasible and appropriate preventive measures are important issues in this field. Methenamine hippurate is frequently prescribed in Norway and Sweden as prophylaxis for recurrent UTI (9). Methenamine hippurate is hardly used outside of Scandinavia. Methenamine hippurate acts via the production of formaldehyde from hexamine, which in turn acts as a bacteriostatic agent, therefore methenamine hippurate is not defined as an antibiotic. According to a Cochrane review 2012 the rates of adverse events for preventing UTI was low (10). Although this review showed methenamine hippurate might be effective in preventing UTI in the short term, there is a need for large well-conducted randomised controlled trial (RCT) to clarify both the safety and effectivity of preventive methenamine hippurate for longer term use (11-16). This is particularly important for longer term use for people without neuropathic bladder disorders (10). A Norwegian longitudinal observational study including women aged 50-80 years with recurrent UTI indicated a significant and large reduction of more than 50% in antibiotic prescriptions for UTI after start of prophylactic methenamine hippurate (Gjelstad, personal communication). This further strengthens the need for an RCT of methenamine hippurate as prophylaxis for recurrent UTI.

Escherichia coli (E. coli) is a part of the human gastrointestinal microbiota (17). Uropathogenic E.coli from fecal reservoirs are the predominant causative microbes in uncomplicated UTIs (18-20). Previous studies have shown that strains of E.coli can be divided into phylogenetic subgroups (A, B1, B2, C, D, E and F), and that subgroup B2 and D represents the most virulent types and are associated with extra-intestinal infections (21-23).
We aim to investigate whether the phylogenetic subgroups of E.coli present in the urine cultures at inclusion can have a modifying role on the preventive effect of Methenamine hippurate in this study. If feasible, we will also investigate whether or not subsequent episodes of acute UTIs in elderly women with recurrent UTI are caused by E.coli of the same phylotype.

1.2. Rationale for conducting this study

Existing knowledge suggests that methenamine hippurate is a safe drug with few and mild side effects and with the potential to significantly reduce antibiotic usage for women with recurrent UTIs. Methenamine hippurate has been on the market for a long time but has never been tested to prevent recurrent UTIs in larger RCTs with long time follow-up. Hence, this must be proven in a large randomised trial before recommending large scale use of this drug (10).

1.3. Risk/Benefit evaluation

Potential benefits from IMP:

- decreased total use of UTI antibiotics
- reduced antibiotic pressure on gut microbiota in the population and possibly reduced antimicrobial resistance (AMR) in the population
- decreased number of UTIs
- increased quality of life.

Potential risks from IMP:

- polypharmacy, many patients have a large number of regular medication, and methenamine hippurate will be a new one for six months
- simultaneous intake of sulphonamide antibiotics can increase risk of crystalluria. Therefore methenamine hippurate will temporarily be paused if the participant gets a course of sulphonamide antibiotics. There are no other known clinical relevant interactions between methenamine hippurate and other pharmaceuticals.

Anticipated adverse drug reactions in the study:

Methenamine hippurate is well tolerated and adverse effects are rare and generally mild (10). Possible side effects might be minor gastrointestinal upsets, dysuria (seldom), abdominal cramps, anorexia, rash and stomatitis (10). The trial team will be available on telephone for urgent cases during the whole study period. This will be solved for each country.

Risk/benefit rationale:

- The benefit of the study is potentially great for elderly women with recurrent UTI resulting in fewer UTI episodes, reduced antibiotic usage and therefore also reducing the risk of AMR.
- The risk of the study is considered to be very small.

In summary the benefits greatly outweigh the potential small risks. This will be evaluated and confirmed by relevant ECs before commencing the trial.

2. STUDY OBJECTIVES AND ENDPOINTS

The primary objective of this study is to investigate if taking methenamine hippurate reduce the need for antibiotic usage due to recurrent UTI (measured as number of antibiotic courses). The remaining objectives are considered secondary. Pyelonephritis, hospitalization and death will be registered as safety endpoints in the study.

Objectives		Outcome Measures / variables / endpoints	Time point(s) of evaluation of this outcome measure (if applicable)
Primary Objective			
1	The primary objective of this study is to investigate if taking methenamine hippurate reduces the need for antibiotic usage due to recurrent UTI (measured as number of antibiotic courses).	Number of UTI antibiotic treatments during the six months of treatment. If the participant receives >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	After six months of treatment.

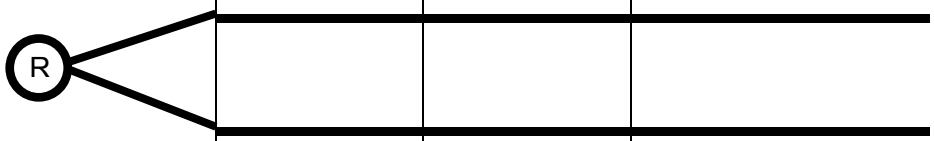
		courses, this is regarded as a new antibiotic treatment.	
Secondary Objectives			
2a	To investigate if methenamine hippurate will have a prolonged effect on antibiotic usage even after discontinuation.	Number of UTI antibiotic treatments during the six months following completion of treatment. If the participant receives >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.	Six months after completing (12 months after commencing) treatment.
2b	To investigate if taking methenamine hippurate reduces the incidence of UTI.	Number of UTIs (acute symptoms specific/related to the urinary tract) during the six months of treatment. If the participant has had >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.	After six months of treatment.
2c	To investigate if methenamine hippurate can reduce severity of UTI symptoms.	Registration of symptom severity when initiating treatment for UTI.	After six months of treatment.
2d	To investigate if methenamine hippurate can reduce duration of UTI episodes.	Registration of number of days of symptoms during UTI episodes.	After six months of treatment.
2e	To investigate if number of complications such as pyelonephritis and hospital admission for UTI differ between methenamine hippurate and placebo.	Registration of number of pyelonephritis and hospital admission for UTI.	Six and 12 months after commencing treatment.
2f	To investigate if phylogenetic subgroups of E. coli found at inclusion is an effect modifier in the above outcomes.	(see above)	(see above)

3. STUDY DESIGN AND PROCEDURES

3.1. Overall study design and flow chart

Study design: Blinded randomised controlled phase IV trial where patients are randomised to active intervention (methenamine hippurate) or controls (placebo).
Setting and study population: Women aged ≥70 years with recurrent UTIs in primary care. A total of 400 patients will be randomized in this trial, with approximately 100 patients in each of the participating countries; Norway, Sweden, Poland and the Netherlands.

Diagram 1. Schematic diagram of procedures:

Visit/ Telephone contact	Visit 1 Screening and randomization (®)	Telephone follow-up in case of acute UTI episode(s)	End of treatment	End of study
Day(s)	1	2-360	180	360
Methenamine hippurate (N=200) Placebo (N=200)				

3.2. Rationale for study design

This is a triple blinded RCT in women aged ≥70 years with recurrent UTIs, defined as ≥3 episodes of antibiotic treated acute cystitis (acute symptoms specific/related to the urinary tract) during the last twelve months or ≥2 episodes during the last six months.

The trial will be triple blinded in order to avoid bias by the patient, the doctor or the person doing statistical analysis. As methenamine hippurate is a prophylactic treatment six months of therapy is necessary. To be able to evaluate if there is a prolonged effect of treatment another six months follow-up is necessary.

The effect of methenamine hippurate is dependent on acidic urine. The hippurate component work as acidifying the urine in patients. We will register urine pH for all patients in the study and see if this has a modifying effect on the results. We will not use lack of acidic urine as an exclusion criterion.

Potential effect modifiers to be registered in CRF and adjusted for in the analysis:

- patient's age
- urine acidity (pH)
- number of antibiotic courses for UTIs in the 12 months preceding inclusion in the study
- presence of urease/stone-producing bacteria in urine culture day 1 such as proteus, some klebsiella species, Morganella morganii, Corynebacterium urealyticum and providencia
- use of local oestrogen
- patient has diabetes mellitus
- obesity defines as BMI ≥30
- presence of known abnormality of the urogenital tract
- if the patient is sexually active
- if the patient previously have experienced kidney stone.

3.3. Table 1. Study visits

	Visit 1 Screening and randomisation	Telephone follow-up in case of acute UTI episode(s)	Telephone follow-up every 30 days in all patients	Telephone contact by end of treatment	Telephone contact by end of study
Day(s)	1	2-360	2-180	180	360
Informed consent	X				
Demography, level of care	X				
Medical history	X				
Physical examination***	X				
Dipstick urinalysis and urine culture	X	X			
Inclusion/exclusion criteria	X				
Randomisation	X				
Patient Reported Outcome		X	X	X	X
Concomitant medication**	X				
Serious Adverse Events		X	X	X	X*

* In case of SAE present and not resolved by day 360, this will be followed until resolution.
** After visit 1 concomitant medication will only be registered in case of SAE, otherwise not.
*** If needed to determine eligibility or complete baseline data.

3.4. Study assessments

Visit 1 – Screening, inclusion and randomisation
Visit 1 (screening and inclusion) is performed by a trial team member or specially trained local investigators at primary health care centres. Before screening, the Investigator will provide thorough oral and written information about the study to the subject. The subject will be given the

opportunity to ask questions and be given sufficient time to consider participation. Subject who agree to participate will give signed and dated informed consent prior to any study-related activity. The investigator will keep a subject screening log and a subject enrolment log.
The patients will when possible be found through a screening procedure of each GPs (General Practitioners) Electronic Patient Record, finding patients who had at least 3 courses of UTI antibiotics last year. Otherwise eligible patients will be identified through doctors and nurses in clinical work with frail elderly. Only patients fulfilling the inclusion criteria and consenting to participate will be included. Demography and level of care will be registered. Medical history including current medication, risk factors for recurrent UTI such as urinary bladder dysfunction (e.g. overactive bladder), diabetes mellitus, obesity (BMI >30), local treatment with oestrogen, sexual activity or abnormality of the urogenital tract. A voided urine specimen will be collected and dipstick urinalysis regarding pH, nitrite and leukocyte esterase will be performed as well as a urine culture, also asking for ureas-producing bacteria. In case of growth of pure cultures of E. coli in the inclusion urine culture, we will freeze the isolates of E.coli and send them to the department of clinical microbiology at Sahlgrenska University Hospital in Sweden for analysis of phylogenetic subgroups according to published protocols using PCR-technique.

If the patient presents with symptoms of an acute UTI or are on antibiotic treatment for a UTI at the inclusion visit, the infection is handled by regular health services (GP or out of Hours (OOH) service). The patient will wait until 2 weeks after finishing treatment for the UTI before the researcher completes the inclusion and takes the baseline urine sample. The treatment with IMP will start the day after the completed inclusion of the patient. The current UTI should be registered at the baseline form as a UTI prior to inclusion in the study. The same procedure will be followed if the patient is on prophylactic treatment with UTI antibiotics, but is willing to stop the prophylactic treatment to enter the study. A note of the actions taken will be written in the comments section in the baseline CRF by the responsible researcher.

All data related to inclusion visit including trial name, study-ID and informed consent will be documented in the medical record of the patient.

Telephone follow-up in case of acute UTI episode(s)
Any episodes of acute UTI during the follow-up period (day 2-360) will be handled by regular health services (GP or out of Hours (OOH) service). Participants are informed at inclusion (Visit 1) to contact the trial team in case of any UTI-related health care contacts during the follow-up period. The study team will follow up each UTI episode until resolved with registration of relevant data by telephone contact and by ordering copies of medical records regarding the UTI episode including laboratory results regarding urinary dipsticks and urine culture.

Following data will be collected in case of acute UTI episode(s) during day 2-360 (telephone follow-up and from medical record):

- confirmation and registration of UTI symptoms (acute symptoms specific/related to the urinary tract), registration of symptom severity when initiating treatment for UTI. This will be measured by a scale 0-6 (no symptoms to worst possible) for each of the three cardinal

symptoms and general condition, Patient Reported Outcome (PRO) – grading of symptoms, see appendix
- UTI antibiotic treatment (name of drug, dosage and duration)
- registration of any pyelonephritis and hospital admission for UTI
- ordering copies of medical records regarding the UTI episode including laboratory tests performed by regular health service (dipstick urinalysis regarding nitrite and leukocyte esterase and urine culture)
- SAEs, whereas relationship with IMP cannot be excluded.

In case of an episode of UTI all clinically relevant data have already been recorded in the patient's medical record by the physician, therefore these telephone follow-ups will only be recorded in the CRF. In case of SAE this will be recorded in the medical record.

Telephone contacts every 30 days during the first six months as well as day 360
During telephone contacts every 30 days during the first six months as well as day 360 registration of any symptoms and side effects from the trial medication will be recorded as well as SAEs, whereas relationship with IMP cannot be excluded. Participants will be asked if they have forgotten to contact the study team in case of any UTI-related health care contacts. If so, the study team will follow up these UTI episode(s) with registration of relevant data as described above.
In case of new UTI not recorded, we will record PRO using the scale. In case of an episode of UTI all clinically relevant data have already been recorded in the patient's medical record by the physician, therefore these telephone follow-ups will only be recorded in the CRF. In case of SAE this will be recorded in the medical record. By the end of the project period, the study team will contact the patients' GP, and ask the GP to go through the patients' records during the project period in order to validate the number of UTI episodes.

4. STUDY POPULATION

4.1. Inclusion criteria

- woman
- age ≥70 years
- recurrent UTIs defined as ≥3 episodes of antibiotic treated acute cystitis (acute symptoms specific/related to the urinary tract) during the last twelve months or ≥2 episodes during the last 6 months
- able and willing to comply with all trial requirements
- able and willing to give informed consent.

4.2. Exclusion criteria

- the patient has taken methenamine hippurate within the last 12 months
- the patient is allergic to methenamine hippurate
- the patient is having current antibiotic prophylaxis for UTI

- the patient has a urinary catheter (chronic indwelling catheters as well as intermittent urinary catheterisation)
- the patient has known severe chronic renal failure or estimated creatinine glomerular filtration rate ≤30 ml/min (known = registered in GP' clinical records)
- the patient has a known condition or treatment associated with significant impaired immunity (e.g. long-term oral steroids, chemotherapy, or immune disorder) (known = registered in GP clinical records)
- the patient has a known severe hepatic impairment (known = registered in GP clinical records)
- the patient is suffering from severe dehydration
- the patient has shown signs of gout
- the patient has a need for long term use of antacids such as magnesium hydroxide, magnesium carbonate, aluminium hydroxide
- the patient has a life expectancy estimated by a clinician to be less than six months
- the patient has been involved in, including completion of, follow-up procedures, in another clinical trial of an investigational medicinal product in the last 90 days
- the patient suffers from incontinence too severe to be able to provide a voided urine specimen
- the patient is participating in ImpresU Work Package 2
- the patient is suffering from significant known abnormal renal tract anatomy/physiology (i.e. single kidney, persistent urinary tract stone disease, severe vesicoureteral reflux) or neuropathic bladder disorders
- the patient has lactose intolerance.

4.3. Subject enrolment and randomization

Included participants will be randomised strictly sequentially, as subjects are eligible for randomisation. If a subject discontinues from the study, the subject number will not be re-used, and the subject will not be allowed to re-enter the study.

Four sets of 100 random numbers each, one for each participating country, will be created using Research Randomizer. A block randomisation will be performed (the block size is concealed to prevent functional unblinding). The outcome will be transferred to a separate Excel spreadsheet for each country where each row, representing one patient, is sequentially numbered. Norway will have the numbers 1-100, Sweden 101-200, the Netherlands 201-300 and Poland 301-400. Each country will follow their randomisation list strictly sequentially. The inclusion will stop when a total of 400 participants are included in the study.

4.4. Discontinuation and withdrawal of subjects

4.4.1. Withdrawal of subjects

Subjects are free to discontinue their participation in the study at any time without prejudice to further treatment. In either case, serious adverse events where relation to IMP cannot be excluded, will be followed up. Other reasons for discontinuing a subject are incorrect enrolment and subjects lost to follow-up.

Any subject fulfilling any of the pre-defined exclusion criteria will be withdrawn from the study:

- participating patients withdrawing their consent, subjects are free to discontinue their participation in the study at any time without prejudice to further treatment
- participating patients developing allergic reactions or any other SAE possibly due to methenamine hippurate
- participating patients requiring long term use of alkalizing substances (such as antacids) during the first six months when taking IMP as alkalizing substances reduces the effect of methenamine hippurate and should be avoided
- participating patients developing serious illness making it impossible for them to continue taking the study tablets.

Simultaneous intake of sulphonamide antibiotics can increase risk of crystalluria. Therefore, methenamine hippurate will temporarily be paused if the participant is prescribed a course of sulphonamide antibiotics, but will continue with IMP after that.

Participating patients developing clinically significant dehydration will not receive IMP until clinically resolved dehydration, but will continue with IMP after that.

Those patients who have to prematurely stop taking the IMP, except for patients' withdrawing their consent, will be followed up in the same framework of the study and in the same way as participants receiving IMP.

4.4.2. Premature termination of the study

The difference between groups in SAEs deemed to be linked to methenamine hippurate will be continuously monitored (appendix 5). 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 done by comparing the two groups without breaking the code. The code will be broken if the difference between groups in these adverse effects are statistically significant ($p<0.05$). The study will be prematurely terminated if the statistical difference is to the disadvantage of active IMP. SAE, SAR and SUSAR possibly related to the trial medication or UTI will be registered but not used for decision making for eventual premature termination of the study. The investigator will promptly inform the participants, the Ethics Committee (EC) and other relevant regulatory authorities according to national regulations providing a detailed written explanation.

5. STUDY TREATMENTS

5.1. Identity of investigational medicinal products

IMP will be provided by the pharmaceutical company Mylan A/S who will send the IMP and corresponding placebo to Kragerø Tablettproduksjon AS (see attachment), who will be responsible for packing and labelling of boxes according to the randomisation list. Kragerø Tablettproduksjon AS will deliver IMP to a designated pharmacy in each country which in turn will distribute IMP to

participating sites. The IMP will be handed out consecutively to participants for six months use (four boxes with 90 tablets each), in accordance with the randomisation list.

Kragerø Tablettproduksjon AS will create 200 sets of boxes containing methenamine hippurate and 200 sets of boxes containing placebo (lactose). The boxes will have identical labelling (see attachment). Only patient ID on the label will be linked to the randomisation list, telling which medication the patient has received.
Boxes with active substance consist of tablets with the active substance methenamine hippurate 1 gram. This is equivalent to the standard recommended dose of methenamine hippurate as presented in Summary of Product Characteristics (SmPC) (attachment). Boxes with placebo drug will contain the equivalent dose of lactose.

5.1.1. Doses and length of treatment.

Participants will be instructed to take one study tablet morning and evening for 180 days. This corresponds to a daily dose of 2 g methenamine hippurate or placebo daily. The dosage is according to SPC for preventive treatment. The length of treatment is line with previous studies which have used 6-12 months as length of treatment (13-16, 24-25). This is also in line with clinical practice, and we have chosen 6 months to maximise compliance in this vulnerable patient group.

5.1.2. Labelling

The acquisition, labelling, Qualified Person release and delivery of the methenamine hippurate will be performed by Kragerø Tablettproduksjon AS. The boxes will be labelled according to example (attachment) with corresponding labels for each country in local language.

5.1.3. Storage and handling

One pharmacy/medical distributor will be designated to be responsible for sending out the medication to the relevant sites in each country. The medication will be stored at each site in a locked cupboard in a secure access room. The sealed code envelopes will be kept together with the IMP in a locked cupboard. The monitor will check if any unauthorised code breaks has been performed during the study. IMPs will be stored according to storage instructions and local requirements with a controlled temperature not exceeding 30 degrees Celsius. Each study site will sign for sending out the IMP to the patient. Each study site will keep accountability logs and temp logs.

5.1.4. Drug accountability and treatment compliance

Any remaining non-used IMP will be gathered by a study nurse/phd-student by the end of 180 days of the trial and will be stored at the study site. The monitor will count remaining IMP and control treatment compliance and report this. Finally, the non-used IMP will be sent to the designated pharmacy for destruction. An accountability log will be made for each patient, including the batch number.

5.1.5. Destruction

Destruction of IMP will be performed at the designated pharmacy as stated above. Current medication taken by participants will be registered at inclusion. As interaction with other

medications are limited, there is no necessity to register changes in ongoing medication during the trial period with the exception of prescribed UTI antibiotics, sulphonamide antibiotics, alkalizing substances (such as antacids), or in case of SAE report.

5.2. Blinding

Boxes are to be handed out sequentially to each participating patient following the number on the boxes, 4 identical boxes with 90 tablets in each box, in total 360 tablets. No information on the boxes reveals if the content is active drug or placebo. The electronic version of the Excel files (one for each country) will be available for the monitor in order to assist with emergency unblinding when needed. The staffs involved in these procedures are not to disclose this information to anyone else until all statistical analysis is done. One exception is if there is an SAE and it is deemed important to break the code.

Kragerø Tablettproduksjon AS will produce 400 identical sets of boxes labelled either “ImpresU study drug – number ZZZ” or “ImpresU study drug – number ZZZ” (ZZZ is a sequential number from 1-400). Patients, 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).

5.3 Breaking the blinding in an emergency situation

The study code should only be broken for valid medical or safety reasons e.g. in the case of a severe adverse event where it is necessary for the treating physician to know which treatment the patient is receiving. There will be one sealed opaque envelope for each medication ID available, at the study sites, containing information of active substance or placebo regarding IMP. These envelopes will be stored together with the IMP. The treating physician contacts the coordinating centre or the PI via phone numbers available on patient/physician information cards regarding the study medication. On these cards, there will also be an emergency number provided by the Sponsor to be able to reach the code break envelope/list in emergency situations. The coordinating centre (or the Sponsor) provides the treating physician with the information as requested. On receipt of the treatment allocation details, the treating physician deals with the participant’s medical emergency as appropriate. The PI documents the breaking of the code and the reasons for doing so on the CRF and in the site file. The PI notifies the Sponsor as soon as possible following the code break detailing the necessity of the code break.

5.4 Concomitant medication

Medications considered necessary for the patient’s safety and well-being may be given at the discretion of the investigators unless not specified in the exclusion criteria. Concomitant medication will be recorded in the Case Report Form (CRF) at inclusion. As interaction with other medication is limited, there is no necessity to register changes in routine medication during the trial period with the exception of prescribed UTI antibiotics or in case of SAE report. In case of severe dehydration, or treatment with sulphonamide antibiotics the participant should temporarily pause IMP. Alkalizing substances (such as antacids) reduces the effect of methenamine hippurate and should be avoided.

Hence, patients requiring long term use of antacids will not be included, or withdrawn if there will be a need for long term use of alkalizing substances during the first six months when taking IMP.

6. STUDY MEASUREMENTS AND VARIABLES

- number of UTI antibiotic treatments (name of drug, dosage and duration) during day 2-360
- number of UTIs (acute symptoms specific/related to the urinary tract) during day 2-360
- registration of symptoms and severity when initiating treatment for UTI. This will be measured by a scale 0-6 (no symptoms to worst possible) for each of the three cardinal symptoms and general condition.
- registration of number of pyelonephritis and hospital admission for UTI
- laboratory tests at Visit 1: urine culture and dipstick urinalysis regarding pH, nitrite and leukocyte esterase
- laboratory tests ordered by the ordinary clinician in case of episodes of UTI during the study period (urinary dipsticks regarding nitrite and leukocyte esterase and urine culture)
- level of care: general practice, residential home care or nursing home
- SAEs, whereas relationship with IMP cannot be excluded.

6.1. Primary variable

(See section “2 Study Objectives and Endpoints”).

6.2. Secondary variable(s)

(See section “2 Study Objectives and Endpoints”).

6.3. Safety variable(s)

Pyelonephritis, hospitalization and death will be registered as safety endpoints. Methenamine hippurate has a well-documented safety profile and is a commonly used medication in primary care settings in Scandinavia. Therefore, non-serious adverse events (AE) will not be recorded in this study. All SAEs, whereas relationship with IMP cannot be excluded, occurring during the study period are recorded and reported according to guidelines in each country.

6.4. Biological sampling procedures

6.4.1. Handling, storage and destruction of biological samples

A urine specimen will be taken at the inclusion for culture and dipstick urinalysis regarding pH, nitrite and leukocyte esterase. The urine specimen will be destroyed after this.

In case of growth of pure cultures of E. coli in the inclusion urine culture, we will freeze the isolates of E.coli and send them to the department of clinical microbiology at Sahlgrenska University Hospital in Sweden for analysis of phylogenetic subgroups according to published protocols using PCR-technique.

Any episodes of acute UTI during the follow-up period (day 2-360) will be handled by regular health services (primary health care centres, OOH services or hospitals). The study team will order copies of medical records from acute UTI episodes including laboratory results regarding urinary dipsticks and urine culture. If feasible, we will also send pure culture E. coli isolates for phylogenetic typing as previously described.

6.4.2. Total volume of blood per patient

No blood tests will be taken in this study.

6.4.3. Biobank

The urine specimen taken at the inclusion visit for analysis of a urine dipstick and culture will not be registered in a biobank (if not required in national guidelines), as the urine specimen will be destroyed immediately after analysis. We will freeze isolates of E.coli from the inclusion urine culture, and if possible from some of the cultures taken during subsequent episodes of acute UTIs. Bacteria is not regarded human material and does not need a biobank registration.

7. SAFETY

7.1. Reference Safety Information

Anticipated adverse drug reactions in the study:

- Methenamine hippurate is well tolerated and adverse effects are generally mild (10)
- *According to SPC:*
- *Gastrointestinal disorders*
    - Uncommon: gastric irritation, irritation of the bladder, nausea, vomiting
    - Not known: diarrhoea, abdominal pain
- *Skin and subcutaneous disorders*
    - Uncommon: Rash, pruritus
- Alkalizing substances (such as antacids) reduces the effect of methenamine hippurate and should be avoided. Hence, patients requiring long term use of antacids will not be included or withdrawn if there will be a need for long term treatment with alkalizing substances when taking IMP during the first six months.
- Simultaneous intake of sulphonamide antibiotics can increase risk of crystalluria. Therefore, methenamine hippurate will temporarily be paused if the participant is prescribed a course of sulphonamide antibiotics.
- Except for those described above, there are no other known clinically relevant interactions between methenamine hippurate and other pharmaceuticals

7.2. Definitions

7.2.1. Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Causality
The investigator is responsible for determining whether there is a causal relationship between an AE and the use of a medicinal product.

AEs are categorized either as unrelated, possibly related or related, as defined below:

- **Unrelated**: the AE is not reasonable in relation to the use of the medicinal product, or another cause can itself explain the occurrence of the event.
- **Possibly related**: the AE may be explained by the medicinal product and the onset is reasonable in relation to the use of the medicinal product, however there is insufficient information to determine the likelihood of this possibility.
- **Related**: the AE is most likely explained by the medicinal product and the onset is reasonable in relation to the use of the medicinal product.

Severity
In addition to assessing the relationship of the administration of the investigational product(s) to adverse events, an assessment is required of the intensity (severity) of the event. The following over-all classifications should be used:

- **Mild:** An adverse event which is relatively mild and transient in nature, but can be an annoyance, and does not interfere with normal activities.
- **Moderate:** An adverse event which may be uncomfortable but is not hazardous to health. It may be sufficiently discomforting to interfere with normal activities but does not completely prevent them.
- **Severe:** An adverse event which is incapacitating and/or it is a hazard to the subject.

7.2.2. Adverse Drug Reaction (ADR)

Regarding marketed medicinal products: A response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function.

7.2.3. Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect.

Medical and scientific judgement should be exercised in deciding whether an event is “serious” and if expected reported is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered SAEs.

7.2.4. Suspected unexpected serious adverse reaction (SUSAR)

A SUSAR is a serious adverse reaction of which nature or severity is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

7.3. Reporting

7.3.1. Adverse Event (AE)

Methenamine hippurate has a well-documented safety profile and is a commonly used medication in primary care settings in Scandinavia. As a result of this no non-serious adverse events will be recorded in this study. All SAEs, whereas relationship with IMP cannot be excluded, occurring during the study period are recorded as detailed in Section 7.3.3 Reporting Procedures for Serious Adverse Events.

It will be left to the Investigator’s clinical judgment to decide whether or not a symptom or side effect is of sufficient severity to require the participant’s removal from treatment. A participant may also voluntarily withdraw from treatment due to what the participant perceives as an intolerable symptom or side effect.

7.3.2. Adverse Drug Reaction (ADR)

Methenamine hippurate has a well-documented safety profile and is a commonly used medication in primary care settings in Scandinavia. Therefore, non-serious AE will not be recorded in this study.

7.3.3. Serious Adverse Event (SAE)

All SAEs that is life threatening or results in death must be reported using the SAE Report Form by the person who has discovered the SAE or nominated delegate. The SAE form will be electronically submitted to the sponsor or delegate within 24 hours of the site study team becoming aware of the event.

SAEs requiring inpatient hospitalization or prolongation of existing hospitalization and AEs resulting in persistent or significant disability/incapacity will not be reported if being expected events in a frail elderly population (e.g. hip fracture, heart failure, ischemic heart disease). If these SAEs are related to UTI (e.g. pyelonephritis) they must be reported using the SAE Report Form by the person who has discovered the SAE or nominated delegate. If relationship with IMP cannot be excluded these SAEs are possibly, probably or definitely related to the trial medication. If so these adverse events must be reported as SAR (Serious Adverse drug Reaction) if expected and included in SmPC or as SUSAR (Suspected Unexpected Serious Adverse Reaction) if unexpected and not included in SmPC. SUSAR is further described in 7.3.4. The reason why only reporting these when relationship to IMP cannot be excluded: Methenamine hippurate is a well-known and widely used drug in Scandinavia with few and mild side effects which has been clinically used since many decades. There is no reason to expect any previously unknown AE and SAE to occur in this trial. Judgement whether related to UTI or the trial medication will be done by the PI of each country.

SAEs consisting of a congenital anomaly or birth defect is not relevant in this trial as all participants are women aged ≥70 years.

Please find safety reporting flow-chart in appendix 5.

SAEs will be registered throughout the studied period. In case of SAE present and not resolved by day 360, this SAE will be followed until resolution.

The sponsor or delegate will perform an initial check of the report, request any additional information, and ensure it is reviewed by the PI or other delegated personnel for relatedness and expectedness as soon as possible considering the reporting time for a potential SUSAR according to the relevant competent authority. Additional and further requested information (follow-up or corrections to the original case) will be detailed on a new SAE Report Form and submitted to the sponsor or delegate. See safety reporting flowchart in appendix 5. If the event has not resolved by day 360 the SAE will be reviewed again to see if resolution has occurred. If the event is considered “resolved” or “resolving” no further follow-up is required. If not, the event must be followed up until such a time point.

7.3.4. Suspected Unexpected Serious Adverse Reaction (SUSAR)

All SUSARs will be reported by the Sponsor or delegate to the relevant Competent Authority (CA) (EudraVigilance database) and to the Ethics Committee and other parties as applicable. For fatal and life-threatening SUSARs, this will be done no later than seven calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within eight calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

This study is an investigator initiated non-commercial study where the PI lacks the ability to report directly into the European database of side effects (EudraVigilance) and we therefore ask CA for help. SUSAR is reported via CIOMS-form.

7.3.5. Annual Safety Report

A safety report will be completed by the Sponsor once a year and sent to the relevant CA and the EC. The document will define the time period reported and summarize all occurred serious events (SAEs and SUSARs). The safety report should also always include a summary assessment of the safety of subjects that are still included in the trial and whether the benefit-risk assessment changed since the study was approved.

8. STATISTICS

8.1. Sample size calculation

The sample size calculation is made for the primary objective described in section "2 Study Objectives and Endpoints".

- We assume these selected older individuals will have an average of two courses of antibiotics for suspected UTI every six months (4).
- We assume a 25% reduction of antibiotic prescriptions during the first six-month period after introduction of methenamine hippurate. Hence the intervention group would have an average of 1.5 while the control group is assumed to remain around 2.0. We assume the standard deviation in each group to be 1.5. This will result in an effect size of 0.33 (small effect). We decided a smaller effect size would not be worth looking for.
- 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-Whitneys test (to be used if the outcome variable is not normally distributed). The planned statistical method to be used will be multivariate linear regression. Student's t-test and Mann-Whitneys 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's 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 at least 397 patients. We will aim to include 400 patients.

8.2. Statistical analysis

It is the intention to adjust all analysis for the following confounding variables obtained at visit 1

- patient's age
- urine acidity (pH)
- number of antibiotic courses for UTIs in the 12 months preceding inclusion in the study
- presence of urease/stone-producing bacteria in urine culture day 1 such as proteus, some klebsiella species, Morganella morganii, Corynebacterium urealyticum and providencia

- use of local oestrogen
- patient has diabetes mellitus
- obesity defines as BMI ≥30
- presence of known mild abnormality of the urogenital tract
- if the patient is sexually active.
- If the patient previously have experienced urinary tract stone

Phylogenetic subtype of pure cultures of E.coli in the urine culture at inclusion will be analysed in a separate analysis if the number of cultures available for typing are not too small.

The statistical calculation relates to the study objectives described in section "2 Study Objectives and Endpoints":

1 Standard linear regression will be used where 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.

2a Will be analysed using the same statistical approach as objective 1 above.

2b Will be analysed using the same statistical approach as objective 1 above. Number of UTIs will be the dependent variable.

2c The outcome variable is measured at first day of a UTI using a six grade ordinal scale. The median value from 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. It will be analysed using linear regression using the same covariates as when analysing objective 1. This will deliver a p-value but no useful effect size.

2d Will be analysed using the same statistical approach as objective 1 above. Number of days with symptoms will be the dependent variable.

2e Will be analysed using the same statistical approach as objective 1 above. Number of severe events such as pyelonephritis or hospital admission will be the dependent variable.

2f Phylogenetic subtype of pure cultures of E.coli in the inclusion urine culture at inclusion will be analysed in a separate statistical analysis if the number of cultures available for typing are at least 60 patients. All statistical above will be redone adding phylotype as an extra independent variable. Purely descriptive statistics will be presented in case the number is below 60.

<u>Intention to treat analysis and missing data</u>
The primary statistical analysis is intention to treat. Patients leaving the study completing only a part of the first six months will contribute with data up until they leave the study. Their data will be recalculated as if they had participated all six months. Patients leaving during the second six months period will also contribute with data as above. Patients leaving the study before the second six-month period commence will have their value for this period set to be the median value for both groups.

<u>Complete case analysis</u>
A complete case analysis will also be made where only patients having a complete data set will be included.

<u>Per protocol analysis</u>
A per protocol analysis will not be made.

9. DATA MANAGEMENT

9.1. Recording of data

The investigator will ensure that all data collected in the study are recorded in a timely manner according to any instructions provided. An electronic Case Report Form (eCRF) will be used for data collection. The investigator will ensure that the data are recorded and that any corrections in the CRF as specified in the study protocol and in accordance with the instructions provided. The investigator ensures the accuracy, completeness and timeliness of the data recorded.

Research Online (RO) is an electronic data capture (EDC) system that will be used for data collection. Web-based case report forms (eCRF) are implemented into the system to facilitate the study specific data collection. These forms can easily be accessed by all standard web browsers. The baseline CRF at inclusion, telephone follow-up in case of acute UTI episode(s), telephone contact by end of treatment, telephone contact by end of study and SAE Forms will be entered onto this system. Some sites may choose to first register data in a paper version of the CRF that will later be entered into the eCRF by the coordinating centre. The investigator will sign the completed CRF. A copy of a completed paper CRF will be archived at the study site. The original paper CRF will be archived at the coordinating centre in each country.

Multiple validation and range checks will be programmed in the eCRF to assure complete and high-quality data. Data that does not comply with these rules or ranges will generate a query that must be resolved immediately or at a later stage. Electronic workflows will employ multiple skip and jump rules to ensure that only information that is applicable to the patient will appear. After the data of the last subject is entered, the clean file will be produced and thereafter the database will be closed and data made available for further analysis and publication purposes.

RO meets all requirements according to GCP standards for electronic data entry with respect to safeguarding data integrity and data security regulations. Users will have role-based access to the system by logging in using their personal username and password. The system will log all data entry steps with timestamps and user information. The role-based access to the system will avoid unauthorised data access and prevents users from performing actions that they do not have authorisation for.

Project management of the study is facilitated by the integrated real live study progress reports. RO data traffic over the Internet is encrypted using secured data communication protocols. Dedicated databases and web servers are hosted in a secure data centre, the database (PostgreSQL) is backed up on a daily basis.

Participants will be identified by a unique trial specific number and/or code in any database. The name and any other identifying detail will not be included in any trial data electronic file, only within a separate password protected administration database.

9.1.1. Source data

The investigator must maintain source documents for each subject in the study. A source data verification log will be included in the Investigator Study File (ISF). The investigator must ensure that all source documents are accessible for monitoring.

Source documents are original documents, data, and records from which participants' CRF data are obtained. These include, but are not limited to, general practice and hospital medical records. CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). In this study the CRF will be used as the source document for the documentation of inclusion and exclusion criteria, and baseline assessment information (visit 1), which will include, but not be limited to, comorbidities (see point 3.4. study assessment visit 1) and severity of UTI-symptoms.

All documents will be stored safely in confidential conditions. On all study-specific documents, other than the signed consent and contact details form, the participant will be referred to by the study participant ID, not by name. Requested reports from medical records and laboratory results will be entered into CRF.

9.2. Data storage and management

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification. All source data including informed consent, a copy of the completed CRF, original protocol with amendments and the final report will be stored at the coordinating centres for a minimum period of fifteen years after termination of the trial, in accordance with country specific regulation/law.

Staff designated by the Sponsor will review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are issued electronically. Designated investigator site staff is required to respond to the query and confirm or correct the data.

At the conclusion of the study, the occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and available for data analysis.

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

10. QUALITY CONTROL AND QUALITY ASSURANCE

10.1. Monitoring

A study monitor will be appointed by the sponsor. The monitor will be appropriately trained and informed about the nature of the study, subject written information, GCP and applicable regulatory requirements. The monitor's qualifications will be documented. Monitor Hege Øvergaard will

monitor the study in all 4 countries, and separate agreements between monitor and PI in each country will be made.

The quality control of this study will have a risk-based approach. The monitor will have regular contacts with the clinic to verify informed consents of participating subjects, to confirm that facilities remain acceptable, that the investigational team is adhering to the protocol, that data are being accurately recorded in the CRFs, to verify inclusion/exclusion criteria, study main endpoints, check SAE reporting and that therapy accountability is being carried out. The investigator should ensure that all persons assisting with the trial are adequately informed and trained about the protocol, the investigational product(s) and their trial related duties and functions. The monitor will check that training has been performed and that this is documented. The monitor will also ensure source data verification (comparison of the data in the CRF with the medical records and other source data). The monitor must have direct access to source data. The extent of monitoring will be defined in a monitoring plan.

10.2. Audits and inspections

Authorized representatives of the sponsor, a Competent Authority or an Ethics Committee may perform audits or inspection at the centre, including source data verification. The investigator must ensure that all source documents are accessible for auditing and inspection. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed and accurately reported according to the protocol, Good Clinical Practice (GCP) and any applicable regulatory requirements.

10.3. Data safety monitoring committee

A data safety monitoring committee will be established and will consist of 3 external researchers with experience from clinical trials on UTI infections in primary care. They will meet every 6 months during the trial to ensure data safety. For premature termination of the study, see 4.2.2.

11. ETHICS

The study will be performed in accordance with the protocol, with the latest version of the Declaration of Helsinki, with Good Clinical Practice (ICH-GCP E6(R2) and applicable regulatory requirements.

11.1. Ethics committee

The final study protocol, including the final version of the Informed Consent Form and other information given to subjects e.g. advertisements, must be approved or given a favourable opinion in writing by an Ethics Committee (EC) as appropriate. The Principal Investigator is responsible for informing the EC of any amendment to the protocol, in accordance with local requirements. Progress reports and notifications of any serious and unexpected adverse drug reactions will be provided to the EC according to local regulations and guidelines.

11.2. Informed consent

The Principal Investigator at each centre will ensure that the subject is given full and adequate oral and written information about the nature, purpose and possible risks and benefits of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The monitor(s), the auditor(s), and the CA(s) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.

The original signed Informed Consent Form (ICF) must be stored in the Investigator's Study File. A copy of the signed ICF must be given to the subject.

The EC must approve modifications that lead to a revised ICF before the revised form is used.

11.3. Subject data protection

The ICF will incorporate wording that complies with relevant data protection and privacy legislation. Pursuant to this wording, subjects will authorize the collection, use and disclosure of their study data by the investigator and by those persons who need that information for the purposes of the study.

The ICF will explain that study data will be stored in a computer database, maintaining confidentiality in accordance with national data legislation. All data computer processed by the sponsor will be identified by ImpresU WP3/Subject ID/Initials.

The ICF will also explain that for data verification purposes, authorized representatives of the sponsor, a regulatory authority or an EC may require direct access to parts of the hospital or practice records relevant to the study, including subjects' medical history.

11.4. Insurances

The Norwegian study subjects are covered by Legemiddelansvarsforsikringen.
The Swedish study subjects are covered by Svenska Läkemedelsförsäkringen, LFF Service AB.
The Dutch study subjects are covered by CNA Insurance Company (Europe) S.A.
The Polish study subjects are covered by Towarzystwo Ubezpieczeń i Reasekuracji „WARTA".

12. PROTOCOL DEVIATIONS AND AMENDMENTS

Modifications to the signed protocol are only possible through approved protocol amendments and with the agreement of all responsible persons. Details of non-substantial amendments are to be clearly noted in the amended protocol.

A change that concerns; a new trial site, new principal investigator and or a new informed consent form should only be submitted to the concerned EC.
In case of a substantial protocol amendment (e.g. change of; main purpose of the trial, primary/secondary variable, measurement of primary variable, investigational product, or dosing), the concerned EC and CA must be informed and should be asked for its opinion/approval prior implementation of amended protocol, as to whether a full re-evaluation of the ethical aspects of the study is necessary by the committee. This will be fully documented.

The Investigator must not implement any deviation from, or change to the protocol, without discussion with, and agreement by the Sponsor and prior review and documented approval/favourable opinion of the amendment from the relevant EC and CA, except where it is necessary to eliminate an immediate hazard to study subjects, or where the change(s) involves only logistical or administrative aspects of the study (e.g. change in monitor(s), change of telephone numbers).

13. REPORT AND PUBLICATIONS

After completion of the study, the results will be analysed and a clinical study report will be prepared. Within one year after the end of the study, the sponsor will submit a study report with the results of the study, including any publications/abstracts of the study, to the accredited EC and the CA. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

14. STUDY TIMETABLE

14.1. Study Period

Subject enrolment is estimated to start by November 1st 2019, subject enrolment is estimated to stop on December 31st of 2020 and last subject last visit is estimated to be on December 31st 2021.

14.2. Definition of “End of study”

Data collection will stop when the target number of participants are included. The study ends when the last follow up is made for all included participants. Hence, the study may formally end before results are accepted for publication. The sponsor will notify the concerned EC and the CA of the end of the study within a period of 90 days.

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