

Protocol 19-01: Canadian, Single Centre, Pilot, Open Label Study to Evaluate the Efficacy and Safety of the Bacterial Vaccine Uromune® in Treating Recurrent Urinary Tract Infections in Women.

An Investigator Initiated Study

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Background:

Recurrent urinary tract infections (recUTIs) are a major clinical problem in Canada resulting in over 500,000 visits to physicians annually. Over 50% of women will suffer from a UTI and 20-30% of women who previously experienced a UTI will develop recUTIs (defined as 3 or more UTIs during a 12 month period). Many women are treated with multiple courses of antibiotics while others are managed with long-term low dose antibiotic therapy. This is contributing to not only the ill health of individual patients being treated with antibiotics (disrupting the natural human microbiome) but also to the alarming rise in antibiotic resistance in Canada. There is a large unmet need to develop alternate strategies to prevent UTIs in women in Canada.

Uromune® is a sublingual spray mucosal type vaccine [1, 2], currently in the pre-license phase development stage and is available in a number of countries in Europe, the UK and New Zealand under various patient programs. Spanish studies comparing Uromune® therapy with antibiotic therapy in women with recUTIs have reported a significant decrease in UTI recurrence with a 90.3% absolute risk reduction (95% CI: 87.2-93.4). There were no reported side effects in any participant in the Uromune arm of the study [3]. An early experience study of women with recUTI in the UK reported that 78% (59/75) had no subsequent UTI in the 12 months after the vaccine was administered. Only one participant reported a skin rash requiring treatment cessation [4].

Rationale:

The proposed study will be undertaken to provide early clinical experience in regard to the efficacy and safety of the vaccine Uromune® in Canadian women identified with recUTI.

Objective:

To determine the effectiveness and safety of Uromune® in preventing recUTI in Canadian women.

Study Synopsis

The proposal is for a real life clinical practice study in which female participants with a predefined history of recurrent UTIs in the previous year will be treated with 3 months of oral vaccine with a further 9 months of follow-up. The primary outcome will be no UTI in the 12 months following initiation of the vaccine (definition of a responder). A clinically significant and important outcome will be defined as a responder rate of 50% (50% of participants who had at least 3 UTIs in the previous year reporting no UTIs after therapy initiated).

Study Protocol

Study Participants

Main Inclusion Criteria:

Eligible participants will include women with at least 3 reported UTI episodes requiring antibiotics in the preceding 12 months or at least 2 reported UTI episodes requiring antibiotics in the preceding 6 months. In both cases, at least one of the episodes must be associated with a positive urine culture with a traditional and accepted uropathogen.

Other inclusion Criteria:

- Female participant ≥ 18 and ≤ 75 years of age at time of screening.
- Can provide written consent and willingness to comply with all aspects of study treatment and study requirements.
- Individuals who have had at least 3 episodes of a UTI in the past 12 months or 2 UTI episodes in the past 6 months. At least one of the UTI episodes must be associated with a positive urine culture with a traditional uropathogen including *Escherichia coli*, *Proteus spp.*, *Staphylococcus sp.*, *Enterococcus sp.*, *Klebsiella sp.*, or *Pseudomonas aeruginosa*.
- Post-menopausal for a minimum of 1 year or negative pregnancy test if participant is of child bearing potential and agreement to acceptable contraceptive use from Screening Visit 1 to final follow up visit if

participant is sexually active. Medically acceptable methods of contraception include hormonal contraception (i.e. estrogen, and/or progesterone or preparations that contain a combination of these hormones), non-hormonal intrauterine device or double barrier method (i.e. condom with foam or vaginal spermicidal suppository, or diaphragm with spermicide) or vasectomy of sole sexual partner. Complete abstinence alone can be used as a method of contraception.

- Free of a urinary tract infection at the time of trial inclusion.

Exclusion Criteria

- History of bladder tumours including uterine, cervical, vaginal or urethral cancer.
- Worrisome post-voiding residual (investigator's discretion).
- Infection related to urinary lithiasis.
- Any immunological disease requiring active therapy.
- Currently receiving Immunotherapy.
- Taking any prophylactic antibiotics at screening. Any prophylactic antibiotics must be stopped the day of the screening visit.
- Any known intolerance to the ingredients of the Uromune® Immunotherapy.
- Have any other condition or disease which, in the opinion of the investigator, could compromise participant safety or interfere with the participant's participation in the study or in the evaluation of the study results.

If a participant is found to have a UTI at screening, they are not excluded from the trial. Participants found to have a UTI at screening should be put on antibiotics. After completion of antibiotics and once negative urine test results have been received, participants may be eligible for screening deferral or re-screening as outlined below.

Participant Withdrawal

All participants may withdraw from the study at any point for any reason. They may withdraw at their own request or at the discretion of the investigator.

If a participant is withdrawn at any point between the Screening Visit and the Baseline Visit (Day 1) they will not be required to complete an Early Termination Visit as they will not yet have started study treatment. At any point after the participant begins taking study treatment (Baseline Visit), if they should withdraw for any reason, every effort should be made to complete the Early Termination Visit detailed below in the protocol. It should be documented in the CRF the reason for withdrawal and discontinuation of the study treatment. Any AEs or

SAEs should also be documented in the CRF at this end of study visit. Despite early discontinuation from the study, every effort should be made to follow AEs and SAEs as outlined in the Safety Reporting section of this protocol.

Screening Deferral and Re-Screening

At the time that a participant is screened, if they are found to have a current UTI, they are eligible for screen deferral or re-screening.

Deferral

A participant presenting with a UTI at the screening visit will be deferred from further participation in the study until after antibiotic treatment and receipt of negative urine results. These results must be received within the 4-week time period between the screening and the baseline visit in order for the participant to continue in the study. The participant will not be assigned a new study number.

Rescreen

If the participant presents with a UTI at the screening visit and is not able to meet the requirements as indicated in the deferral section above, the participant will be rescreened **one time only** at a later date and assigned a new study number

Study Assessments and Procedures

Table 1: Schedule of Assessments. The following table outlines the timing of each study assessment. More detailed descriptions regarding each study visit can be found below the table.

Study Assessment or Procedure	Screening Visit	Baseline Visit	3 Month Clinic Visit	6 Month Phone Call	9 Month Phone Call	12 Month Clinic Visit	Unscheduled visit	Early Termination
Informed consent process	X							
Inclusion/exclusion criteria	X	X						
Participant demographics	X							
Vital Signs	X	X	X			X	X	X
Complete medical history	X							
Physical examination	X							
UTI history	X		X	X	X	X	X	X
Midstream urine sample for urinalysis, bacterial culture and pregnancy test	X	X	X			X	X	X
Quality of Life and Satisfaction Questionnaires		X	X			X		X
Concomitant medications	X	X	X	X	X	X	X	X

Diary instructions		X	X					
Vaccine instructions and first dose administration		X						
Return finished study treatment bottle			X					
Vaccine compliance check			X				X	
Diary compliance check			X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X

Pre-Treatment Evaluations:

Screening visit:

At the initial clinic visit the participant will undergo:

- Informed consent process.
- Review of inclusion and exclusion criteria.
- Participant demographics including birth year and ethnicity.
- Vitals (blood pressure and heart rate), height and weight.
- Urine (midstream specimen) for urinalysis, bacterial culture and pregnancy test (if participant is of child bearing potential) will be collected.
- A review of any concomitant medications.
- Complete medical history.
- Physical examination.
- UTI history including number of UTIs experienced in the past 12 months, previous urine culture results and review of previous treatments received for past UTIs.

Baseline Visit (Day 1):

Within 4 weeks (30 days) of the screening visit the potential participant will have a return visit to the clinic and undergo the following:

- Review of inclusion and exclusion criteria.

If participant meets all of the requirements for study eligibility they will undergo the following:

- Baseline Quality of Life (SF-12) and Satisfaction Questionnaires will be completed.
- Vitals (blood pressure and heart rate), height and weight.
- Urine (midstream specimen) for urinalysis, bacterial culture and pregnancy test (if participant is of child bearing potential) will be collected.
- Review of any changes in concomitant medications.
- Reporting of any adverse events or changes in health status.
- Receive oral and written instructions for participant weekly diary use.
- Participants will receive 3 month (90 day) supply of Uromune® treatment and be given instructions on administration of study treatment. The participant will administer first dose of study treatment during this visit.
- Review of any adverse events after study treatment administration.

Participant Follow-Up:

3 Month Clinic Visit (90 days +7 from Baseline Visit):

Participants will return to the clinic for a predetermined visit following the three month (90 day) vaccine administration. During this visit participants will undergo:

- Completion of Quality of Life Questionnaire (SF-12) and Satisfaction Questionnaire prior to any other study procedures.
- Vitals (blood pressure and heart rate), height and weight.
- Urine (midstream specimen) for urinalysis, bacterial culture and pregnancy test (if participant is of child bearing potential) will be collected.
- Return of study treatment bottle.
- Diary compliance check and return of treatment period diary.
- Vaccine compliance check. This will be conducted through a review of the participant's diary.
- Reporting of any adverse events or changes in health status.
- Review of any changes in concomitant medications.
- Review of UTI history including symptoms, number of diagnosed UTIs, review of cultures performed, bacteria responsible for UTI and any treatments participant has received over the preceding 3 month period (If the participant has reported a UTI, all efforts will be made to complete the CRF with documentation of physician notes and/or culture reports if available).
- Instructions on how to complete the post treatment symptom diary.

6 Month Phone Call (+/- 7 days):

Participants will be contacted by phone 6 months after their baseline visit and asked about the following:

- Diary compliance check to ensure participant has been completing their symptom diary.
- Reporting of any adverse events and a check of health status.
- Review of any changes in concomitant medications.
- Review of UTI history including symptoms, number of diagnosed UTIs, review of cultures performed, bacteria responsible for UTI and any treatments participant has received over the preceding 3 month period (If the participant has reported a UTI, all efforts will be made to complete the CRF with documentation of physician notes and/or culture reports if available).

9 Month Phone Call (+/- 7 days):

Participants will be contacted again by phone 9 months after their baseline visit and asked about the following:

- Diary compliance check to ensure participant has been completing their symptom diary.
- Reporting of any adverse events and a check of health status.

- Review of any changes in concomitant medications.
- Review of UTI history including symptoms, number of diagnosed UTIs, review of cultures performed, bacteria responsible for UTI and any treatments participant has received over the preceding 3 month period (If the participant has reported a UTI, all efforts will be made to complete the CRF with documentation of physician notes and/or culture reports if available).

12 Month End of Study Clinic Visit (+/- 7 days):

Participants will return to the clinic for a predetermined visit 12 months after their baseline visit. During this visit participants will undergo:

- Completion of Quality of Life Questionnaire (SF-12) and Satisfaction Questionnaire prior to other study procedures.
- Vitals (blood pressure and heart rate), height and weight.
- Urine (midstream specimen) for urinalysis, bacterial culture and pregnancy test (if participant is of child bearing potential) will be collected.
- Diary compliance check and return of post treatment period diary.
- Reporting of any adverse events and check of health status.
- Review of any changes in concomitant medications.
- Review of UTI history including symptoms, number of diagnosed UTIs, review of cultures performed, bacteria responsible for UTI and any treatments participant has received over the preceding 3 month period (If the participant has reported a UTI, all efforts will be made to complete the CRF with documentation of physician notes and/or culture reports if available).

Unscheduled Study Visit:

Should a participant return to the clinic for an unscheduled visit they will undergo the following:

- Urine (midstream specimen) for urinalysis, bacterial culture and pregnancy test (if participant is of child bearing potential) will be collected.
- Vitals (blood pressure and heart rate), height and weight.
- Reporting of any adverse events.
- Reporting of changes in concomitant medications.
- Diary compliance check.
- Study treatment compliance check (only if unscheduled visit occurs during the 90 day treatment period).
- Review of UTI history including symptoms, number of diagnosed UTIs, review of cultures performed, bacteria responsible for UTI and any treatments participant has received over the preceding 3 month period (If the participant has reported a UTI, all efforts will be made to complete the CRF with documentation of physician notes and/or culture reports if available).

Early Termination:

If the study is stopped early based on planned protocol interim analysis and/or stopping rules or if the participant withdraws from the study every effort should be made to bring the participant in for an Early Termination Visit. At this visit the participant will undergo the following:

- Completion of Quality of Life Questionnaire (SF-12) and Satisfaction Questionnaire prior to other study procedures.
- Vitals (blood pressure and heart rate), height and weight.
- Urine (midstream specimen) for urinalysis, bacterial culture and pregnancy test (if participant is of child bearing potential) will be collected.
- Diary compliance check and return of treatment period diary or post treatment period diary depending on timing of visit.
- Reporting of any adverse events and a check on health status.
- Review of any changes in concomitant medications.
- Review of UTI history including symptoms, number of diagnosed UTIs, review of cultures performed, bacteria responsible for UTI and any treatments participant has received over the preceding 3 month period (If the participant has reported a UTI, all efforts will be made to complete the CRF with documentation of physician notes and/or culture reports if available).
- Vaccine compliance check and return of study treatment bottle (only if visit occurs during the 90 day treatment period).

Specimen Collection and Procedures:

Midstream urine specimen:

To perform a midstream urine specimen collection, please instruct all participants to follow the same procedure. Participants should be given instruction to hold the labial folds open, clean the urinary opening with the provided cleaning towelette, begin urinating into the toilet and then bring the open specimen bottle into the urinary stream to collect the “midstream urine”. Participants can be told to stop collecting when the specimen container is half to two thirds of the way full. They should then firmly tighten the lid on the container.

A urinalysis, urine culture and pregnancy test (if indicated) will then be performed on the midstream urine sample.

This sample will only be kept for the time period required to conduct the testing and any left-over sample will be destroyed. Samples will be analyzed by the study staff and then sent to the local lab for analysis.

Quality of Life (SF-12) and Satisfaction Questionnaires:

At each clinic visit, participants will be asked to complete the Quality of Life Questionnaire (SF-12) and the Satisfaction Questionnaire. At the beginning of the clinic visit, both questionnaires should be given to the participant and they should be given ample time to complete them prior to any other study procedures

or assessments being conducted. Both questionnaires must be done before any other study related activities so as not to have any influence on the way that the participant answers the questions.

Treatment Period Diary

At the baseline visit, participants will be given their treatment period diary and receive instructions on how to complete it. This diary will be done on a weekly basis during the 90 days they are on study treatment. Participants should be instructed to complete one page of their diary at the end of each week (7 days). In the diary participants will record whether or not they have taken their vaccine every day for the past 7 days. If they have not, they will need to record how many times they did take it. They will also record any symptoms they have experienced that week. If participants do experience symptoms they will be instructed to record any medical attention they sought and any treatment they received. Detailed instructions for the participants can be found on the front page of the diary. Participants will return their diary at their 3 month clinic visit.

Post Treatment Period Diary

At the 3 month clinic visit participants will receive their post treatment period diary, along with instructions on how to complete it. This diary does not need to be completed at any specific time. From the 3 month visit until their 12 month end of study visit, participants will be instructed to fill out this diary only when they experience a symptom. They will record the date of their symptom, what symptom they experienced, any medical attention they sought and any treatment they received. Detailed instructions for the participant can be found on the front of the diary. Participants will be asked about this diary at their 6 and 9 month follow up phone calls and they will return their diary at their 12 month end of study visit.

Study Treatment

Description of Investigational Product

The investigational product, Uromune®, being used in this study will be supplied by Immunotek, Spain to Red Leaf Medical in Mississauga, Ontario. Red Leaf Medical will distribute the investigational product. Properties and characteristics of Uromune® can be found in the Investigators Brochure.

9mL vials of the investigational product will be shipped from Red Leaf Medical to the investigator, Dr. Nickel. Should the site require additional vials of study treatment they will be required to contact Red Leaf Medical. Participants will be provided with 9 mL vials of Uromune® treatment. This will be enough to last participants the 3 month treatment period (90 days).

Packaging

The investigative product will be packed in a sterile topaz glass vial, closed with a white plastic swivel top containing a spray insert. Each vial will contain 9 mL of Uromune®. Sufficient quantities will be dispensed to enable the participant to continue to take the study medication up to the next study visit.

Labelling

Each bottle will be labelled in accordance with all applicable regulatory requirements.

Storage

Authorized study staff will supply the study treatment to participants. All investigational products must be stored in a secure and locked location where only the investigator and study staff may access it.

The investigative product is to be stored in its original packaging in order to protect it from light. It is to be kept refrigerated at 5 (± 3) degrees Celsius without excursions. It is important not to freeze the product.

Temperature excursions outside of the accepted range will be immediately reported to the Investigator, Dr. Nickel and the study drug affected will be quarantined. Documentation of the excursion is to be recorded and sent to Dr. Nickel by email or in person for review and determination of continued use of the study drug. Dr. Nickel will consult with Red Leaf Medical.

Dosage and Administration (Day 1)

Once all Baseline Visit procedures are completed eligible participants will receive a 3 month supply of Uromune® treatment. Participants will be instructed to take 2 sprays of the treatment under their tongue, once daily for 3 months (90 days). The liquid is to be held under the tongue for 2 minutes without swallowing. After the 2 minutes has passed the liquid is to be swallowed. The Uromune® treatment is to be taken before breakfast each day to avoid mixing it with foods or beverages.

If a dose is missed, participants should take the dose as soon as they remember on the same day and inform the study staff. However, if it is the next day, the missed dose should be skipped and the next dose taken as normal. **Only one dose of study drug (2 sprays) should be taken each day** and a double dose should not be taken.

Study Treatment Compliance

Participant compliance with the study treatment will be assessed through a review of the participant's Treatment Diary during their 3 month clinic visit. At the 3 month clinic visit, the participant will return the study treatment bottle and any unused study treatment.

Drug Accountability

The investigator will be responsible for product accountability. Site staff will be required to maintain a drug accountability log throughout the duration of the study. These records shall include dates, quantities, batch numbers, and expiry dates, receipt date of study medication at site, dispense date of study drug to each participant and return date of each participants study drug.

Safety Reporting

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE. The research coordinator will record all clinical AEs, noted during the trial, on the AE event log, report to the Investigator, Dr. Nickel, and enter into the electronic data capture database (EDC). All adverse events will be reported to the ethics board as per local guidelines.

For this study, the following standard AE definitions are used:

Adverse Event (AE)

An AE, also known as an adverse experience, is defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment (ICH GCP/Health Canada Division 5).

An AE can therefore be any unfavorable and unintended sign, symptom, abnormal results of an investigation, or disease (new or exacerbated) temporally associated with the use of the investigative product, without any judgement on causality

Events that do not meet the definition of an AE include:

- Medical or surgical procedures; the condition that leads to the procedure is an AE.
- Anticipated day-to-day fluctuations of a pre-existing disease or condition present at the start of the study that do not worsen.
- The disease/disorder being studied (eg. Recurrent urinary tract infections) or expected progression, signs or symptoms of the disease being studied, unless more severe than expected for the participant's condition.

AEs that are serious, unexpected and at least possibly related to study participation will be reported to the Research Ethics Board and to Health Canada within the timelines indicated below.

All other AEs such as those that are not serious, expected and not related to the study participation will not be reported to the local Research Ethics Board, as per local guidelines.

Serious Adverse Event Definition/ Reporting Requirements

An adverse event is considered serious if any untoward medical occurrence includes any of the following:

- a) Results in death:
This includes any death that occurs while the participant is in the study.
- b) Is immediately life-threatening.
When in the view of the Investigator, the AE places the participant at immediate risk of death. It does not include a reaction that had it occurred in a more severe form, might have caused death.
- c) Event requires in-patient hospitalization or prolongation of existing hospitalization.
In the absence of an AE, hospitalization or prolongation of hospitalization should not be reported as an SAE in the following circumstances:
 - Hospitalization or prolongation of hospitalization is part of a routine procedure followed by the study centre.
 - Hospitalization for survey visits or annual physicals.
 - For hospitalization planned and documented before the start of the study for preexisting condition which has not worsened.
- d) Is a congenital anomaly/birth defect.
- e) Results in persistent or significant disability or incapacity.
- f) Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

Recording Adverse Events

All adverse events, which include any detrimental change in the participant's condition, will be collected from the time the participant signs the consent form until the follow up period is completed at the 12 month clinic visit.

AEs will be captured wherever possible as a diagnosis and it is the Investigator's responsibility to ensure this is done. All AEs including SAEs are to be accurately recorded on the Adverse Event case report form(s). The Investigator will carefully evaluate each AE to determine severity, expectedness, relatedness and outcome as indicated below.

Severity:

- **Grade 1 Mild:** Participant is aware symptoms but they are easily tolerated and have no or mild impact on regular activities. Symptoms do not require medical attention or treatment.
- **Grade 2 Moderate:** An event the participant experiences that is of minor concern or convenience. These events may have an impact on

daily activities but can typically be improved with simple therapeutic measures. These experiences may interfere with the participant's normal functioning.

- **Grade 3 Severe:** These events are usually incapacitating to the participant. They impact normal daily activities and typically require treatment or systemic drug therapies.
- **Grade 4: Life threatening or disabling.**
- **Grade 5: Death**

Expectedness

AEs must be classified based on whether or not they were expected given current knowledge of the study treatment and procedures:

- **Unexpected:** The event is not expected based on current information of the condition or the study treatment as outlined in the protocol, investigator's brochure or consent form. Is considered for expedited reporting purposes when the type or event or severity of the event is not listed in the current IB.
- **Expected:** The event is known to be associated with the condition being studied or the intervention.

Expected AES

Expected transient AEs associated with treatment reported occurrence <10%.

- Post nasal drip
- Stinging around mouth
- Pruritus over old BCG scar
- Pruritus over abdomen
- Intermittent abdominal pain
- Mild nausea
- Asthma exacerbation

Serious Adverse Event

Reported occurrence <2%.

- Severe rash face and neck within 2 days of start of treatment and after restarting the treatment several times a month later. No evidence of airway compromise or anaphylaxis reaction. Antihistamines given to relieve symptoms.

Relatedness

The Investigator must attempt to determine if an AE or SAE is related to the use of the study treatment or procedures:

- **Related:** The adverse event is clearly related to the procedures or the study treatment.
- **Possibly Related:** An adverse event that follows study treatment administration. The event follows a known or expected response but could have been produced by other factors.
- **Not Related:** The adverse event is clearly not related to the procedures or investigational product.

Outcome of an SAE

Each SAE will need to be followed for outcome. The outcome of each SAE will need to be reported on throughout the duration of the study. Each SAE can be reported as:

- Resolved
- Recovered with minor sequelae
- Recovered with major sequelae
- Ongoing/Continuing treatment
- Condition worsening
- Death
- Unknown

This information will be collected on the AE Log case report form.

Follow-up of Unresolved Adverse Events

During the course of the study, all AEs and SAEs will be proactively followed up for each participant for as long as the event is ongoing. Every effort will be made to obtain a resolution for all events, even if the events continue after the participant has discontinued study drug or the study has completed.

Any AEs that are unresolved at the participant's last visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the case report form. The Investigator of this study, Dr. J. Curtis Nickel retains the right to request additional information for any participant with ongoing AEs or SAEs at the end of the study, if judged necessary.

Serious Adverse Event and Serious and Unexpected Suspected Adverse Reaction Review and Potential Impact on Trial

The investigator will review each SAE report and evaluate the relationship of the SAE to the study drug and to the participant's underlying condition.

Based on the Investigator's assessment of causality of the AE and discussions with the Safety Lead, a decision will be made by the Investigator concerning the need for further action with respect to the future conduct of the study. The primary consideration governing action is whether new findings affect the safety

of the participants taking part in the clinical study. If a new AE related to the study drug raises concern over the safety of the its continued administration to participants, the Investigator will take immediate steps to notify Health Canada, other regulatory authorities.

Further action required may include:

- Alteration of the existing research protocol.
- Discontinuation or suspension of study.
- Alteration of the informed consent and informing current study participants.
- Modification of previously identified expected suspected adverse reaction lists to include AEs newly identified as study drug related.

All SAEs must be reported, whether or not considered related to the investigational product or to the study procedures. From the time the participant consents to participate in the study until they have completed the study, all serious adverse events must be reported to the Investigator, study monitor and safety lead within 24 hours of becoming aware of the event.

All SAES to be reported in person or by email to:

1. Study Investigator, Dr. Nickel @ jcn@queensu.ca
2. Study monitor: kr105@queensu.ca
3. Study safety lead: ntouma@gmail.com

Risk Management in Participants

Pregnancy Risk/ Use of Birth Control:

The effects of the study drug on the unborn child or nursing infant are not known. For this reason, the participant should not be in the study if pregnant, planning to become pregnant, or breast feeding a child. If the participant is of childbearing potential, pregnancy during this study must be avoided. The participant and partner must use a medically acceptable method of birth control, which may include hormonal contraception, from the time of the screening visit to the final follow up visit of the study. The Investigator, Dr. Nickel, can talk to you about these birth control methods. If the participant becomes pregnant during the study the Investigator must be notified immediately and the study drug will be stopped. The Investigator will continue to monitor the participant to obtain information on general health and the outcome of the pregnancy (including the health of the baby) until 30 days after birth. The Investigator, Dr. Nickel will ask your doctor for information about the outcome of the pregnancy, which may include access to the child's medical records.

Risk Mitigation

The Principle Investigator provides oversight of the study with assistance from the research coordinator. One of the purported advantages of sublingual administration is greater safety, which allows for administration of this treatment outside of the medical setting.

First dose will occur in medical setting and research coordinator will monitor and record any adverse reactions. Participants will be provided with specific instructions as to how to administer treatment at home and advised to call the research coordinator if bothersome adverse events are experienced. If a dose is missed the participant is not to make up missed dose but resume next scheduled dose. Additionally, the research coordinator will follow-up with each participant **within one week of start of treatment** to assess any adverse reactions.

The PI will review all study data and any adverse events in real time and reports all SAEs to the study monitor, study safety lead, research ethics board as per local guidelines. AEs are assessed at each study visit by the study team or during review of hospital chart at hospital admission.

All AEs will be assessed and therapeutic strategies implemented according to medical opinion of the PI. Additionally, SAEs will be assessed by the study safety lead.

Occurrence of a UTI

Should a study participant experience a UTI throughout the course of the trial, it will not be captured as an AE. The UTI, along with the symptoms, medical attention and treatment received will be captured through the participant's diary and recorded in the electronic data capture system.

The Investigator must submit sufficient initial information to Health Canada should the SAE report meet the criteria (serious, unexpected and possibly or related to study treatment) for completion of an Adverse Event Drug Reaction Expedited Reporting Summary form and CIOMS report. As much of the following information about the participant and the event will be requested:

- Participant study code, gender, age, or date of birth
- Underlying diagnosis and extent of disease
- Lot number and expiration date of study drug
- Date of last study drug administration
- Date of death (if applicable)
- Intervention required
- Concomitant medications
- Pertinent laboratory data
- Pertinent medical history
- Study drug status (dose interrupted, discontinued)

- Did event abate after interruption of study drug administration (if applicable)
- Did event recur after study drug was reintroduced (if applicable)
- Severity of AE
- Relationship of the AE to the study drug
- Outcome of AE.

Follow-Up Information

Follow-up data concerning the SAE must also be submitted to the Investigator, Dr. Nickel, the study monitor and safety lead as they become available.

Governing Regulatory Authorities

Compliance with this request for prompt reporting is essential because the Investigator for this study is assuming Sponsor responsibility for informing Health Canada.

Under Health Canada Division 5/ICH Guidance Document Clinical Safety Data Management Definitions and Standards for Expedited Reporting the Investigator, assuming the Sponsor role, is required to submit written documentation on an Adverse Drug Reaction Expedited Reporting Summary form and CIOMS report.

Where the event is neither fatal nor life-threatening, the Investigator must submit documentation within **15 calendar** days after becoming aware of the information.

Where the event is fatal or life-threatening, the Investigator must submit documentation within 7 calendar days after becoming aware of the information. No later than 15 calendar days after having initially informed Health Canada of the fatal or life-threatening ADR, submit as complete a report as possible.

Follow-up reports of fatal or life-threatening reactions **must** include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar drugs..

Study and Data Management

Quality Control (QC) and Quality Assurance (QA)

QA and QC systems will be employed and supported with Standard Operating Procedures, as appropriate to ensure this clinical trial is conducted, data generated, documented and reported in compliance with the protocol, ICH GCP and applicable regulatory requirements.

The study monitor will review the protocol, IB, CRFs and completion instructions, informed consent process, AE and SAE reporting requirements with the investigator.

The study monitor will monitor the conduct of the clinical study by contacting the site by telephone and email. The study monitor will assure accurate, reliable data collection by verifying CRF data against source documentation and medical records.

Every effort will be made to protect the confidentiality of records in accordance with applicable regulatory requirements.

Study Monitoring

The Investigator, Dr. Nickel has assumed Sponsor responsibility to the governing regulatory authorities to take all reasonable steps to ensure the proper conduct of the study with respect to ethics, protocol adherence, and data integrity and validity.

This single centre clinical trial will be closely monitored in real-time throughout its duration utilizing an electronic data capture (EDC) database. On-site monitoring will occur up to one time per week after first participant signs consent and is started on the study vaccine. The on-site monitoring will include 100% ICF verification and 100% source verification with electronic data entry. Continued appropriate communications will occur by email correspondence or telephone. The study monitor, Investigator and study safety lead reviews AEs in aggregate on a monthly basis. The study statistician provides study data reports to the Investigator prior to each review. The following may be assessed during monitoring:

- Regulatory documentation
- Signed ICFs
- Case Report Forms within 5 days post visit.
- Investigative product inventory records
- SDV-source data verification. Data is complete, accurate and verifiable to source documents.
- Participant accrual and follow-up visits.
- Investigator and participant compliance to the study protocol.
- Concomitant medication documentation
- Adverse event documentation
- Protocol deviation documentation

The investigator and study team are expected to cooperate with the study monitor during monitoring times and permit direct access to all relevant documents.

Audits and Inspections

All documentation relating to this clinical trial may be subject to a QA audit by the Investigator, Dr. Nickel, or Regulatory Authorities (Health Canada). Upon

request, the auditor will inspect, copy, review and audit all source documents, CRFs, medical records, correspondence and signed ICFs. Other documentation subject to the audit includes the research ethics files, certifications, and quality control of supporting laboratories and pharmacies.

Data Collection

The primary tool for data collection to be used in this study will be the participant's weekly symptom diary. This will be used to gain information on any symptoms participants have experienced. This will be reviewed with the participant at each of their visits and used to help fill out the Case Report Forms (CRFs). **All information collected on the CRFs will be entered into the online database by the site within 5 days of each study visit.**

Data Management

A secure computer-based database will be created for the collection of study data. The study team will have access to the database and will be required to input and edit participant's data. Database access will be controlled by user-specific logins. Only the study participant's partial date of birth (month and year), with the default day of 15 will be entered into the database. There will not be any other participant identifying information entered into the database. The data will be labelled with the study participant's unique identification number (i.e. 01-01). All of the data entered into the electronic database must be supported by appropriate source documents.

Within 5 days of the completed study visit, all data should be entered into the electronic data capture system. **The site is also responsible for responding to any data queries from the study monitor within 5 days of receiving the query.**

Retention of Records

All study records must be kept by the Investigator for a minimum of 25 years following completion of the study as specified by Division 5 of the Health Canada Food and Drug Regulations. Records must be kept in a safe and secure location where they can be easily retrieved. All records must be kept confidential.

If the Investigator relocates, retires or withdraws for any reason from the study, trial records may be transferred to an acceptable designate within the institution.

Ethical Considerations

All study activities, procedures and assessments outlined in this protocol are designed to abide by the governing principles of the Declaration of Helsinki, consistent with ICH- GCP, Health Canada, and all other applicable laws and regulations.

Prior to starting the study, all sites must provide documented approval from the appropriate research ethics board (REB) or institutional review board (IRB).

The Investigator must report any changes in the research activity including all unexpected issues involving risks to the participant or others to the Research Ethics Board. The Investigator will supply progress reports as required to the Research Ethics Board. The Investigator is responsible for assuring continuing review and approval of the clinical trial on an annual basis. The Investigator will provide documentation to the Research Ethics Board when study participation is completed.

Written Informed Consent

The Investigator agrees to protect the rights, safety, and welfare of the participants enrolled into the trial, including obtaining written informed consent prior to performing any study-related procedures and informing each participant that the investigative product is being used for investigational purposes. A copy of the research ethics approved ICF will be used during the study.

The purpose and description of the study along with possible adverse effects must be explained to the participant prior to entry into the study. All questions should be answered to the satisfaction of the participant or participant's legal representative. The investigator or designate is responsible to obtain written informed consent from each participant thus attesting freely given consent. A copy of the signed and dated ICF will be given to the participant. Documentation of the informed consent process must be clearly indicated in the participant's clinical files and the original ICF must be available for review by the study monitor.

In the event that modifications of the experimental design, dosages, tests and assessments, etc. of the protocol are required and where potential risk to participants is increased, revisions to the ICF are also required. Such revisions will be reviewed and approved by the research ethics board and documentation of this approval will be forwarded to the Investigator for submission to Health Canada.

Any changes to the protocol will be informed of all study design modifications or increase in potential risk and written informed consent will be obtained.

Records and Case Report Forms

The Investigator is required to prepare and maintain accurate case histories designed to record all observations and other data related to the investigation on each participant treated with investigative product. Data reported on the CRF, derived from the source documents, must be consistent with the source documents, or any discrepancies must be explained.

Protocol Deviations

The study is to be conducted as described in the protocol without deviation unless there is a safety concern. The protocol must not be modified for any participant without the prior consent of the Research Ethics Board responsible at the investigative site.

Termination of the Study

If the Investigator discovers conditions during the course of the trial that indicate that the study should be discontinued an appropriate procedure for termination will be instituted.

Reasons for closure of the trial or termination of the study by the Investigator may include the following:

- Successful completion of the study at study site.
- Failure of Investigator to comply with the protocol, GCP guidelines or regulatory requirements
- Safety concerns

Rationale for Study Design

It would be difficult and really impossible to undertake a large multicenter randomized placebo controlled prophylaxis trial with limited funding. The need for evaluation of this type of intervention in Canadian female patients is unquestionable and the general efficacy and safety of Uromune® in Canadian women can be assessed using an open label real life observational study design employing using each participant's history of UTI as their own individual control. We will be able, within the number of participants planned for enrollment (convenience sample based on the number of individual Uromune® doses to be provided by supporting company) to answer our aim: To determine if Uromune therapy provides a clinically acceptable (efficacy and safety) prophylactic option in lieu of continuous and/or interval antibiotic dosing for Canadian women with a history of recurrent UTI.

We do not want to prove that this intervention is better than other interventions (in fact there are no other real non-antibiotic alternatives) but rather reduce the risk of recurrent UTI in women who are suffering from multiple UTIs requiring antibiotics. Each individual participant will be their own control based on the number of UTIs that are documented over the previous 12 months (to be included participants must meet the criteria of 3 documented UTIs requiring antibiotics over the last 12 months or 2 UTIs requiring antibiotics over the previous 6 months).

Number of Participants: Inmunotek, through its Canadian distributor, has offered the principle investigator at no cost, vaccine product (Uromune®) to treat up to 80 participants. The number of participants enrolled will be a convenience

sample based on the early UK experience [2]. It is expected that 80 participants in total (with an expected drop out rate of 15%) enrolled at the Urology Centre at Queen's University site will allow a preliminary assessment of efficacy and safety. The UK early experience study reported that 78% (59 participants of a total of 75 evaluable participants) had no subsequent UTI in the 12 months after the vaccine was administered. One participant reported a treatment related rash while <10% of participants experience mild adverse reactions with only one participant temporarily suspending treatment. We anticipate that based on this experience, 80 participants will be sufficient to determine safety and potential efficacy.

Analysis

Primary outcome: The individual participant will be considered a complete responder if they have no UTI requiring antibiotics reported in the 12 months since initiating therapy. A 50% responder rate of all enrolled participants will be considered a very clinically significant result. Based on the results from the first experience report from the UK (Yang and Foley, 2017) with Uromune® which demonstrated that 78% of the 75 women who completed treatment had no subsequent UTIs in the follow-up period, our convenience sample should be sufficient to power our analysis. The primary efficacy endpoint will be considered to have been achieved if a clinically significant and important level of more than 50% of participants undergoing therapy has no reported UTI in the 12 months after initiation of therapy.

Secondary outcome: The number of UTI in individual participants requiring antibiotics in the 12 months after starting therapy will be compared to the number of UTIs requiring antibiotics before therapy is initiated (number over previous 12 months or 2 X the number over the preceding 6 months). The analysis will include individual participant data comparisons as well as the mean number of UTI before and after initiation of therapy in the entire cohort. Based on the results from the comparison of Uromune® vs antibiotics from Spain (Lorenzo-Gomez MF et al 2012) which demonstrated a mean UTI rate after Uromune® therapy (n=136) of 0.36 (CI 0.29-0.44) at 6 months, 0.72 (CI 0.60-0.85) at 9 months, the study should be adequately powered to show a statistically significant difference in our convenience sample of participants enrolled with a history of at least 3 UTI in the preceding 12 months.

Quality of life and satisfaction questionnaires will also constitute secondary endpoints

The analysis for both efficacy and safety will be an intent to treat analysis of all participants who took at least one dose of the Uromune®. A per protocol efficacy analysis will include all participants who completed the 3 month treatment regime.

Interim Analysis Plan and Stopping Rules

An interim analysis will be carried out when 50% of participants reach the 6-month follow up interval. Stopping rules will be based on safety considerations – the study would be stopped if >20% (8 participants) experienced Treatment Emergent Serious Adverse Events (TESAEs). Safety will be monitored continuously for the rest of the study and the study will be stopped if at any time, if >20% of participants experience TESAEs.

Summary Statement: Rationale for this Investigator Initiated Early Experience Real Life Clinical Practice Study

We hope that this study will provide guidance for the use of Uromune® (when or if it is released in Canada) by providing information on the best way to manage recurrent UTI in individual participants using their own clinical data (in this case the number of recurrent UTI). The ultimate goal is to reduce participants' suffering (and therefore improve quality of life), participant time spent dealing with this problem, indirect costs (time off work or other activities), antibiotic use, antibiotic resistance and health care utilization (including costs). We plan to undertake this study with great enthusiasm with limited funding (and "in kind" supply of Uromune® from Red Leaf Medical) because of the huge unmet need for better preventative therapy for our Canadian women with recurrent UTI.

Responsibilities:

Principle Investigator (JCN) Responsibilities – will assume sponsor responsibilities: The PI (Nickel) will be responsible for protocol development, diary and CRF development, IRB approvals, informed consent, inclusion/exclusion criteria confirmation, safety monitoring, data analysis, and presentation/publication of results..

Supplier (Red Leaf Medical) Responsibilities: Red Leaf Medical will be committed to providing Uromune® for 80 participants to be enrolled in the trial. The Supplier is not committed to provide funds to the investigator, Dr. Nickel or provide any further financial support for the trial.

References:

1. Cuburu N, Kweon MN, Song JH et al. Sublingual immunization induces broad-based systemic and mucosal immune responses in mice. *Vaccine* 2007; 25: 8598–610
2. Benito-Villalvilla C, Cirauqui C, Diez-RiveroCM. MV140, a sublingual polyvalent bacterial preparation to treat recurrent urinary tract infections, licenses human dendritic cells for generating Th1, Th17, and IL-10 responses via Syk and MyD88 *Mucosal Immunology* Received 10 May 2016; accepted 8 November 2016; advance online publication 14 December 2016. doi:10.1038/mi.2016.112
3. Lorenzo-Gomez MF, Padilla-Fernandez B, Garcia-Cenador MB et al. Comparison of sublingual therapeutic vaccine with antibiotics for the prophylaxis of recurrent urinary tract infections. *Front Cell Infect Microbiol* 2015; 5: 50
4. Yang B, Foley S. First Experience in the UK of treating women with recurrent urinary tract infections with the bacterial vaccine Uromune®. *BJU Int.* 2017; doi:10.1111/bju.14067

Attachments:

Investigator Brochure