A DOUBLE BLIND PLACEBO CONTROL TRIAL OF MIRABEGRON FOR MEDICAL EXPULSIVE THERAPY AND TO MANAGE STENT PAIN FOR URETERAL STONES

(Protocol # 01-16-20-02)

Version: February 20, 2019

PRINCIPAL INVESTIGATOR: Wesley A. Mayer, MD
Assistant Professor
Scott Department of Urology
Baylor College of Medicine
7200 Cambridge 10th Floor, Suite B
Houston, TX 77030
713-798 - 4001
wesley.mayer@bcm.edu

KEYWORDS: Medical expulsive therapy; ureteral stone; beta agonist; stent pain;

IND#: 131892 EXEMPT

ClinicalTrials.gov: NCT02744430

This clinical research protocol will be conducted in accordance with OHRP, FDA, ICH and IRB regulations and guidelines. The Scott Department of Urology complies fully with the HIPAA guidelines.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
BCM	Baylor College of Medicine
BMP	Basic Metabolic Panel
BOO	Bladder Outlet Obstruction
C	Celsius
CBC	Complete Blood Count
CFU	Colony Forming Units
CT	Computed Tomography
CYP2D6	Cytochrome P450 2D6 - an enzyme
DPB	Diastolic Blood Pressure
ED	Emergency Department
EPIC	Electronic Medical Record System
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
Hg	Mercury
HIPAA	Health Insurance Portability and Accountability Act
HPF	High Powered field
ICD	Informed Consent Document
ICH	International Conference on Harmonization
INR	International Normalized Ratio
IRB	Institutional Review Board
IT	Information Technology
KUB	Kidney, Ureters, Bladder Plain Film
MET	Medical Expulsive Therapy
mg	Milligrams
mGy	milligray
MHRA	Modern Humanities Research Association
mm	millimeter
mSv	millisieverts
OAB	Overactive Bladder
OHRP	Office of Human Research Protection
OTC	Over-The-Counter

PI	Principal Investigator
PT	Prothrombin time
PTT	Prothrombin Time Test
RUS	Renal Ultrasound
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SDU	Scott Department of Urology
UAE	Unanticipated Event
USSQ	Ureteric Stent Symptom Questionnaire

1. BACKGROUND

Kidney stone passage down the ureter into the bladder often results in severe abdominal pain called ureteral colic. Ureteral colic is a common presenting symptom in emergency departments (ED).

Approximately 550,000 episodes of ureteric colic are seen in ED in the United States per year costing nearly $3 billion.[1] The current standard of care for ureteral stone passage involves hydration and pain control as approximately 47-80% of stones will pass within approximately 4 weeks, depending on size and location.[2] Patients who cannot achieve spontaneous stone passage or have a subsequent complication (including recurrent pain, compromised renal function, or infection) often require surgical therapy, typically either with extracorporeal shock wave lithotripsy or ureteroscopy. Two decades ago, the first randomized trial demonstrating the potential efficacy of a calcium channel blocker (nifedipine) for medical expulsive therapy of ureteral stones was performed.[3] Subsequently, tamsulosin, a selective alpha-1a antagonist, has also been demonstrated as a potentially useful agent for medical expulsive therapy (MET) in randomized trials.[4] Over the past decade, off-label MET has become more commonplace. However, the strength of findings from randomized trials is weak due to variability in quality and power of study design.

In 2015, a large multi-center randomized placebo-controlled trial (SUSPEND Trial) included 1167 patients and compared the efficacy of nifedipine and tamsulosin for the reduction in surgical therapy in patients passing ureteral stones within 4 weeks after randomization.[5] This trial demonstrated that both nifedipine and tamsulosin were ineffective for MET and were associated with an increase in adverse effects (AE) compared to placebo. These findings suggest that current off-label therapy with calcium-channel blockers and alpha-blockers may be ineffective and inappropriate. Because ureteral stones remain an important and expensive medical problem, identification of other potential agents for MET may reduce the frequency of serious complications and necessity of surgical intervention as well as improve patient- centered outcomes.

Mirabegron is a selective beta-3 adrenergic agonist that was approved for overactive bladder in the United States in 2012. Several human and animal studies have also shown the presence of beta-3 adrenergic receptors in the ureter and efficacy of agonists for the relaxation of the ureter.[6, 7] Stimulation of the beta-3 adrenergic receptors in the human ureter have been shown to promote urothelial relaxation in a pre-clinical model.[6] We hypothesize that mirabegron may be useful as MET through beta-3 adrenergic-mediated ureteral relaxation which may enhance ureteral stone passage in patients who are expectantly managed. Because ureteral colic results from sustained ureteric smooth muscle contraction, we hypothesize that relaxation of the ureter may reduce pain associated with ureteral stones and ureteral stents that are placed after surgical intervention.[8] As secondary endpoints, we will assess the efficacy of mirabegron for the reduction of pain during the expectant management period and during the post- surgical stent period.

2. SIGNIFICANCE

Ureteral obstruction due to kidney stones is a common and costly condition that requires surgical intervention in 20-50% of patients. It is associated with severe pain and discomfort along with

other serious adverse health outcomes such as renal failure and sepsis. If mirabegron can reduce either the need for surgical intervention or the pain associated with ureteral colic, this may alter standard of care for expectant stone management. Furthermore, stent pain is a major common adverse sequela of surgical intervention for kidney stones.[9] If mirabegron can reduce stent pain, it would greatly improve quality of life for patients undergoing invasive surgical therapy for urolithiasis.

3. OBJECTIVES

A. Primary Objective

The primary objective of this study is to determine whether the use of mirabegron can improve the spontaneous passage rate of patients with ureteral single ureteral calculi within 30 days of presentation.

B. Secondary Objectives

The secondary objectives of the study are to evaluate the effects of mirabegron on the reduction of pain level during the expectant management as well as stent-associated pain of those patients who had surgery.

4. DRUG INFORMATION

Mirabegron is a FDA-approved medication used in the treatment of overactive bladder (OAB) with symptoms of urgency, frequency, and leakage in adults. Both Mirabegron and placebo will be formulated and provided by Astellas Pharma US, Inc. The FDA-approved Mirabegron (50mg) product will be used without manipulation or reformulation (Mirabegron package insert; Rev. Jun 2012).[10]

The efficacy and safety of mirabegron have been evaluated in three 12-week studies and one long-term (12-month) safety study.

In clinical trials, mirabegron was shown to be effective in treating symptoms of OAB within the first several weeks. Those taking mirabegron made fewer trips to the bathroom and had fewer leaks than those not taking mirabegron. Results may vary.

5. PHASE OF STUDY: Phase 2

6. ELIGIBILITY CRITERIA

A. Inclusion

Subjects are eligible to be included in the study only if they meet all of the following criteria and provide signed informed consent at Visit 1.

1) Males and females age 18-70 years of age
2) Resident of Harris County
3) Single unilateral ureteral calculus 4 to 10 mm visible on CT scan or

Ultrasound/KUB within the ureter
4) Ability to tolerate oral fluids and oral pain medication
5) Able to make informed medical decisions regarding consent
6) Willingness to follow-up in the Urology Clinic in approximately 30 days
7) Willing to undergo ureteroscopic extraction should the stone not pass in this time period

B. Exclusion

Subjects will be excluded from the study if they meet any of the following criteria:

1) Adults unable to consent
2) Age less than 18
3) Solitary kidney
4) Horseshoe kidney
5) On immunosuppressant therapy
6) On digoxin
7) Uncontrolled hypertension (SBP > 170, DBP > 110)
8) Allergy to mirabegron
9) Current calcium antagonist or corticosteroid or alpha-adrenergic antagonist usage
10) Patients already taking a beta-adrenergic agonist medication
11) Patients taking thoridazine, flecainide, or propefenone (narrow CYP2D6 therapeutic index)
12) Renal insufficiency (GFR less than 45)
13) Patients with Childs B and C liver failure
14) Signs of infection
    i. Temperature greater than 38C
    ii. Circulating white blood count >15,000 x 10^9/L
    iii. Urinalysis with any of the following positive:
        a) Positive nitrites
        b) Positive urine culture (defined as a single isolated bacterial species population of greater than 100,000 CFU)
15) Patients with chronic pain already undergoing treatment with narcotic medications
16) Pregnant women and nursing mothers
17) Prisoners
18) No working phone number

7. DESIGN

The study will be a prospective randomized double-blind placebo-controlled trial of mirabegron for MET in patients with a CT scan or Ultrasound/KUB-proven ureteral stone between 4 to 10 mm undergoing expectant management. Subjects will be distributed at a 1:1 ratio between the control and treatment groups. The treatment group will receive mirabegron and the control groups will receive a placebo. Both groups will receive analgesics and hydration will be recommended. All subjects will then be followed for 30 days to determine the proportion of subjects with spontaneous passage. Patients will record narcotic usage and pain scores during

this time. If there is stone persistence in the ureter based on imaging (CT scan or Ultrasound/KUB of the abdomen and pelvic, then the patient will undergo ureteroscopy with stent placement. In these patients, treatment will continue while the stent is in place and patients will fill out a validated questionnaire regarding stent pain.

8. RANDOMIZATION

Study participants will be randomized to the treated arm (mirabegron 50 mg orally once every 24 hours starting immediately) or placebo in a 1:1 ratio using a randomized block design, stratified by stone size (≤5 mm versus >5 mm) and location (upper versus lower ureter). The randomization will be implemented through a database with software designed by the Director of Research Informatics at the Baylor College of Medicine's (BCM) Dan Duncan Institute of Clinical and Translational Research. It will be a HIPPA-compliant secure database accessible via internet.

Each randomly assigned participant will be given 60 capsules of trial medication (over-encapsulated mirabegron or placebo) supplied by Astellas Pharm US, Inc. and dispensed by the Harris Health System Pharmacy. Both Astellas Pharm US, Inc. and Harris Health Pharmacy will have no further involvement in the trial, ensuring that participants, clinicians, and trial personnel remained unaware of the allocated group.

Justification:
Two decades ago, the first randomized trial demonstrating the potential efficacy of a calcium channel blocker (nifedipine) for medical expulsive therapy of ureteral stones was performed.[3] Subsequently, tamsulosin, a selective alpha-1a antagonist, has also been demonstrated as a potentially useful agent for MET in randomized trials.[4] Over the past decade, off-label MET has become more commonplace. However, the strength of findings from randomized trials is weak due to variability in quality and power of study design.

In 2015, a large multi-center randomized placebo-controlled trial (SUSPEND Trial) included 1167 patients and compared the efficacy of nifedipine and tamsulosin for the reduction in surgical therapy in patients passing ureteral stones within 4 weeks after randomization.[5] This trial demonstrated that both nifedipine and tamsulosin were ineffective for MET and were associated with an increase in adverse effects compared to placebo. These findings suggest that current off-label therapy with calcium-channel blockers and alpha-blockers may be ineffective and inappropriate. Because ureteral stones remain an important and expensive medical problem, identification of other potential agents for MET may reduce the frequency of serious complications and necessity of surgical intervention as well as improve patient- centered outcomes.

9. PROCEDURES

Visit 1 – Emergency Department
In the ED, the subjects will receive a full history and physical, blood tests (including CBC and BMP), urinalysis and culture, urine pregnancy test, CT scan or Ultrasound/KUB of the abdomen

and pelvis, and KUB as part of standard of care for ureteral colic. The radiology department will note on all imaging the largest diameter of the stone and the Hounsfield units. Research study staff will screen potential subjects in the ED by reviewing their charts and will obtain written and verbal consent (in Spanish when necessary) from subjects who meet all inclusion and exclusion criteria. Baseline data, including demographics, medical and surgical history, and current medications, will be collected before randomization.

Each subject will be assigned a unique, consecutive three-digit identification number (i.e., 001, 002…). The study number will be utilized for identification of the subject throughout the study. The clinical study coordinator of the trial will maintain the code that links the name of the participant to their study identification number. The study coordinator will maintain the code in a secured cabinet and the code will be kept confidential. Only the clinical study coordinator and Principal Investigator (PI) can access and view the codes.

Subjects will be asked to complete the Wong-Baker FACES pain scale (available with validated Spanish translation as well). Subjects will be discharged from the ED with a (1) 60 day prescription for the study drug (mirabegron or placebo) (2) urine strainer (3) 60 day log for recording medication adherence, narcotic/analgesic usage, and ureteral pain. Subjects will be instructed to take one pill per day beginning immediately and continuing until they have completed all pills or until they have been instructed to discontinue by the study staff.

Subjects will be provided instructions for use of the urine strainer and collection of any stone or stones that may be passed. They will be instructed to bring any stones that have been passed to the next clinic visit.

Subjects will be informed that they may also discontinue the study drug at any time if they would like to drop out of the trial and they may do so by contacting Dr. Mayer or designee. Subjects will be informed to contact Dr. Mayer or designee if they believe that they have passed their ureteral stone before discontinuing therapy. Subjects will be told to bring their medication bottles when they return to the clinic.

In the event that a subject has additional pain, discomfort, or other symptoms that may be related to their ureteral stone they may follow-up for an unscheduled visit to either the emergency department or the Urology clinic. The subject will be treated according to standard of care and information regarding their visit will be collected. If the subject must undergo an emergent procedure for their stone they will be determined to have failed therapy but will remain in the study to evaluate the study drug to reduce stent pain. Subjects that fail therapy early will undergo Visit 3 and will be evaluated at Visit 4 for the removal of their stent. Subjects will remain in the study for all outcome measurements if they do not require surgical intervention.

Interim Phone Follow-up #1 – (7 Days ± 3 days post-Visit 1)
The research study staff will contact the subject by phone approximately 7 days after Visit 1. Research staff will assess ureteral pain, medication/strainer compliance, and adverse events. Research staff will also identify whether or not the subject subjectively or objectively has passed their ureteral stone. The research staff will also answer any questions that the subject may have during this follow-up event.

Interim Phone Follow-up #2 – (21 Days ± 3 days post-Visit 1)
The research study staff will contact the subject by phone approximately 21 days after Visit 1. Research staff will assess ureteral pain, medication/strainer compliance, and adverse events. Research staff will also identify whether or not the subject subjectively or objectively has passed their ureteral stone. The research staff will also answer any questions that the subject may have during this follow-up event. The research staff will also remind the subjects to bring in their medication bottles to Visit 2 (see below).

Visit 2 – Urology Clinic (30 days ± 5 days post-Visit 1)
Subjects will follow-up in the Harris Health Urology Clinic approximately 30 days after Visit 1. Subjects will provide a blood sample for a CBC, BMP, coagulation studies (PT/INR/PTT), a urine sample for a urinalysis and culture, urine pregnancy test, and have their blood pressure taken, as per standard of care. Subjects will also undergo a CT or KUB plus renal ultrasound at the Harris Health Radiology Department to radiologically identify the status of their ureteral stone, as per standard of care.

In the Urology Clinic, staff will perform a brief history and physical, review clinical imaging, observe any stones that the subject has collected, and determine whether or not the subject has passed their ureteral stone. Clinical and research staff will assess blood pressure, ureteral pain, pain medication and pain score log compliance, medication/strainer compliance, and adverse events using the adverse event checklist. Subjects will be asked to bring in their medication bottles at this visit to assess medication compliance. Subjects with persistent ureteral stones will be scheduled for ureteroscopy with laser lithotripsy and ureteral stent placement. These subjects will continue the study drug and strain their urine. Subjects will be provided additional study drug if necessary and instructed to continue until Visit 4, regardless of if they believe they passed their stone or not. They will be asked to bring the study drug bottle and any collected stones upon their return to Visit 3.

Subjects who have passed their stone will discontinue the study drug and exit the study.

Visit 3 – Ureteroscopy (14 days ± 5 days post-Visit 2)
Subjects who have failed the expectant management period as determined on Visit 2 will undergo ureteroscopy with laser lithotripsy approximately 14 days after Visit 2.
Blood pressure will be checked prior to the procedure. Stone fragments will be collected for composition analysis. All subjects will be stented using the preferred 6-French Boston Scientific Contour Injection Ureteral Stent Set that has been appropriately sized for each patient. If this particular catheter cannot be used, any 6-French catheter is preferred, but any ureteral catheter may be utilized during this visit. The string will not be removed from the ureteral stent to facilitate easier removal later. In subjects for whom the ureteroscope cannot successfully be passed into the ureter after reasonable attempts, the surgeon will place a ureteral stent and the subject will remain on the trial until their ureteral stent has been in 1 week or until Visit 4. Subjects will receive 10 days of ciprofloxacin, Tylenol #3, phenazopyridine, per standard of care. Subjects will not be prescribed alpha-adrenergic blockers or anticholinergics.

Clinical and research staff will assess blood pressure, ureteral pain, pain medication and pain

score log compliance, medication/strainer compliance, and adverse events using the adverse event checklist.

They will be asked to bring the study drug bottle upon their return to the clinic at Visit 4. It is possible that some patients will pass their stone between visit 2 and visit 3. If the patient has physically seen the stone pass or has collected the stone, they will exit the study; otherwise, they will proceed with a diagnostic versus therapeutic ureteroscopy with stent placement.

Visit 4 – Removal of Ureteral Stent (7 days ± 3 days post- Visit 3)
Subjects will return the Harris Health Urology Clinic approximately 7 days after ureteroscopy to remove their ureteral stent. In the Urology Clinic, staff will perform a brief history and physical, including blood pressure, per standard of care. Subjects will complete the USSQ. Stent pain, medication compliance, and medication-related adverse events, if any, will be assessed. Subjects will be asked to return any unused study drug and the study drug bottle at this visit. For subjects in whom the ureteroscope could not be passed and a stent was left in place, this visit will be a return to the operating room for completion ureteroscopy or stent removal, as clinically indicated.

Early Completion of the Trial Period
Subjects will be asked to call the study staff if they believe that they have passed their ureteral stone during the expectant management period or before ureteroscopy. Subjects that have objectively passed their stone will be asked to bring stone fragments for composition analysis. Subjects that have subjectively passed their stones will be asked to continue on their study medication until they can undergo a CT or KUB plus renal ultrasound and be interviewed in person by the clinical staff to determine stone passage. If a subject completes the trial before Visit 4, they will be asked to return any unused study drug.

Protocol Exceptions
Under the circumstance that any clinic visit cannot be made within the given timeframe due to system or subject issues unrelated to the study staff, the PI can review each case on an individual basis. If the PI determines that standard of care is ongoing, the subject may remain on the study. Under the circumstance that this may delay time to completion, the PI may extend study drug until completion of the trial. Extension of the study drug may continue in continuation with the initial 60 day dose or may be restarted after a period of drug cessation. This extension is not to exceed 60 additional days.

Monitoring of Adverse Events
Safety outcomes will be reported when they happened (via the case report form, patient questionnaires, and patient and clinician report). Suspected serious adverse events will be graded at site by the principal investigator. Safety events will be monitored by Astellas research ethics committee, and MHRA. Reporting of unanticipated problems will be in accordance to the current IRB guidelines and FDA regulations. An adverse event log will be maintained at the clinical site. The logs will be tabulated into a master log and submitted with each annual IRB renewal report.

10. LABORATORY CONSIDERATIONS

Blood and urine samples will be obtained at the first visit in the ED and during the 30 day follow-up visit in the Urology clinic. Up to 10 ml of blood will be drawn for laboratory assessment of CBC, BMP, and the coagulation panel.

The samples for standard of care testing will be sent to the laboratory at Ben Taub General Hospital. After tests are completed, any remaining samples will destroyed per laboratory's Standard Operating Procedures.

No cell lines will be developed. If a subject withdraws, the samples will have already been destroyed; therefore, the subject will not be able to have the samples returned to them.

Subjects may see and get a copy of their research related health information. The research doctor may be able to provide subjects with part of their information while the study is in progress and the rest of their information at the end of the study.

11. SAMPLE SIZE

The primary outcome measure is spontaneous stone passage. The proportion of patients who spontaneously pass the stone within 30 days will be compared between the mirabegron and placebo groups using Fisher's exact test. Previous research suggests that about 50% of subjects in the placebo group will have a spontaneous stone passage. A sample size of 45 subjects per group will provide 80% power to detect a 0.30 unit difference in proportions using Fisher's exact test assuming alpha=0.05 and half of the patients in the placebo group have spontaneous stone passage. Therefore, a total of 104 subjects will be enrolled into this study to allow for 15% attrition.

12. STATISTICAL CONSIDERATIONS

The primary analysis will evaluate the difference in the proportion of subjects who successfully pass their ureteral stone between subjects who received mirabegron and placebo. This analysis will provide information regarding the efficacy of mirabegron to improve stone passage rates for patients undergoing expectant stone management.

The secondary analyses will involve a multivariable analysis to compare the difference in pain during passage and pain with a ureteral stent in place. This may include co-variates such as age, gender, location of ureteral stone, prior history of ureteral stones, pain medication used during expectant management, and stone size.

13. DATA ANALYSIS

Patient demographics and clinical characteristics will be summarized by means with standard deviations, medians with minimum and maximum values, or frequencies with percentages. Summary statistics will be stratified by treatment group. No univariable analysis will be completed in this randomized clinical trial.

The primary analysis will compare the proportion of subjects with spontaneous stone passage within 30 days between study groups using Fisher's exact test. Statistical significance with be assessed at the 0.05 level (two-sided). A logistic regression model will also be used to estimate the odds ratio for spontaneous stone passage in the mirabegron group versus the placebo with a 95% confidence interval.

A multiple logistic regression model, adjusting for treatment group, will also be used to test for significant associations between spontaneous stone passage and patient demographics or clinical characteristics. Parameter estimates significant at the 0.05 level will be included in the final multiple regression model. No adjustments will be made for multiple hypothesis testing.
A secondary objective of this study is to compare pain measures between treatment groups. The Wong Baker FACES pain scale will be measured daily for each patient. A general linear mixed model will be used to compare pain scores between treated and placebo groups. The model will include fixed effects for treatment group, time (discrete) and a group-time interaction term. The matrix of correlated residual terms will assume an unstructured format. This model will account for the correlation between repeated measures within the same subject and will allow for all available data to be included in the model.

Missing data will not be imputed. Model fit will be assessed using influence diagnostics and residual analysis. Data transformations (e.g., natural logarithm) will be used if departure from model assumptions is evident. The model will also be used to explore associations between pain scores and demographic and clinical characteristics, adjusting for treatment group and time.

The USSQ will be observed in patients who require surgical intervention, and will be observed during study visit 4. A general linear model will be used to compare USSQ pain scores between the treated and placebo groups. The model will also be used to explore associations between pain scores and demographic or clinical characteristics adjusting for treatment group. Secondary analyses will be assessed at the 0.05 level (two-sided) without adjusting for multiple comparisons.

14. END-POINTS

Endpoints will include spontaneous passage rate during the 30-day expectant management period or completion of the expectant management period without a requirement for surgery. Secondary endpoints will include ureteral pain during the expectant management period (Visit 1, Interim Follow-up #1 and #2, Visit 2) and pain with a ureteral stent in place (Visit 4).

15. RISKS

There are risks to any medication. However, mirabegron is a FDA-approved medication and has passed rigorous trials for safety.

A. Mirabegron: Mirabegron is contraindicated in patients who have known hypersensitivity reactions to mirabegron or any component of the tablet. Mirabegron can increase blood pressure. Periodic blood pressure determinations are

recommended, especially in hypertensive patients. Mirabegron is not recommended for use in severe uncontrolled hypertensive patients (defined as systolic blood pressure ≥180 mm Hg and/or diastolic blood pressure ≥110 mm Hg).

Urinary retention in patients with bladder outlet obstruction (BOO) and in patients taking antimuscarinic medications for the treatment of OAB has been reported in post-marketing experience in patients taking mirabegron. A controlled clinical safety study in patients with BOO did not demonstrate increased urinary retention in Mirabegron patients; however, Mirabegron should be administered with caution to patients with clinically significant BOO. Mirabegron should also be administered with caution to patients taking antimuscarinic medications for the treatment of OAB.

Angioedema of the face, lips, tongue and/or larynx has been reported with Mirabegron. In some cases angioedema occurred after the first dose. Cases of angioedema have been reported to occur hours after the first dose or after multiple doses. Angioedema associated with upper airway swelling may be life threatening. If involvement of the tongue, hypopharynx, or larynx occurs, promptly discontinue Mirabegron and initiate appropriate therapy and/or measures necessary to ensure a patent airway.

Since Mirabegron is a moderate CYP2D6 inhibitor, the systemic exposure to CYP2D6 substrates such as metoprolol and desipramine is increased when co-administered with Mirabegron. Therefore, appropriate monitoring and dose adjustment may be necessary, especially with narrow therapeutic index drugs metabolized by CYP2D6, such as thioridazine, flecainide, and propafenone.

Most commonly reported adverse reactions over 2% and greater than with placebo) were hypertension, nasopharyngitis, urinary tract infection and headache.

Subjects will be monitored carefully for such side effects and should the subject feel uncomfortable continuing treatment, he will be allowed to discontinue participation in the study.

PREGNANCY: It is possible that the medicines used in this study could injure a fetus if the subject or partner becomes pregnant while taking them. Because of the potential risks involved, the subject or partner should not become pregnant while you are participating in this study.

If subject is sexually active or become sexually active and can get pregnant or can get the partner pregnant, the subject must agree to use one of the following forms of birth control every time the subject has sex from now until 3 months after stopping the study drug:

* oral contraceptives ("the pill"),
* intrauterine devices (IUDs),
* contraceptive implants under the skin, or contraceptive injections,

* condoms with foam.

Should pregnancy occur while on this study, the subject must immediately notify the study personnel.

The investigator will assist in finding appropriate medical care. The investigator also may ask to be allowed to continue getting information about the pregnancy. The subject can choose not to provide this information.

B. Blood Draw: Inserting needles into veins for collecting blood may be uncomfortable. Risks include slight bruising at the puncture site, fainting, the formation of a small blood clot or swelling of the vein and surrounding tissue, bleeding from the site, and the remote possibility of infection at the site of the needle puncture. Fainting is usually harmless, of short duration, and typically produces feelings of weakness, sweating, slowing of the heart rate and an abnormal decrease in blood pressure. Care will be taken to avoid these complications.

C. Blood Pressure: Subjects may feel a slight discomfort while the band on the arm is tightened in order to take the reading.

D. Scans: CT scans, ultrasounds, and plain x-rays do not cause any physical discomfort. Anxiety in anticipating these procedures might be experienced. CT scans and plain x-rays subject patients to small amounts of radiation. In the field of radiation protection, it is commonly assumed that the risk for adverse health effects from cancer is proportional to the amount of radiation dose absorbed and the amount of dose depends on the type of x-ray examination. A CT examination with an effective dose of 10 millisieverts (abbreviated mSv; 1 mSv = 1 mGy in the case of x rays) may be associated with an increase in the possibility of fatal cancer of approximately 1 chance in 2000. This increase in the possibility of a fatal cancer from radiation can be compared to the natural incidence of fatal cancer in the U.S. population, about 1 chance in 5. In other words, for any one person the risk of radiation-induced cancer is much smaller than the natural risk of cancer. Nevertheless, this small increase in radiation- associated cancer risk for an individual can become a public health concern if large numbers of the population undergo increased numbers of CT screening procedures of uncertain benefit. It must be noted that there is uncertainty regarding the risk estimates for low levels of radiation exposure as commonly experienced in diagnostic radiology procedures.

E. Loss of Confidentiality: The loss of confidentiality regarding research information is a possibility, although, the risk is extremely small. The investigator and his/her research staff will make every effort to maintain the confidentiality.

F. Ureteroscopy with stent placement: Patients will have a small camera placed in their bladder. A smaller camera will be placed in the kidney which will be used to find the stone. If unable to introduce this smaller camera in the kidney a stent will be left to open up the ureter, the tube that drains the kidney and another attempt will be made

in a few weeks. The stone will be broken apart by a laser. The small fragments may be individually removed. An x-ray will be used for the procedure. A stent will be left in the kidney after the procedure and will be removed in clinic.

G. Questionnaires: Completing the questionnaires may cause some level of emotional discomfort due to the personal nature of the questions. The study doctor and staff will maintain a professional and caring attitude while administering the questionnaires.

16. ASSESSMENT OF SAFETY

A. Adverse Events Reporting

All adverse event (Severe Adverse Event (SAE), Unanticipated Event (UAE), or Adverse Event (AE) will be assessed by the Principal Investigator using the BCM PI Determination form. The IRB will be notified according to current rules, regulations, and procedures.

B. Serious Adverse Event Reporting

Within 24 hours of awareness of a serious adverse event, whether or not related to the study drug, the Investigator will complete and submit a Medwatch 3500A Form to FDA, containing all required information (reference 21 CFR 312.32). The Investigator will submit a copy of this MedWatch 3500A form to Astellas by either e-mail or fax, within the same timeframe. If submission of this SAE to FDA or Astellas or is not possible within 24 hours, the Investigator's local drug safety contact (IRB, etc.) should be informed by phone.

The SAE documentation, including the Medwatch 3500A Form and available source records should be emailed or faxed to:

Astellas Pharma Global Pharmacovigilance – United States
Email: Safety-us@us.astellas.com
Fax number: (847) 317-1241

The following minimum information is required:

- Study number/IIT regulatory identifier
- Subject number, sex and age
- The date of report
- A description of the SAE (event, seriousness of the event)
- Causal relationship to the study drug

Follow-up information for the event should be sent promptly (within 7 days) as necessary.

C. Additional safety analyses will be conducted in the safety population, defined as all subjects who receive at least one treatment with study drug.

Safety and tolerability will be assessed by evaluating physical, clinical laboratory tests, and reported AEs.

17. WITHDRAWAL OF SUBJECTS

Subjects for the study will be selected during screening based on the inclusion and exclusion criteria and clinical assessment listed below. Subjects will be discontinued from the study prematurely if:

A. Unacceptable AEs considered by the investigator to be associated with use of the study drug occur
B. The subject requests to be withdrawn from the study
C. A need for concomitant medication prohibited by the protocol arises
D. The Principal Investigator decides that it is in the subject's best interest
E. The subject is significantly non-compliant with the protocol

18. BENEFITS

Subjects assigned to the mirabegron group may experience a reduction in their risk for surgical intervention or may experience reduced pain associated with ureteral colic or ureteral stenting.

Should mirabegron prove beneficial in reducing the need for surgical stone extraction or reduce the pain associated with ureteral colic or ureteral stenting this medication may be used during the expectant management period for ureteral stones. This may decrease the adverse effects and morbidity associated with ureteral stones. Preventing the need for surgical intervention may reduce healthcare costs and reduce complications and morbidity associated with surgery.

The anticipated benefits outweigh potential risks. The study medication used in this study has been approved as safe by the FDA.

19. ALTERNATIVES

Patients may choose not to participate in this study. Other treatment for small ureteral stones includes nifedepine or tamsulosin (off-label) in addition to hydration and NSAIDs.

20. COSTS TO SUBJECTS

The subjects and/or their insurance will cover the emergency department visit as well as follow-up office visits, blood tests, diagnostic imaging, and surgical intervention that are standard of diagnosing and managing ureteral stones.

The study medication, mirabegron, and the placebo are not considered standard of care. Astellas will provide these study drugs.

21. PAYMENT TO SUBJECTS

Subjects will receive $50 ClinCard for their participation in this study. It will be provided to the subject at the follow-up visit.

22. CONFIDENTIALITY

Research data will be maintained and stored in the PI's office located at McNair Campus Medical Office Building, 7200 Cambridge, 10th floor, Suite B. Entry to this location is by electronic badge scanner. All computers are password protected and data is stored on encrypted servers that are managed by BCM IT. At times of analysis, all computers for analysis will also be password protected/encrypted.

Research data will also be accessible via a database designed by the Director of Research Informatics at the BCM's Dan Duncan Institute of Clinical and Translational Research. It is a HIPPA-compliant secure database accessible via internet.

Regulatory documents will be managed by Research Administration of the Scott Department of Urology located at Main Baylor, Rooms 502D and 506D. The Main Baylor offices have keyed entries. All computers are password protected and stored on encrypted BCM servers that are managed by IT.

The Scott Department of Urology complies fully with the HIPAA Privacy Rule.

23. ETHICS

A. Informed Consent Process:

Subjects will be identified from those visiting in the Emergency Room of Ben Taub General Hospital, a BCM-Affiliated Institution. Patients will be informed both verbally and in written form of the study and procedures involved and be given adequate opportunity to read it and discuss with family before it is signed. The PI and/or the study coordinator will obtain a signed/dated Informed Consent Document (ICD) before enrolling each subject and prior to the occurrence of any study events procedures. The original signed/dated ICD will be kept with the research study documents, a copy will be given to the subject, and a copy will be scanned to the subject's EPIC record.

Spanish speaking participants will be consented using a Spanish language consent form and subjects will be provided Spanish translated questionnaires.

B. Institutional Review Board

The PI will provide the IRB with all requisite material, including a copy of the informed consent. The study will not be initiated until the IRB provides written approval of the protocol and the informed consent and until approved documents have been obtained by the PI. Appropriate reports on the progress of this study by the PI will be made to the IRB in accordance with the applicable government regulations.

C. Study Monitoring

The BCM, SDU, Quality Assurance Program Guidelines protocol will be in effect for monitoring and auditing of this study.

D. Monitoring Case Report Forms

The principal investigator or their designee will monitor all aspects of the study with respect to current GCP and standard operating procedures for compliance with applicable federal regulations. These individuals will have access to all records necessary to ensure integrity of the data and will periodically review progress of the study with the Principal Investigator.

E. Study Record Retention

In accordance with FDA regulations and GCP guidelines, all study-related documentation shall be retained by the Principal Investigator as required.

F. Changes to the Protocol

Study procedures will not be changed without the approval of the BCM IRB. The revised informed consent document must be approved by the BCM IRB prior to it being used to enroll patients.

24. REFERENCES

1. Ghani KR, Roghmann F, Sammon JD, et al. Emergency department visits in the United States for upper urinary tract stones: trends in hospitalization and charges. *J Urology.* 2014;191:90-96.
2. Preminger et al G. MANAGEMENT OF URETERAL CALCULI: EAU/AUA NEPHROLITHIASIS PANEL (2007). Vol 2016: American Urological Association; 2007.
3. Borghi L, Meschi T, Amato F, et al. Nifedipine and methylprednisolone in facilitating ureteral stone passage: a randomized, double-blind, placebo-controlled study. *The J Urology.* 1994;152:1095-1098.
4. Porpiglia F, Ghignone G, Fiori C, Fontana D, Scarpa RM. Nifedipine versus tamsulosin for the management of lower ureteral stones. *J Urology.* 2004;172:568-571.
5. Pickard R, Starr K, MacLennan G, et al. Medical expulsive therapy in adults with ureteric colic: a multicentre, randomised, placebo-controlled trial. *Lancet.* 2015;386:341-349.
6. Matsumoto R, Otsuka A, Suzuki T, et al. Expression and functional role of beta3 - adrenoceptors in the human ureter. *International journal of urology : official journal of the Japanese Urological Association.* 2013;20:1007-1014.
7. Wanajo I, Tomiyama Y, Yamazaki Y, Kojima M, Shibata N. Pharmacological characterization of beta-adrenoceptor subtypes mediating relaxation in porcine isolated ureteral smooth muscle. *J Urology.* 2004;172:1155-1159.
8. Bultitude M, Rees J. Management of renal colic. *BMJ.* 2012;345:e5499.
9. Joshi HB, Okeke A, Newns N, Keeley FX, Jr., Timoney AG. Characterization of urinary symptoms in patients with ureteral stents. *Urology.* 2002;59:511-516.
10. Astellas Pharm US, Inc. Mirabegron package insert 2012.

INVESTIGATOR SIGNATURE PAGE

H-38959: A DOUBLE BLIND PLACEBO CONTROL TRIAL OF MIRABEGRON FOR MEDICAL EXPULSIVE THERAPY AND TO MANAGE STENT PAIN FOR URETERAL STONES (Protocol # 01-16-20-02)

I agree to:

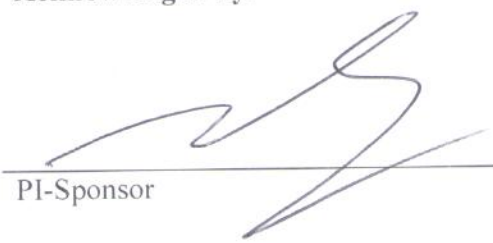
Implement and conduct this study diligently and in strict compliance with the protocol, good clinical practices, and all applicable laws and regulations.

Maintain all information concerning this research study in confidence and, when this information is submitted to the Institutional Review Board (IRB), Independent Ethics Committee (IEC), or another group, it will be submitted with a designation that the material is confidential.

I have reviewed the protocol and study drug package insert and I agree to conduct this study as outlined in the protocol and in compliance with applicable FDA, OHRP, and ICH/GCP Guidelines.

I have read this protocol and its entirety and I agree to all aspects.

Acknowledged by:



PI-Sponsor

2/21/19

Date

Wesley A. Mayer, MD,

Name

Assistant Professor

Title

APPENDICES

A. Schedule of Events

B. Questionnaires:

i. Wong Baker FACES Pain Scale and Narcotic Usage Diary
ii. Wong Baker FACES Pain Scale, and Narcotic Usage Diary, Spanish
iii. USSQ
iv. USSQ, Spanish
v. Adverse Event Checklist

APPENDIX A: SCHEDULE OF EVENTS

Highlighted events are considered standard of care.

Events/Time	Visit 1 Screening/ Randomization (D1)	Interim Follow-up #1 (D7 ± 3 days) Phone Call	Interim Follow-up #2 (D21 ± 3 days) Phone Call	Visit 2 Urology Clinic (D30 ± 5 days)	Visit 3 Ureteroscopy (D44 ± 3 days)	Visit 4 Removal of Ureteral Stent (D51 ± 3 days)
Complete History/Physical	X[1]					
Office Visit w/brief H&P				X		X
Blood Pressure	X[1]			X	X	X
Ureteroscopy, laser lithotripsy, stent placement					X	
Phlebotomy	X[1]			X		
CBC	X[1]			X		
BMP	X[1]			X		
Coagulation Panel				X		
Urine Collection						
Urinalysis	X[1]			X		
Culture	X[1]			X		
Pregnancy test	X[1]			X		
CT	X[1]			X[2]		
KUB	X[1]					
KUB plus ultrasound				X[2]		
Stone Analysis					X	
Randomization	X					
Mirabegron/Placebo Dispense	X					
Urine Strainer	X[1]					
Ciprofloxacin, Tyleynol3, phenazopyridine					X	
Medication Accountability		X	X	X		X
Straining Accountability		X	X	X		
Wong-Baker FACES Pain Rating Scale, Narcotics Diary	X	X	X	X		X
USSQ						X
Informed Consent	X					
Adverse Events		X	X	X	X	X
Review Concomitant Meds	X			X		

[1]May be done prior to enrollment into study

[2]May be used instead of CT

APPENDIX B: QUESTIONAIRES

A DOUBLE BLIND PLACEBO CONTROL TRIAL OF MIRABEGRON FOR MEDICAL EXPULSIVE THERAPY AND TO MANAGE STENT PAIN FOR URETERAL STONES (Protocol # 01-16-20-02)

You have agreed to participate in the clinical research study conducted by Dr. W. A. Mayer. As part of that study, we need to review your pain levels while you are in the study. Please complete the follow diary **once a day** until you return to the clinic.

Example of completed row:

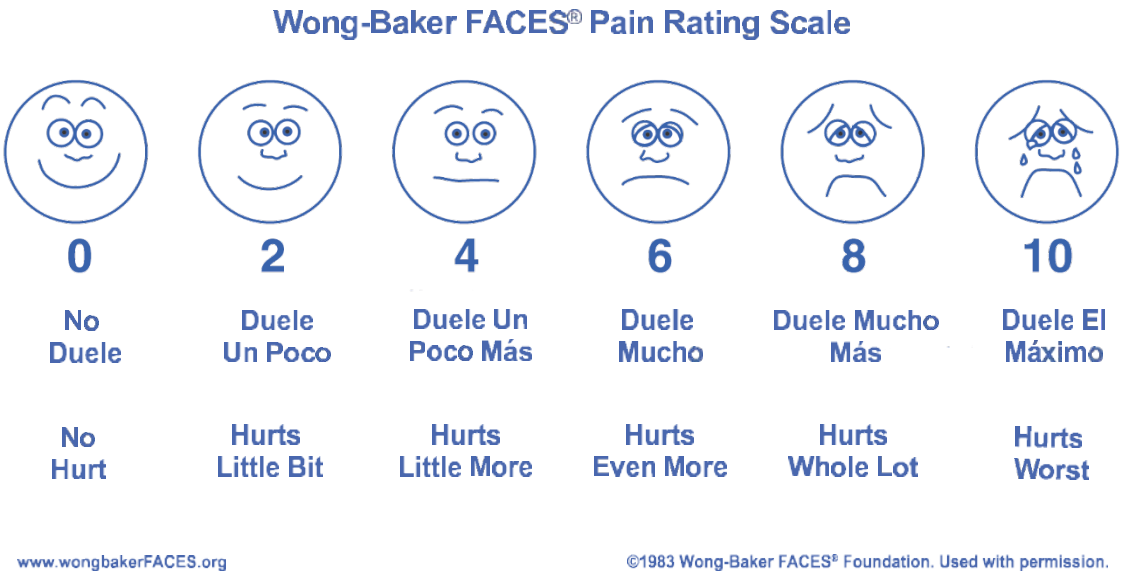
Day	DATE	Time of Day	Pain Scale	Medication for Pain (if needed)
5	2/5/16	9:30 AM	6	Aspirins x 2

Please complete the follow diary once a day until you return to the clinic.

Day	DATE	Time of Day	Pain Scale	Medication for Pain (if needed)
1				
2				
3				
4				
5				
6				
7				
8				

Day	DATE	Time of Day	Pain Scale	Medication for Pain (if needed)
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				
29				
30				
31				
32				
33				
34				
35				
36				

Day	DATE	Time of Day	Pain Scale	Medication for Pain (if needed)
37				
38				
39				
40				
41				
42				
43				
44				
45				
46				
47				
48				
49				
50				
51				
52				
53				
54				
55				
56				
57				
58				
59				
60				



A DOBLE CIEGO PLACEBO CONTROL ESTUDIO DE MIRABEGRON PARA TERAPIA MEDICA DEL MANEJO DEL DOLOR Y EXPULSION DE PIEDRAS DE LOS URETERS (Protocol # 01-16-20-02)

Usted acepto participar en un estudio de investigación clinica conducido por el Dr. W. A. Mayer. Como parte del studio, necesitamos revisar su nivel de dolor mientras usted esta en el estudio.
Por favor complete el siguiente diario una vez al día hasta que usted regrese a la clinica.

Ejemplo de como completer la tabla:

Dia	Fecha	# Hora Del Dia	Escala del Dolor	Medicina para el dolor (si necesita)
5	2/5/16	9:30 AM	6	Aspirina x 2

Please complete the follow diary once a day until you return to the clinic.

Dia	Fecha	# Hora Del Dia	Escala del Dolor	Medicina para el dolor (si necesita)
1				
2				

3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				
29				
30				
31				
32				

33				
34				
35				
36				
37				
38				
39				
40				
41				
42				
43				
44				
45				
46				
47				
48				
49				
50				
51				
52				
53				
54				
55				
56				
57				
58				
59				
60				

URETERIC STEMT SYMPTOMS QUESTIONNAIRE

The English and Spanish versions of this questionnaire are provided in the PDF version only.