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)

Background

You are being asked to participate in this clinical research study because you are in the Ben Taub General Hospital's emergency room with pain that may be associated with a stone in your urethra (the tube that takes urine from your kidneys to the bladder). This event is called ureteric colic [pain in your back, side, or lower abdomen which may travel towards your testicles (if male), vagina (if female), or leg)].

Please read this form carefully. Take time to ask the doctor or study staff as many questions about the study as you would like. If there are any words or information that you do not understand, the doctor or study staff will explain them to you. Reading this form and talking to the doctor or study staff may help you decide whether to participate or not. If you decide to take part in the study, you must sign and date the statement of consent and authorization on the last page of this form.

Your participation in this research study is voluntary and whether or not you decide to be a part of this research study, your regular clinical care will not affected.

Approximately 550,000 patients with ureteric colic are seen in the emergency rooms in the United States per year. The current standard of care for ureteral stone passage involves providing fluids and pain control. About 47-80% of stones will pass by themselves within approximately 4 weeks, depending on size and location. Patients who cannot pass their stone or have a complication (including pain that comes and goes, problems with the kidney, or infection) often require treatment with surgery. This surgery is done mostly with either with shock wave lithotripsy which breaks the stone into small pieces or ureteroscopy. Ureteroscopy is a procedure in which a small scope (like a flexible telescope) is inserted into the bladder and ureter. It allows the urologist to actually look into your ureter, find the stone, and remove it.

In this clinical research study, a drug name mirabegron (Myrbetriq) may be given to you. The Food and Drug Administration (FDA) has approved this drug for use for other medical problems but not for ureteral stones.

This research study is funded by ASTELLAS PHARMA GLOBAL DEVELOPMENT , INC.

Purpose

We hope to determine whether the use of mirabegron can help the passage of your ureteral single ureteral stone within 30 days of your visit to the emergency room. We also want to find out if your pain level improves while taking the mirabegron.

Procedures

The research will be conducted at the following location(s):
Baylor College of Medicine and HCHD: Harris County Hospital District Ben Taub.

As a patient in the emergency room, you will have the routine care that is given to all patients suffering

with pain caused by a ureter stone. The results of your routine tests and procedures and CT scan, Ultrasound, or X-rays will be reviewed. If you meet the requirements for this clinical research study, you will be asked if you would like to volunteer to be a patient on this study. If you agree, you will sign and date this informed consent document.

You will be randomized (selected) to receive either the mirabegron or a placebo pill. The placebo pill does not have medication in it. The selection is determined by a computer program. You will have a 50-50 chance of being assigned to either study drug. Only the pharmacist will know which pill you will be taking. The study doctors and the study team members will not know which pill you are taking.

You will be given a questionnaire that is used for you to tell us how much pain you are having.

You will be given a 60 day supply of study drug. You must take one pill every morning until you come back to the clinic. You MUST bring all unused study drug and the empty bottles with you when you come back to the Urology clinic.

You will be given a urine strainer to use each time you urinate (pee). You will save any small pieces of stone that you pass and bring them to your next clinic visit.

You will be given a medication diary to complete that tells us about all medications that you take during the 60 days. You MUST bring the completed diary when you return to the clinic.

TELEPHONE FOLLOW-UP VISIT #1 (7 Days plus/minus 3 days after Visit 1):

You will receive a telephone call from a study team member to ask how you are feeling, have you passed your stone, how is your pain, are you taking your study drug every day, and do you have any questions.

TELEPHONE FOLLOW-UP VISIT #2 (21 Days plus/minus 3 days after Visit 1):

You will receive a telephone call from a study team member to ask how you are feeling, have you passed your stone, how is your pain, are you taking your study drug every day, and do you have any questions. You will be reminded to bring the remaining study drug and bottles, and the completed medication diary with you when you visit the clinic.

VISIT 2 - Urology Clinic (30 days plus/minus 5 days post-Visit 1)

You will come to the urology clinic about 30 days after your emergency room visit.

You will have a brief physical exam. The results of your routine tests and procedures and CT scan, ultrasound, or X-rays will be reviewed. A study team member will review your medication diary and your medication bottles.

If you have passed your stone, you participation in this study will end and no further study visits are required.

If you have not passed your stone, you will be scheduled for ureteroscopy.

You will continue your study drug and the medication diary.

VISIT 3 - Ureteroscopy (14 days plus/minus 5 days post-Visit 2)

It is possible that you will pass your stone between visit 2 and visit 3. If you have physically seen the stone pass or have collected the stone, you will exit the study.

If you have not passed the stone, you will undergo an ureteroscopy with stent placement. The ureteroscopy procedure is routinely done for patients with stones that are too large to pass without help. On the day of the procedure, you will be given general anesthesia (meaning you will be asleep for the procedure). General anesthesia is a combination of medications that you breathe through a mask or receive through a needle in a vein. The medications cause you to be asleep.

The details of the procedure will be discussed with you at the time of obtaining your consent for the surgical procedure.

You will be asked to rate your pain using the pain scale as you did at Visit #1.

VISIT 4 ¿ Removal of Ureteral Stent (7 days plus/minus 3 days post- Visit 3)

You will return the Harris Health Urology Clinic approximately 7 days after ureteroscopy to have your stent removed. In the Urology Clinic, staff will perform a brief history and physical. The results of your routine tests and procedures will be reviewed. You will complete the USSQ Stent pain questionnaire which takes about 10 minutes. Your medication diary will be reviewed, and you will be asked about any side effect you may have had. You will be asked to return any unused study drug and the study drug bottle at this visit.

If the ureteroscope could not be passed during Visit 3 and the stent was left in place, you will return to the operating room for completion ureteroscopy for this visit instead of coming to the office.

Research related health information

Authorization to Use or Disclose (Release) Health Information that Identifies You for a Research Study

If you sign this document, you give permission to people who give medical care and ensure quality from Baylor College of Medicine and HCHD: Harris County Hospital District Ben Taub to use or disclose (release) your health information that identifies you for the research study described in this document.

The health information that we may use or disclose (release) for this research includes:

- Information from health records such as diagnoses, progress notes, medications, lab or radiology findings, etc.
- Demographic information (name, D.O.B., age, gender, race, etc.)

The health information listed above may be used by and or disclosed (released) to researchers, their staff and their collaborators on this research project, the Institutional Review Board, Baylor College of Medicine, HCHD: Harris County Hospital District Ben Taub, and ASTELLAS PHARMA GLOBAL DEVELOPMENT , INC. and their representatives.

Agents of the U.S. Food and Drug Administration may inspect the research records including your health information. Agents of regulatory agencies such as the U.S. Department of Health and Human Services will be permitted to inspect the research records including your health information.

The data coordinating center will have access to the research records including your health information.

Use or Disclosure Required by Law

Your health information will be used or disclosed when required by law.

Your health information may be shared with a public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury, or disability and conducting public health surveillance, investigations or interventions.

Baylor College of Medicine and HCHD: Harris County Hospital District Ben Taub are required by law to protect your health information. By signing this document, you authorize Baylor College of Medicine and HCHD: Harris County Hospital District Ben Taub to use and/or disclose (release) your health information for this research. Those persons who receive your health information may not be required by Federal privacy laws (such as the Privacy rule) to protect it and may share your information with others without your permission, if permitted by laws governing them.

Please note that the research involves treatment. You do not have to sign this Authorization, but if you do not, you may not receive research-related treatment. To maintain the integrity of this research study, you generally will not have access to your personal health information related to this research until the study is complete. However, your health information that is necessary to your care will be provided to

you or your physician. At the conclusion of the research and at your request, you generally will have access to your health information that Baylor College of Medicine and HCHD: Harris County Hospital District Ben Taub maintain in a designated record set, which means a set of data that includes medical information or billing records used in whole or in part by your doctors or other health care providers at Baylor College of Medicine and HCHD: Harris County Hospital District Ben Taub to make decisions about individuals. Access to your health information in a designated record set is described in the Notice of Privacy Practices provided to you by representatives of the specific institution where you are being enrolled into this research study which are: Baylor College of Medicine and HCHD: Harris County Hospital District Ben Taub.

Please note that you may change your mind and revoke (take back) this Authorization at any time. Even if you revoke this Authorization, researchers, their staff and their collaborators on this research project, the Institutional Review Board, ASTELLAS PHARMA GLOBAL DEVELOPMENT , INC. and their representatives, regulatory agencies such as the U.S. Department of Health and Human Services, FDA, Baylor College of Medicine, data coordinating center, and HCHD: Harris County Hospital District Ben Taub may still use or disclose health information they already have obtained about you as necessary to maintain the integrity or reliability of the current research. If you revoke this Authorization, you may no longer be allowed to participate in the research described in this Authorization.

To revoke this Authorization, you must write to: Dr. Wesley A. Mayer, MD
Baylor College of Medicine
Scott Department of Urology
One Baylor Plaza, BCM380
Houston, TX 77030

This authorization does not have an expiration date. If all information that does or can identify you is removed from your health information, the remaining information will no longer be subject to this authorization and may be used or disclosed for other purposes.

No publication or public presentation about the research described above will reveal your identity without another authorization from you.

Potential Risks and Discomforts
MIRABEGRON: Mirabegron can make your blood pressure go higher in 3% of patients (3 patients in 100 patients on the medication will experience this). You may also have trouble emptying your bladder while taking Mirabegron. You may also develop cold-type symptoms while taking Mirabegron. You may also have headaches. You may also have swelling of your face, tongue, or throat. If you experience these symptoms, please contact 911.

PLACEBO: Taking placebo is the same as not taking any medication for your stone. It is possible that your condition may get worse if you are placed in this group.

URETEROSCOPY: The risks that may happen when you have a ureteroscopy are:
- urine infection which usually requires only antibiotics to correct
- bleeding and this usually stops quickly
- the ureter may be damaged resulting in narrowing of the ureter
- a tear of the ureter may happen but this is rare

SCANS or X-rays: Participation in this research study involves exposure to radiation in the form of scans, ultrasounds or x-rays. People are exposed to radiation every day from both natural and man-made sources. The radiation dose that is received during this study is greater than the annual radiation dose to a member of the U.S. from natural and man-made sources, but less than the limit for radiation workers. With the radiation dose received, the risk of potential harmful effects is considered minimal.

QUESTIONNAIRES: Completing the questionnaires may cause you to have or to experience 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.

LOSS OF CONFIDENTIALITY: There is a small risk for the loss of confidentiality. However, the study personnel will make every effort to minimize the risks.

Women of Childbearing Potential ¿ Risk to Fetus - Contraception
It is possible that the medicines and procedures used in this study could injure a fetus if you or your partner becomes pregnant while taking them. Because of the potential risks involved, you or your partner should not become pregnant while you are participating in this study.

If you are sexually active or become sexually active and can get pregnant or can get your partner pregnant, you must agree to use one of the following forms of birth control every time you have sex and for (3) months afterwards:

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

Should you become pregnant while on this study, you must immediately notify a study team member.

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

There may be unknown risks or discomforts involved. Study staff will update you in a timely way on any new information that may affect your decision to stay in the study. There is a small risk for the loss of confidentiality. However, the study personnel will make every effort to minimize these risks.

Potential Benefits

The benefits of participating in this study may be: less pain and less chance of needing surgery for the stone if you are taking the Mirabegron. If you are taking the placebo, your symptoms may stay the same or get worse. However, you may receive no benefit from participating.

Alternatives

The following alternative procedures or treatments are available if you choose not to participate in this study: other medications that might help dissolve the stones, drinking lots of water, and taking NSAIDs (aspirin, Aleve).

Subject Costs and Payments

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

The study drugs are considered research not standard of care. The study sponsor will provide the study drugs at no cost to you.

You will receive a ClinCard for $50 at your follow-up visit to help pay for your transportation and food. costs

Research Related Injury

In the event of injury resulting from this research, Baylor College of Medicine and/or the Harris County Hospital District (Ben Taub General Hospital) are not able to offer financial compensation nor to absorb the costs of medical treatment.

However, necessary facilities, emergency treatment and professional services will be available to you, just as they are to the general community.

Be sure to tell the ER doctor that you are on a research study and to contact Dr. Mayer.

Research personnel will try to reduce, control, and treat any complications from this research. If you are injured because of this study, you will receive medical care that you or your insurance will have to pay for just like any other medical care.

Subject's Rights

Your signature on this consent form means that you have received the information about this study and that you agree to volunteer for this research study.

You will be given a copy of this signed form to keep. You are not giving up any of your rights by signing this form. Even after you have signed this form, you may change your mind at any time. Please contact the study staff if you decide to stop taking part in this study.

If you choose not to take part in the research or if you decide to stop taking part later, your benefits and services will stay the same as before this study was discussed with you. You will not lose these benefits, services, or rights.

The investigator, WESLEY ADAM MAYER, and/or someone he/she appoints in his/her place will try to answer all of your questions. If you have questions or concerns at any time, or if you need to report an injury related to the research, you may speak with a member of the study staff: WESLEY A.. MAYER at 713-798-4001 24 hours a day.

Members of the Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals (IRB) can also answer your questions and concerns about your rights as a research subject. The IRB office number is (713) 798-6970. Call the IRB office if you would like to speak to a person independent of the investigator and research staff for complaints about the research, if you cannot reach the research staff, or if you wish to talk to someone other than the research staff.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, (NCT02744430) as required by U.S. law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

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Signing this consent form indicates that you have read this consent form (or have had it read to you), that your questions have been answered to your satisfaction, and that you voluntarily agree to participate in this research study. You will receive a copy of this signed consent form.

Subject	Date
Investigator or Designee Obtaining Consent	Date
Witness (if applicable)	Date
Translator (if applicable)	Date

WAM v 2/20/19