

**A Pilot Study of the Effects of Mirabegron on Symptoms in
Patients with Interstitial Cystitis**

ID# MYRB-15G02

NCT02787083

Date: July 29, 2016

Protocol Title:**A Pilot Study of the Effects of Mirabegron on Symptoms in Patients with Interstitial Cystitis****Investigators:**

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Background:

Bladder pain syndrome/interstitial cystitis is an elusive disease processes and treatment conundrum, with few patients achieving immediate, durable and or complete resolution of symptoms with any single treatment modality[1]. It is defined as an unpleasant sensation (pain, pressure, or discomfort) perceived to be related to the urinary bladder and associated with lower urinary tract symptoms for at least 6 weeks duration, in the absence of infection or other identifiable causes[2]. Pain is the universal symptom, but many may also experience symptoms of overactive bladder, possibly directly related to the mechanism of pain. Treating pain may influence the symptom of urgency, if the urge arises from a need to alleviate pain. In some patients whose pain improves with treatment, troubling overactive bladder symptoms still remain [3].

There are certain medications currently on the market with multiple mechanisms of action, each of which can address a different symptom in BPS/IC patients, but no single medication or even combination of medications have achieved remarkable symptom control[2]. This may be because the disease process itself is poorly understood and because BPS/IC may actually be a spectrum of a disease processes. Nonetheless new medications and treatment options must still be explored.

A medication on the market that, alone, has a Grade B Recommendation by the Oxford System Recommendations for treatment of BPS/IC is amitriptyline, a tricyclic antidepressant[2]. It has at least three pharmacological actions that may be responsible for alleviating symptoms of BPS/IC, first of which is its anticholinergic properties. It has also been theorized that tricyclic agents may predominately stimulate beta adrenergic receptors in the bladder leading to relaxation of the bladder muscle, as well as possibly function on the afferent signaling of bladder C-fibers[4, 5]. C-fibers, unmyelinated afferents, have been found to comprise up to 70% of bladder afferents in animal models. Generally considered "silent", they are upregulated in disease states and inflammatory conditions[6]. Interestingly, beta-adrenergic agonists have been found to decrease signaling of C-fibers in animal models[7]. Because of this, we hypothesized that mirabegron, a medication that recently became FDA-approved for treatment of OAB, would also improve symptoms in patients with BPS/IC. As a selective β_3 -agonist, mirabegron is

the first of a new class of pharmaceuticals for the treatment of OAB in over 30 years[8]. More than 95% of the beta adrenergic receptors found in the bladder are β_3 receptors and when activated, mediate relaxation of the detrusor muscle. This medication has been shown to significantly decrease the number of micturition episodes, urgency episodes, and increased mean volume of urine voided per micturition; all of which have been shown to improve quality of life[8]. Additionally, Mirabegron has been shown to have a favorable tolerability profile[9, 10]. Mirabegron may decrease rates of constipation and bowel symptoms compared to anticholinergic medications. This is particularly important in patients with IC, given the likelihood of concomitant Irritable Bowel Syndrome[11]. As mentioned previously, Mirabegron may also have properties effecting afferent nerve signaling, via mediation of afferent C-fibers. This may also have important implications in the bladder pain/IC patient. In an effort to find a novel treatment option, we hypothesized that this β_3 agonist will be efficacious in symptom control in patients with BPS/IC demonstrated through an overall improvement in patient symptom scores.

Objectives

Primary objective: to determine if using Mirabegron in patients diagnosed with bladder pain syndrome/interstitial cystitis (BPS/IC) improves symptoms. Improvement will be measured by evaluating symptoms of urgency, frequency and pain using the validated instrument O'Leary-Sant Indices (goal of 3 point improvement).

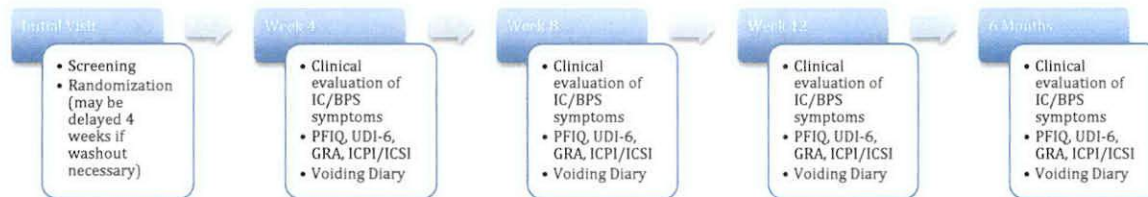
Secondary endpoints are:

- Improvement in incontinence episodes (bladder diary, UDI-6)
- Improvement in bladder symptoms (PFIQ-7)
- Improvement in bowel and vaginal/pelvic symptoms (PFIQ-7)
- Improvement in Patient satisfaction (Global Response Assessment (GRA))
- Improvement in Female Sexual Function Index (FSFI)
- Number of IC flares during study protocol
- Note any changes in need for other IC treatments

Safety Assessment and Reporting

Patients will be notified of all potential side effects related to Mirabegron use.

All side effects and adverse events self-reported by patients will be collected and reported.



Statistical Plan

This pilot study will require approximately 60 subjects. Based on prior clinical experience, this should be an appropriate number of subjects to provide the suggestion of a clinical difference between groups. As this is a pilot study, a power analysis cannot be performed prior to the start of the study. Hypothesis will be tested at $\alpha = 0.05$ significance level. Depending on the nature of the variable, either the one-way analysis of variables (ANOVA) for the numeric data or chi-square test for categorical data will be employed, with an intent-to-treat. Student T-test will be used to compare the means of subjects' scores on questionnaires. Multivariate regression analyses will be performed to assess impact of confounding clinical variables.

Data management and monitoring

The principal investigator, sub-investigators and research coordinator will be responsible for informed consent and collection and management of all research data, documented in appropriate forms. After initial collection, data will be de-identified and coded for anonymity and entered as described above on data collection sheets for the study, which will then be transferred and entered into a database developed and maintained by the Pelvic and Sexual Health Institute. Each subject, upon enrollment, will have a study identifier assigned to them, which will be the patient's identifier for the purposes of the

Study investigators will inquire about side effects and adverse events during clinical assessments. All side effects and adverse events will be collected and reported.

Investigators will immediately report to Astellas any patient who becomes pregnant during the study or who breastfeeds during the study. All study medication will be immediately discontinued in these circumstances.

Study investigators will immediately notify and report serious and life-threatening adverse events to Astellas. Causation of the study drug, mirabegron, will be investigated for the serious and life-threatening adverse event.

Setting

Patients will be compiled from one academic referral center in an urban setting.

Study Design

This is a prospective, randomized pilot study of patients with an established diagnosis of IC at a single tertiary care center. Patients with an established diagnosis of interstitial cystitis or bladder pain syndrome, stable on current treatment, who have not had any prior anticholinergic treatment, or have had an appropriate washout (4 weeks) of previous anticholinergic medication will be randomized to participate a 12 week trial of oral mirabegron 50mg vs placebo, dosed once daily. Diagnosis of BPS/IC will be based on current AUA guidelines; patients are deemed stable on their current pain treatment regimen if increase or change in medications has not been required for 4 weeks.

Mirabegron dosage of 50mg has been found in our practice to have improved clinical efficacy with few side effects. An IND will be filed for this dose and patient population. Patients will undergo clinical evaluation, including completion of O'Leary-Sant Symptom and Problem Indices, Pelvic Floor Impact Questionnaire, Female Sexual Function Index, bladder diaries and Urogenital Distress Inventory Questionnaire at each study visit and at completion of the medication trial. Patients will record any other IC treatments, symptoms, and/or medication side effects. Demographic and important clinical variables (age, BMI, duration of symptoms, time since diagnosis, co-morbidities, previous and current treatments including flares and remissions) will be collected at initial and follow up visits. All patients will then be evaluated with clinical evaluation and the aforementioned questionnaires at a 6 month follow up. The purpose of this observation period from 12 weeks to 6 months is to provide a descriptive analysis of durability of response. During this observation period, patients may change their medication regimen as needed, as well as receive bladder instillations for BPS/IC flares. This is a pilot study to test the feasibility of the hypothesis that beta adrenergic stimulation may improve pain symptoms in the BPS/IC patient.

Consent can be performed by the principal investigator, sub-investigators or the study coordinator. The consent form will be reviewed in detail with the patient and the consent process will be documented by the person obtaining consent in the patient's source documents.

Subject/Representative Comprehension

Patients will be given the opportunity to read the consent form and take it home with them for discussion with family or other people they care to discuss it with. They will be given the opportunity to ask questions and have their concerns addressed. The consent form will be reviewed with the patients section by section to ensure that they clearly understand what is required of them for this protocol prior to obtaining the patient's signature.

Inclusion Criteria

1. Participants must be diagnosed with BPS/IC with a minimum O'Leary-Sant score of 8 on the ICSI, as well as 8 on the ICPI. Patients should be stable on their regimen (no increase or change in medications, behavioral treatments or physical therapy in previous 4 weeks prior to starting the study) and be willing to remain on this regimen during the duration of the study.
 - a. Patients must be stable on current IC/BPS regimen.
 - b. Participant must have subjective complaints of
 - i. urinary urgency, relieved with voiding or
 - ii. urinary frequency; ≥ 8 voids per day
 - iii. pelvic pain, pressure, hypersensitivity or discomfort
2. Gender of subjects: Subjects in this study will be female. Pregnant women and breastfeeding women will be excluded due to unknown risk of study medication on pregnancy and fetus or nursing infants.
3. Age of subjects: Age of subjects will range from 18 to 95 years.
4. Racial and ethnic origin: There are no enrollment restrictions based upon race or ethnic origin. The racial and ethnic distribution of subjects is entirely based on the population of patients at the study site.
5. Other inclusion criteria:
 - a. Participant must give written informed consent to participate in the study
 - b. Participant must be able to make decisions for herself

study. The subject will be notified at the time of consent that they may elect to withdraw from the study in the event of non-compliance with the study protocol.

Data Storage and Confidentiality

Signed consent forms, with permissions, as well as collected data will be placed into a study binder, to be kept under lock and key at all times at the Pelvic and Sexual Health Institute. Each subject would have a random identifier code generated on enrollment, which will serve as their identification for study purposes; this key will also be kept under lock and key at the Pelvic and Sexual Health Institute. The center research coordinator and principal investigator will have access to the data.

Potential Risks to Subjects

Risk category: the Investigators believe that this study is considered Greater than Minimal Risk.

Potential risks: Side effects most commonly reported with mirabegron include increased blood pressure, common cold symptoms (nasopharyngitis), urinary tract infection, and headache.

Other reported reactions include: urinary retention, dizziness, diarrhea, constipation, arthralgia, tachycardia, nausea. Serious reactions reported by less than 1% of patients are elevated LFT's, lip edema, and atrial fibrillation.

Protection against Risks

Patients will have a full examination at follow up visit to assess for potential adverse reactions.

Potential Benefits to Subjects

Subjects may or may not have direct benefit from participation in this study.

Alternatives to Participation

Participation in this study is voluntary. The alternative to participation in this study would be to not participate. Patients may discuss other options available to them with their doctor or practitioner.

Method of Subject Identification and Recruitment

The patient population will be recruited from patients at the Pelvic and Sexual Health Institute. A convenience sample of 60 patients will be recruited from routine office visits. Subjects will include female patients with a diagnosis of BPS/IC who agree to participate in the study and meet the inclusion/exclusion criteria. The treatment time will be 12 weeks with a 6 month follow up visit.

Process of Consent

15. Participant has history of bladder cancer
16. Participant is currently an alcohol or substance abuser, or is a chronic opioid user
17. Participant has history of renal failure (GFR <30) or liver failure (CHILD score B or C)
18. Participant has urinary retention defined as greater than 150cc post-void residual as diagnosed by catheterization, bladder ultrasound scan or urodynamic testing within the last 14 days.
19. Patient has history of severe uncontrolled blood pressure (defines as systolic greater than or equal to 180mm Hg and/or diastolic blood pressure greater than or equal to 110 mm Hg)
20. Participant has a neurological disease including, but not limited to, multiple sclerosis, Parkinson's disease, Alzheimer's disease, spinal cord injury, brain injury, stroke or dementia
21. Participant has urinary frequency of less than 8 times/day
22. Participant has bladder or lower ureteral calculi
23. Participant has active genital herpes
24. Participant has urethral diverticulum
25. Participant has chemical cystitis
26. Participant has radiation or tuberculosis cystitis
27. Participant has known hypersensitivity to mirabegron or any of the inactive ingredients in the supplied form of mirabegron

Vulnerable Subjects

No vulnerable populations are to be recruited for this study.

Costs to the Subject

There will be no cost to the subject for participation in this study

Payment for Participation

There will be no payment for participation in the study.

Questionnaires:

O'Leary-Sant:

ICPI: Interstitial Cystitis Problem Index

ICSI: Interstitial Cystitis Symptom Index

UDI-6: Urogenital Distress Index

FSFI: Female Sexual Function Index

GRA: Global Response Assessment

c. Participant must have a negative urine dip within 7 days prior to start of the study

d. Female participants who are of childbearing age and sexually active with men must agree to use a medically acceptable method of contraception throughout the study period, and for 7 days after the study period. Medically acceptable methods of contraception include abstinence, oral contraceptive pills, hormonal contraceptive patches, diaphragm with or without spermicide, IUD, condoms, depot medroxyprogesterone acetate, subdermal progestin implants, vasectomized partner, or status post surgical sterilization.

Exclusion Criteria

To participate in the study subjects must not meet any of the following criteria:

1. Participant is currently pregnant or breastfeeding
2. Participant has a positive urinary pregnancy test at the time of screening
3. Participant is currently or has been on antibiotic therapy with the last 7 days prior to the start of the study
4. Participant is an employee of Astellas, or any other pharmaceutical company or the Pelvic and Sexual Health Institute
5. Participant is currently in another pharmaceutical trial
6. Participant has used anticholinergic medications, tamsulosin or opioid narcotic medication within the last 30 days prior to the study or during the study period. Patients will be able to use rescue medications for BPS/IC symptom flares including non-opioid narcotics, non-steroidal anti-inflammatory agents, pyridium and uribel.
7. Patient has had bladder hydrodistention or bladder instillations within the last 4 weeks. Patients may have bladder instillations during the study period if necessary for rescue from symptom flares.
8. Participant has used or currently using CYP2D6 substrates, such as thioridazine, flecainide, propafenone, within the last 7 days prior to the study or during study period
9. Participant has used warfarin or digoxin within the last 7 days prior to the study or during the study period
10. Participant has used cyclosporine within the 7 days prior to the study or during the study period
11. Participant has an active S3 nerve stimulator implanted or has had PTNS within 6 months prior to starting the study
12. Participant has not had intravesical botulinum toxin injection in 6 months prior to starting the study
13. Participant has grade III or IV pelvic organ prolapse
14. Participant has been diagnosed with a urinary tract infection within the last 4 weeks prior to starting the study

References to Background:

Mirabegron Prescribing Information: <http://www.us.astellas.com/docs/myrbetriq-full-pi.pdf>

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11. Chelimsky, G., et al., *Co-morbidities of interstitial cystitis*. *Front Neurosci*, 2012. **6**: p. 114.

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RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE: A Pilot Study of the Effects of Mirabegron on Symptoms in Patients with Interstitial Cystitis

PROTOCOL NO.: None
WIRB® Protocol #20161233

SPONSOR: Philadelphia Urosurgical Associates

INVESTIGATOR: Kristene E. Whitmore, MD
207 North Broad St 4th Floor
Philadelphia, PA 19107
USA

**STUDY-RELATED
PHONE NUMBER(S):** Kristene Whitmore
Hahnemann Urogynecology
215.863.8100 (24 hours)

SUMMARY

You are being asked to be in a research study. The purpose of this consent form is to help you decide if you want to be in the research study.

You should not join this research study until all of your questions are answered.

Things to know before deciding to take part in a research study:

- The main goal of a research study is to learn things to help patients in the future.
- The main goal of regular medical care is to help each patient.
- The decision to join or not join the research study will not cause you to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat you.
- Parts of this study may involve standard medical care. Standard care is the treatment normally given for a certain condition or illness.
- Other parts of this study may involve experimental (investigational) drugs or procedures that are being tested for a certain condition or illness. An investigational drug is one that has not been approved by the U.S. Food & Drug Administration (FDA).
- After reading the consent form and having a discussion with the research staff, you should know which parts of the study are experimental and which are standard medical care.
- Your medical records may become part of the research record. If that happens, your medical records may be looked at and/or copied by the sponsor of this study and government agencies or other groups associated with the study.

- Your medical insurance may be billed for any standard medical care you receive during the research study. If your insurance company is billed then it may have access to the research records. Insurance companies may not pay for treatment that is part of a research study. Taking part in a research study could affect your current or future insurance coverage.

PURPOSE OF THE STUDY

- Bladder Pain Syndrome/Interstitial cystitis (BPS/IC) is a disease that affects many patients. It is associated with pain, pressure or discomfort, and other urinary tract symptoms, such as frequency, urgency.
- It is suggested that treating the pain may improve the symptom of urinary urgency, if the urge arises from the need to alleviate the pain
- There are certain medications on the market for different symptoms of BPS/IC, but no single medication or combination of medications have achieved remarkable symptom control.
- Based on the mechanism of action of mirabegron, this medication may improve bladder pain.
- Our goal is to see if BPS/IC patients benefit from the use of mirabegron in terms of symptoms (pain, urgency and frequency).
- The experimental part of this study is the use of mirabegron for BPS/IC, although it is already FDA-approved for overactive bladder, which has similar symptoms to those of BPS/IC (particularly the urinary urgency and frequency).

PROCEDURES

You will come for an initial visit where you will receive your first dose of either the placebo or mirabegron. Placebo is a capsule that looks like mirabegron but contains no active ingredients. Assignment to either mirabegron or placebo will be determined randomly (much like flipping a coin).

- Patients who receive placebo will continue with their current pain management regimen but without mirabegron.
- Neither you nor the study doctor can choose whether you will receive mirabegron or placebo.
- This study is double-blind, which means that neither you nor the study doctor will know whether you are receiving mirabegron or the placebo. The study doctor can obtain this information in case of a medical emergency.
- If you are randomized to mirabegron, you will receive one 50 mg capsule daily. The dose will be taken orally.
- At the end of each visit, you will receive enough capsules to last you until your next scheduled visit.
- You will follow up for each office visit at 4 weeks, 8 weeks, 12 weeks and 6 months
- You will undergo a routine office visit, with collection of your symptoms, previous and current treatment.
- You will fill out questionnaires regarding your symptom and a 3 day voiding at each visit.
- The medication will be assigned at random; you have a 50% chance of receiving the placebo and a 50% chance of receiving mirabegron.

RISKS AND DISCOMFORTS

- Most common side effects
 - Increased blood pressure
 - Common cold symptoms (nasopharyngitis)
 - Urinary tract infection
 - Headache
- Less common reactions:
 - Urinary retention
 - Dizziness
 - Diarrhea
 - Constipation
 - Arthralgia (joint pain)
 - Tachycardia (abnormally rapid heart rate)
 - Nausea
- Serious but rare
 - elevated liver enzymes
 - lip swelling
 - atrial fibrillation

There may be side effects that are not known at this time.

Women who are pregnant or nursing a child may not take part in this study. Before entering the study, you and your study doctor must agree on the method of birth control you will use during the entire study. If you think that you have gotten pregnant during the study, you must tell your study doctor immediately. Pregnant women will be taken out of the study.

Other Risks

Your condition may not get better or may get worse during this study.

Only you should take the study drug. It must be kept out of the reach of children or anyone else who may not be able to read or understand the label.

NEW INFORMATION

You will be told about any new information that might change your decision to be in this study. You may be asked to sign a new consent form if this occurs.

BENEFITS

Your interstitial cystitis may improve while you are in this study; however, this cannot be promised. The results of this study may help people with interstitial cystitis in the future.

COSTS

Philadelphia Urosurgical Associates will provide the study drug, mirabegron, free of charge during this study. Tests and procedures that are done only for the study will not be billed to you or your insurance company.

You or your insurance company may be billed for:

- Any standard medical care given during this research study.

You may want to talk with your insurance company about its payment policy for standard medical care given during a research study. If your insurance company does not pay, you may be billed for those charges.

You might have unexpected expenses from being in this study. Ask your study doctor to discuss the costs that will or will not be covered by the sponsor. This discussion should include who will pay the costs of treating possible side effects.

PAYMENT FOR PARTICIPATION

You will not be paid for being in this study.

ALTERNATIVE TREATMENT

If you decide not to enter this study, there are other choices available. These include but are not limited to other research studies, approved medications and surgery. Ask the study doctor to discuss these alternatives with you. You do not need to be in this study to receive treatment for your condition.

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

What information may be used and given to others?

The study doctor will get your personal and medical information. For example:

- Past and present medical records
- Research records
- Records about phone calls made as part of this research
- Records about your study visits

Who may use and give out information about you?

The study doctor and the study staff.

Who might get this information?

The sponsor of this research. "Sponsor" means any persons or companies that are:

- working for or with the sponsor, or
- owned by the sponsor.

Your information may be given to:

- The U.S. Food and Drug Administration (FDA),
- Department of Health and Human Services (DHHS) agencies,
- Governmental agencies in other countries,
- Governmental agencies to whom certain diseases (reportable diseases) must be reported, and
- Western Institutional Review Board® (WIRB®).

Why will this information be used and/or given to others?

- to do the research,
- to study the results, and
- to see if the research was done right.

If the results of this study are made public, information that identifies you will not be used.

What if I decide not to give permission to use and give out my health information?

Then you will not be able to be in this research study.

May I review or copy my information?

Yes, but only after the research is over.

May I withdraw or revoke (cancel) my permission?

Yes, but this permission will not stop automatically.

You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to stay in this study.

When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.

Is my health information protected after it has been given to others?

There is a risk that your information will be given to others without your permission.

COMPENSATION FOR INJURY

If you are injured or get sick as a result of being in this study, call the study doctor immediately. The study doctor will provide emergency medical treatment. Your insurance will be billed for this treatment. No other payment is routinely available from the study doctor or sponsor.

VOLUNTARY PARTICIPATION AND WITHDRAWAL

Your participation in this study is voluntary. You may decide not to participate or you may leave the study at any time. Your decision will not result in any penalty or loss of benefits to which you are entitled.

Your participation in this study may be stopped at any time by the study doctor or the sponsor without your consent for any reason, including:

- if it is in your best interest
- if you do not consent to continue in the study after being told of changes in the research that may affect you

If you leave the study before the planned final visit, you may be asked by the study doctor to have some tests or procedures done so that you leave the study safely.

SOURCE OF FUNDING FOR THE STUDY

The sponsor Philadelphia Urosurgical Associates will pay for this research study.

QUESTIONS

Contact Hahnemann Urogynecology at 215.863.8100 (24 hours) for any of the following reasons:

- if you have any questions about your participation in this study,
- if you feel you have had a research-related injury or a reaction to the study drug, or
- if you have questions, concerns or complaints about the research.

If you have questions about your rights as a research subject or if you have questions, concerns or complaints about the research, you may contact:

Western Institutional Review Board® (WIRB®)
1019 39th Avenue SE Suite 120
Puyallup, Washington 98374-2115
Telephone: 1-800-562-4789 or 360-252-2500
E-mail: Help@wirb.com

WIRB is a group of people who independently review research.

WIRB will not be able to answer some study-specific questions, such as questions about appointment times. However, you may contact WIRB if the research staff cannot be reached or if you wish to talk to someone other than the research staff.

Do not sign this consent form unless you have had a chance to ask questions and have gotten satisfactory answers.

If you agree to be in this study, you will receive a signed and dated copy of this consent form for your records.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, 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.

CONSENT

I have read this consent form (or it has been read to me). All my questions about the study and my part in it have been answered. I freely consent to be in this research study.

I authorize the release of my medical and research records for the purpose of this study. By signing this consent form, I have not given up any of my legal rights.

Subject Name (printed)

Signature of Subject

Date