Protocol Title: 1/2-Pramipexole in Bipolar Disorder: Targeting Cognition (PRAM-BD)

Principal Investigator: Katherine Burdick, PhD

Site Principal Investigator:

Description of Subject Population: Bipolar Disorder

About this consent form

Please read this form carefully. It tells you important information about a research study. A member of our research team will also talk to you about taking part in this research study. People who agree to take part in research studies are called "subjects." This term will be used throughout this consent form.

Partners HealthCare System is made up of Partners hospitals, health care providers, and researchers. In the rest of this consent form, we refer to the Partners system simply as "Partners."

If you have any questions about the research or about this form, please ask us. Taking part in this research study is up to you. If you decide to take part in this research study, you must sign this form to show that you want to take part. We will give you a signed copy of this form to keep.

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.

Why is this research study being done?

We are doing this research study to find out if Pramipexole can help people with bipolar disorder who have problems with their cognitive abilities (i.e. attention, memory). We will evaluate the extent of the problems that you are experiencing to determine if they are severe enough for you to be eligible for this study.

Pramipexole is approved by the U.S. Food and Drug Administration (FDA) to treat Parkinson's Disease and restless leg syndrome, but Pramipexole is not approved by the FDA to treat bipolar disorder.

This research study will compare Pramipexole to placebo. The placebo looks exactly like Pramipexole, but contains no Pramipexole. During this study you may get a placebo instead of Pramipexole. Placebos are used in research studies to see if the results are due to the study drug or due to other reasons.

We are asking you to take part in this research study because you have bipolar disorder. Bipolar disorder is a brain disorder that causes unusual shifts in mood, energy, activity levels, and the ability to carry out day-to-day tasks.

About 100 subjects will take part in this research study. About 15 subjects will take part at Brigham and Women's Hospital (BWH).

Funds for conducting this research are provided by Brigham and Women's Hospital.

How long will I take part in this research study?

It will take you about 14 weeks to complete this research study. During this time, we will ask you to make 9 study visits to BWH.

What will happen in this research study?

If you choose to take part in this study, we will ask you to sign this consent form before we do any study procedures.

Screening Visit (Visit 1)

The Screening Visit will take about 2 hours. At this visit, we will do some tests and procedures to see if you qualify to take part in this research study. The study doctor will review the results of these tests and procedures. If you don't qualify, the study doctor will tell you why.

At this visit, we will:

- Ask you about your medical history
- Do a physical exam, including height and weight and blood pressure
- Draw a blood sample (approx. 2 TSP)
- Ask you for a urine sample
- Test your urine for certain drugs

- Test your urine for pregnancy, if you are a female able to become pregnant. Pregnant women cannot take part in this research study.
- Ask you to complete paper and pencil as well as computer tasks that measure cognitive functioning (for example, attention, memory, and reasoning)
- Do an ECG (electrocardiogram)
  This test checks the electrical activity of your heart. We will place several small, sticky pads on your chest, arms, and legs. Each pad has a wire attached. The wires connect to a machine that makes a recording of your heart rhythm. This painless test takes about 15 minutes.
- Ask you to fill out some questionnaires about your general health and well-being, quality of life, mental health, emotional health, mood, and memory

Urine Drug Screen

During this study, we will test your urine for certain drugs, including illegal drugs, e.g., cocaine, marijuana. If your urine shows you have taken any of these drugs, you can't be in this study. The results of the urine drug test will not become part of your medical record. These test results will, however, remain part of your study record.

Baseline Visit (Visit 2) – Assignment to a Study Group

Visit 2 will take about 3 hours. At this visit, we will:

- Ask you about your current mood and behaviors
- Measure your blood pressure and height and weight
- Ask you to complete a battery of pencil and paper and computer tests to look at cognition (for example, thinking, memory, and concentration)

If you still qualify for the study, we will assign you by chance (like a coin toss) to the Pramipexole group or the placebo group. There are 4 study drug assignment groups in total, each of those depends on what medication you are taking and whether or not you meet a cut-off for depressive symptoms. Across these 4 groups, there is an equal chance of being assigned to the Pramipexole group. You and the study doctor cannot choose your study group.

You and the study doctor won't know which study group you are in, but s/he can find out if necessary.

Taking the Study Drug

We will give you a supply of study drug to take home with you.

You will take the study drug by mouth, either once or twice a day for the entire study. The first day you take the study drug, we will ask you to take it at night. For the rest of the study you will take it once in the morning and once in the evening. It is important for you to follow our instructions about how to take the study drug. Although Pramipexole has not been shown to impair your functioning, please exercise caution when driving or participating in activities that require you to be alert, until you know how the medication affects you. In addition, you should avoid drinking alcoholic beverages for the duration of the study. Bring any unused study drug with you to your next study visit.

Your Study Drug Diary

We will give you a study diary to fill out at home each day. You will write down the times each day you take the study drug. Bring this diary with you to each study visit, so we can track your progress.

Study Drug Phase (Visits 3-9)

You will take the study drug for **12 weeks**. While you are taking the study drug, you will come in for a study visit about every **week for the first 4 weeks and then every two weeks for the remaining 8 weeks of the study**. These study visits will take between **1 and 4 hours,** depending on the visit. At the end of each visit, we will remind you of what will happen at your next visit.

Each Visit

At each visit during this part of the study, we will:

- Ask you about your current mood and behaviors
- Ask you to fill out some questionnaires about your general health and well-being, quality of life, mental health, emotional health, mood, and memory
- Measure your blood pressure and height and weight
- Ask you about any side effects you may be experiencing
- Ask you for the previous week's drug diary and any leftover study drug

Some Visits

At some visits, we will also:

- Ask you to complete paper and pencil as well as computer tasks that measure cognitive functioning (for example, attention, memory, and reasoning)
- Do an ECG (electrocardiogram)

After You Complete the Study

After you complete the study, we will refer you back to your own doctor for your ongoing medical care.

Stopping the Study Early

If you decide to stop taking part in the study for any reason, we will ask you to make a final study visit. You will need to return all unused study drug and your study diary at this visit. The final study visit will take about 4 hours. At this visit, we will:

- Do a physical exam, including height and weight and blood pressure
- Draw a blood sample (approx. 2 TSP)
- Ask you for a urine sample
- Test your urine for certain drugs
- Test your urine for pregnancy, if you are a female able to become pregnant. Pregnant women cannot take part in this research study.
- Ask you to complete paper and pencil as well as computer tasks that measure cognitive functioning (for example, attention, memory, and reasoning)
- Do an ECG (electrocardiogram)
- Ask you to fill out some questionnaires about your general health and well-being, quality of life, mental health, emotional health, mood, and memory
- Ask you for the previous week's drug diary and any leftover study drug

When you end your participation in the study, the study drug will need to be tapered for a period of 7-10 days, depending on the amount of drug you were taking at the end of the study. The study doctor will provide you with amount of study drug to take each day during this period. You will not have to return to BWH for a study visit, unless medically necessary, but someone from the study team will reach out to you by phone and/or email to check on how you're doing during this taper period.

Also, the study doctor may take you out of the study without your permission. This may happen because:

- The study doctor thinks it is best for you to stop taking the study drug
- You can't make the required study visits
- We stop doing the study for other reasons

If this happens, the study doctor will explain why you need to stop taking part in the study. We will ask you to come in for a final study visit as described above.

Study Information Included in Your Electronic Medical Record

A notation that you are taking part in this research study may be made in your electronic medical record. Information from the research that relates to your general medical care may be included in the record (for example: list of allergies, results of standard blood tests done at the hospital labs).

Please ask your study doctor if you have any questions about what information will be included in your electronic medical record.

What are the risks and possible discomforts from being in this research study?

Risks of Taking Pramipexole

Taking Pramipexole may cause you to have one or more of the side effects listed below.

Common side effects:

- Headache
- Nausea
- Insomnia, or any difficulty sleeping

Less common side effects:

- Dizziness
- Constipation
- Physical weakness or lack of energy
- Hallucinations

Uncommon side effects:

- Narcolepsy, excessive uncontrollable daytime sleepiness
- Restlessness
- Problems with impulse control

Additionally, in 2012 the FDA announced a potential risk of Pramipexole related to heart failure. The FDA drug safety communication recommends continuing the use of Pramipexole, as there have been no statistically significant findings to date. These findings do not indicate the reported heart failure in patients taking Pramipexole is associated with the drug, however data is still being reviewed. To minimize this potential risk, if you have a history of heart failure you will not be allowed to participate in the study. We will also assess cardiac risk factors at the time of screening and will monitor symptoms of heart failure in all participants throughout the study, including vital signs during all visits and ECGs on weeks 6 and 12.

If you agree to participate in the study, it is possible that your Bipolar I or II Disorder may put you at increased risk of having a manic episode or psychosis or other mood disturbance or impulse control problems due to this drug and its possible side effects. Please notify study staff is you notice any worsening in psychiatric symptoms.

There may be other risks of Pramipexole that are currently unknown.

As with any drug, an allergic reaction can occur. Allergic reactions can be mild or more serious, and can even result in death. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat, or trouble breathing. If you think you are having an allergic reaction, call the study doctor right away. If you are having trouble breathing, call 911 immediately.

Risks to an Embryo or Fetus, or to a Breastfeeding Infant

The effect of Pramipexole on an embryo or fetus (developing baby still in the womb), or on a breastfeeding infant, is unknown and may be harmful. Because of these unknown risks, women cannot take part in this study if they are:

- Pregnant
- Trying to become pregnant
- Breastfeeding

If you are a menopausal woman and have not had a menstrual period for the past 12 months or more, you will not need to have a pregnancy test. Also, if you have had any well-documented method of surgical sterilization, you will not need to have a pregnancy test. Methods of surgical sterilization include having had a hysterectomy (removal of the uterus), bilateral oophorectomy (removal of both ovaries), a tubal ligation (having your tubes tied), and transvaginal occlusion (plugging the opening of the tubes with a coil). All other female subjects must have a negative pregnancy test before starting the study drug.

If you are sexually active and able to become pregnant, you must agree to use one of the birth control methods listed below. You must use birth control **for the entire study and for at least 30 days** after your last dose of study drug.

Acceptable birth control methods for use in this study are:

- hormonal methods, such as birth control pills, patches, injections, vaginal rings, or implants
- barrier methods (such as a condom or diaphragm) used with a spermicide (a foam, cream, or gel that kills sperm)
- intrauterine device (IUD)
- abstinence (no sex)

Hormonal contraceptives, implants, and injections are only considered effective if used properly and started at least one month before you begin the study, continuing throughout the study and

for one month after the end of the study. You should ask your study doctor if you should continue birth control for longer than 30 days after the end of the study. If you are unsure whether the method of birth control you use is acceptable to use while participating in this study, you should ask your study doctor before you begin the study.

If you miss a period, or think you might be pregnant during the study, you must tell the study doctor immediately. If you become pregnant, you must stop taking the study drug and stop taking part in the study. The study doctor may ask for your permission to collect information about the outcome of your pregnancy and the condition of your newborn.

Risks of Taking Pramipexole with Other Medications

Do not take the following family of over the counter medications commonly used to treat gastrointestinal symptoms (heart burn, sour stomach, indigestion, etc.) while you are in the study: over the counter (OTC) H2 blockers such as cimetidine/Tagamet or famotidine/Pepcid or ranitidine/Zantac. Taking these drugs and Pramipexole together may cause serious side effects.

For your safety during this study, call your study doctor BEFORE you take any:

- new medications prescribed by your own doctor
- other medications sold over-the-counter without a prescription
- dietary or herbal supplements

Risks of Blood Draws

You may have a bruise (a black and blue mark) or pain where we take the blood samples. There is also a small risk of infection, lightheadedness, and/or fainting.

Other Risks

Some of the questions that you will be asked during your study participation may be unsettling, but most will not be. You may ask to see the questions before deciding whether or not to participate. You may also become fatigued during the testing. You are encouraged to notify the examiner if you wish to take a break. You may refuse to answer any questions that you so choose and you may discontinue testing if you feel that you cannot continue.

There always exists the potential for loss of private information; however, there are procedures in place to minimize the risk.

What are the possible benefits from being in this research study?

You may not benefit from taking part in this research study. If you receive Pramipexole, it is possible that some of your cognitive problems associated with bipolar disorder will improve while you are taking it.

Others with bipolar disorder may benefit in the future from what we learn in this study.

What other treatments or procedures are available for my condition?

You do not have to take part in this research study to be treated for bipolar disorder. Instead of being in this research study, your choices may include: Pramipexole is available by prescription from your treating doctor to be used off-label without the need to participate in this study.

Talk with the study doctor if you have questions about any of these treatments or procedures.

Can I still get medical care within Partners if I don't take part in this research study, or if I stop taking part?

Yes. Your decision won't change the medical care you get within Partners now or in the future. There will be no penalty, and you won't lose any benefits you receive now or have a right to receive.

Taking part in this research study is up to you. You can decide not to take part. If you decide to take part now, you can change your mind and drop out later. We will tell you if we learn new information that could make you change your mind about taking part in this research study.

What should I do if I want to stop taking part in the study?

If you take part in this research study, and want to drop out, you should tell us. We will make sure that you stop the study safely. We will also talk to you about follow-up care, if needed.

Also, it is possible that we will have to ask you to drop out of the study before you finish it. If this happens, we will tell you why. We will also help arrange other care for you, if needed.

Will I be paid to take part in this research study?

We will pay you $400 if you complete the study. If you do not complete the study, you will receive different amounts depending on the length of the visit. You will be paid $100 for the screening visit; $50 for baseline and week 6; $20 for week 1, 2, 3, 4, 8; $100 for week 12. All payments will be made by check processed through the Partners AP "eCheck" system. In addition, you will receive the study drug at no cost for the entire study period.

What will I have to pay for if I take part in this research study?

Study funds will pay for study drug, study-related procedures, study visits that are done only for research.

What happens if I am injured as a result of taking part in this research study?

We will offer you the care needed to treat any injury that directly results from taking part in this research study. We reserve the right to bill your insurance company or other third parties, if appropriate, for the care you get for the injury. We will try to have these costs paid for, but you may be responsible for some of them. For example, if the care is billed to your insurer, you will be responsible for payment of any deductibles and co-payments required by your insurer.

Injuries sometimes happen in research even when no one is at fault. There are no plans to pay you or give you other compensation for an injury, should one occur. However, you are not giving up any of your legal rights by signing this form.

If you think you have been injured or have experienced a medical problem as a result of taking part in this research study, tell the person in charge of this study as soon as possible. The researcher's name and phone number are listed in the next section of this consent form.

If I have questions or concerns about this research study, whom can I call?

You can call us with your questions or concerns. Our telephone numbers are listed below. Ask questions as often as you want.

Katherine Burdick, PhD is the person in charge of this research study. You can call her at 617-732-5789 Monday-Friday from 9am to 5pm. You can also call Meg Shanahan at phone number 617-732-5790 Monday-Friday from 9am to 5pm with questions about this research study.

To reach a physician member of the study team 24 hours a day, 7 days a week, you can call the BWH hospital operator, 617-732-5500, indicate that it is a research matter, and ask the operator to page the study doctor assigned to you (you will know who your study doctor is once the screening visit takes place).

If you have questions about the scheduling of appointments or study visits, call Meg Shanahan at phone number 617-732-5790.

If you want to speak with someone **not** directly involved in this research study, please contact the Partners Human Research Committee office. You can call them at 857-282-1900.

You can talk to them about:
- Your rights as a research subject
- Your concerns about the research
- A complaint about the research

Also, if you feel pressured to take part in this research study, or to continue with it, they want to know and can help.

If I take part in this research study, how will you protect my privacy?

During this research, identifiable information about your health will be collected. In the rest of this section, we refer to this information simply as "health information." In general, under federal law, health information is private. However, there are exceptions to this rule, and you should know who may be able to see, use, and share your health information for research and why they may need to do so.

In this study, we may collect health information about you from:

- Past, present, and future medical records
- Research procedures, including research office visits, tests, interviews, and questionnaires

Who may see, use, and share your identifiable health information and why they may need to do so:

- Partners research staff involved in this study

- The sponsor(s) of this study, and the people or groups it hires to help perform this research
- Other researchers and medical centers that are part of this study and their ethics boards
- A group that oversees the data (study information) and safety of this research
- Non-research staff within Partners who need this information to do their jobs (such as for treatment, payment (billing), or health care operations)
- The Partners ethics board that oversees the research and the Partners research quality improvement programs.
- People from organizations that provide independent accreditation and oversight of hospitals and research
- People or groups that we hire to do work for us, such as data storage companies, insurers, and lawyers
- Federal and state agencies (such as the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health, and other US or foreign government bodies that oversee or review research)
- Public health and safety authorities (for example, if we learn information that could mean harm to you or others, we may need to report this, as required by law)
- Other:

Some people or groups who get your health information might not have to follow the same privacy rules that we follow and might use or share your health information without your permission in ways that are not described in this form. For example, we understand that the sponsor of this study may use your health information to perform additional research on various products or conditions, to obtain regulatory approval of its products, to propose new products, and to oversee and improve its products' performance. We share your health information only when we must, and we ask anyone who receives it from us to take measures to protect your privacy. The sponsor has agreed that it will not contact you without your permission and will not use or share your information for any mailing or marketing list. However, once your information is shared outside Partners, we cannot control all the ways that others use or share it and cannot promise that it will remain private.

Because research is an ongoing process, we cannot give you an exact date when we will either destroy or stop using or sharing your health information.

The results of this research study may be published in a medical book or journal, or used to teach others. However, your name or other identifying information **will not** be used for these purposes without your specific permission.

Your Privacy Rights

You have the right **not** to sign this form that allows us to use and share your health information for research; however, if you don't sign it, you can't take part in this research study.

You have the right to withdraw your permission for us to use or share your health information for this research study. If you want to withdraw your permission, you must notify the person in charge of this research study in writing. Once permission is withdrawn, you cannot continue to take part in the study.

If you withdraw your permission, we will not be able to take back information that has already been used or shared with others.

You have the right to see and get a copy of your health information that is used or shared for treatment or for payment. To ask for this information, please contact the person in charge of this research study. You may only get such information after the research is finished.

Informed Consent and Authorization

Statement of Person Giving Informed Consent and Authorization

- I have read this consent form.
- This research study has been explained to me, including risks and possible benefits (if any), other possible treatments or procedures, and other important things about the study.
- I have had the opportunity to ask questions.
- I understand the information given to me.

Signature of Subject:

I give my consent to take part in this research study and agree to allow my health information to be used and shared as described above.

Subject	Date	Time (optional)

Signature of Study Doctor or Person Obtaining Consent:

Statement of Study Doctor or Person Obtaining Consent

- I have explained the research to the study subject.
- I have answered all questions about this research study to the best of my ability.

Study Doctor or Person Obtaining Consent	Date	Time (optional)

Consent Form Version: 8/29/18