IRB NUMBER: 203368021611

LOYOLA UNIVERSITY MEDICAL CENTER
MAYWOOD, ILLINOIS
DEPARTMENT OF PSYCHIATRY

INFORMED CONSENT

Participant's Name: _____

Medical Record Number: _____

PROJECT TITLE: Cyclooxygenase-2-Inhibitor Combination Treatment for Bipolar Depression: Role of Inflammation and Kynurenine Pathway Biomarkers.

THE APPROVAL FOR THIS PROJECT EXPIRES ON 11/16/2017.

Participant Information

PRINCIPLES CONCERNING RESEARCH: You are being asked to take part in a research project. It is important that you read and understand the principles that apply to all individuals who agree to participate in the research project described below:

1. Taking part in the research is entirely voluntary.

2. We do not know if you will benefit directly from taking part in the research but the knowledge obtained may help others.

3. You may withdraw from the study at any time without anyone objecting and without penalty or loss of any benefits to which you are otherwise entitled.

4. If during your participation in the research project, new information becomes available which would affect your being in the research project (such as better treatments or the side effects of the treatments), your doctor will discuss this new information with you and will help you make a decision about your continuing in the research.

The purpose of the research, how it is to be done, and what your part in the research will be, is described below. Also described are the risks, inconveniences, discomforts and other important information which you need to make a decision about whether or not you wish to participate. You are urged to discuss any questions you have about this research with the staff members.

PURPOSE OF STUDY: You are being asked to participate in a research project because you suffer from Bipolar Disorder and the doctors recommend treatment for your condition.

In bipolar disorder, the depressive symptoms are more common than manic symptoms; and, it is

depression that most adversely affects the quality of life. Depressive symptoms suffered by bipolar patients are more difficult to treat than manic symptoms, and the suicide rate is highest in patients with bipolar disorder.

Patients suffering from depression also show elevated levels of chemicals in the blood, called biomarkers that indicate ongoing inflammation. This inflammation found in patients suffering from depression may reduce the effectiveness of antidepressant medications. Furthermore, inflammation likely contributes to the increased risk of depressed patients to develop serious and potentially life-threatening complications, such as heart disease and stroke.

The purpose of this research is to determine if treating depression with an antidepressant (Escitalopram-Lexapro) and an anti-inflammatory medication (Celecoxib-Celebrex) increases the effectiveness of treating the depressive symptoms of Bipolar Disorder. The related purpose is also to see if this treatment reduces the levels of inflammatory biomarkers in the blood that suggest patients might be at risk for developing life-threatening conditions like heart disease and stroke. The combination of escitalopram with celecoxib to treat your condition is research.

Approximately 70 participants will participate in this project. This study is being funded by the Stanley Medical Research Institute.

DESCRIPTION AND EXPLANATION OF PROCEDURES: If you agree to participate, you will be asked to come to Loyola University Medical Center up to 8 times during this study. These visits will take place between 8:30am and 12:00pm. Additional visits may be necessary if you report any adverse events or if an unscheduled dose adjustment is necessary. You should be fasting for 12 hours prior to any visit during which a routine blood chemistry blood draw is scheduled.

Screening - Visits 1 and 2

During the Screening (Visits 1 and 2) the following procedures will take place:

- Blood draw for routine clinical lab tests. No more than 3 teaspoons will be drawn.
- Urine sample collection for drug testing and pregnancy screening, if appropriate.
- Medical history including family background history.
- A physical examination including a brief gum exam.
- A psychiatric interview to assess your level of anxiety and depression.
- A saliva sample will be taken for cortisol analysis.

The physical exam and collection of specimens will only take place after your eligibility has been confirmed in the psychiatric interview.

During the psychiatric interview portion of these two study visits, the psychiatrist will complete the following scales to assess your mood and level of depression:

- Hamilton Rating Scales for Depression (HAM-D)
- Portions of the Diagnostic Interview for Genetic Studies (DIGS)
- The Mini-International Neuropsychiatric Interview (MINI)

Meeting with the psychiatrist will require up to 2 hours of your time during each visit in the

Screening process.

You will also be asked to complete the following self-assessments regarding your mood as you perceive it:

- Patient Health Questionnaire (PHQ-9)
- Beck Depression Inventory (BDI)
- Beck Anxiety Inventory (BAI)
- State/Trait Anxiety Inventory (STAI)
- Spielberger Anger Expression Inventory (STAXI)
- International Physical Activity Questionnaire (I-PAQ)
- Quality of Life and Enjoyment Questionnaire (QLES-Q)
- The Short-Form McGill Pain Inventory (MPI)
- Perceived Stress Scale (PSS-14)

Completing the above self-assessments will take between 20 and 30 minutes.

If the tests show that you qualify to participate, you will be scheduled for another visit. You will be instructed by the psychiatrist on how to *taper off* of the antidepressant medication you may have been taking. Completing all of these assessments may take up to 4 hours in total. If the amount of time it takes to complete these assessments and procedures exceeds the allotted time of the scheduled visit due to late arrival, waiting time, etc., the assessments and procedures mentioned above may be completed over the course of two visits.

<u>More information on Screening Visit 2</u>
If you are on an antidepressant upon enrolling in the study, you will be instructed on how to *taper off* the medication as mentioned above. If this wash-out step is necessary, Visit 2 will also include a second administration of the HAM-D to assess your level of depression and anxiety after having stopped taking your antidepressant. If you are still eligible to participate in the study, you will begin taking study pills after this visit. You will be given a one week supply of study pills at the end of Visit 2.

<u>Baseline – Visit 3</u>
During the Baseline visit (Visit 3) you will meet with the psychiatrist again. The following instruments will be used to assess your mood, depression and anxiety:

- Hamilton Rating Scales for Depression (HAM-D)
- Hamilton Rating Scales for Anxiety (HAM-A)
- Montgomery Asberg Depression Rating Scale (MADRS)
- Clinical Global Impression Severity and Improvement Scales (CGI)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Inventory of Clinically Significant Upper and Lower GI events (CSULGIE)

Meeting with the psychiatrist will take approximately 1 hour. You will be asked to complete the following self-assessment regarding your level of depression, anxiety, and mood:

- Beck Depression Inventory (BDI)
- Beck Anxiety Inventory (BAI)

- State/Trait Anxiety Inventory (STAI)
- Spielberger Anger Expression Inventory (STAXI)
- International Physical Activity Questionnaire (I-PAQ)
- Quality of Life and Enjoyment Questionnaire (QLES-Q)
- The Short-Form McGill Pain Inventory (MPI)
- Perceived Stress Scale (PSS-14)

Completing the above self-assessments will take between 20 and 30 minutes.

We will use an approved non-invasive device called the SphgymoCor® apparatus to measure your blood pressure waveforms and obtain heart rate information. You will lie down comfortably for 10 minutes. Then, a probe tonometer – about the size of a ballpoint pen – will be gently applied to the surface of your skin overlying the artery in your wrist. The output from the tonometer is viewed in real time on a nearby computer. This is called pulse-wave analysis (PWA). PWA is a measure of the function and stiffness of your blood vessels when reclining. This procedure will take approximately 15 minutes total.

During this visit, further assessments will be completed using the SphygmoCor® machine. You will be asked to recline for at least 10 minutes in the exam room before the following assessments are performed.

- A 3-lead electrocardiogram (ECG) will record your heart rate for 15 minutes.
- PWV will be recorded by taking your pulse over arteries in your neck and groin.
- PWA will be recorded as it was during Screening.
- Two puffs of albuterol will be administered to you through an aerosol and spacer.
- PWA will then be recorded at 0, 5, 10, and 15 minutes after albuterol inhalation.

More information about the SphygmoCor procedures:
Albuterol is a safe medication commonly used for asthma. The effects of albuterol only last about 45 minutes, allowing your blood vessels to relax and your air passages to open. You should not experience any pain or difficulty breathing during this procedure, but you might become light-headed if suddenly rising to walk. Two puffs of albuterol will be inhaled by you through an aerosol sprayer with the aid of a spacer. You will inhale once slowly for 50 seconds, and then hold your breath for 10 seconds. After a 30 second pause, the second puff will be given in like manner. Pulse waves will then be recorded with the tonometer placed gently on your wrist. This albuterol step will only be performed during the baseline visit and at the last study-visit.

During this visit, a blood draw of about 8 teaspoons will be completed. We will freeze this blood, and use it later to measure the chemicals that are thought to be responsible for inflammation and the development of cardiovascular disease. Also, DNA (genes/heredity) will be isolated and genetic testing will be done using your DNA. The purpose of this genetic testing is to learn more about the genetic basis of heart disease and depression. The genetic testing results will be kept confidential.

During this visit, you will also arrive 30 minutes prior to your scheduled appointment time to

provide a saliva sample after 20 minutes of rest in the exam room.

You will continue taking study pills after this visit. You will be given a one week supply of study pills at the end of the Baseline visit.

Your escitalopram dosing will remain at the discretion of your study psychiatrist. You will be assigned by lottery to receive either celecoxib (Celebrex) or a placebo along with the escitalopram. Your chances of receiving celecoxib or placebo are equal. A placebo is a harmless, inactive substance. Neither you nor your doctor know whether you are taking celecoxib (Celebrex) or placebo. In the event of a medical emergency, the principal investigator of the study will be notified if you are taking celecoxib (Celebrex) or placebo.

All patients participating in this research will receive a placebo at some time during the study.

This visit will last approximately 3 hours.

Week 1 – Visit 4

At Week 1 (Visit 4), the following scales will be completed:

- Hamilton Rating Scales for Depression (HAM-D)
- Hamilton Rating Scales for Anxiety (HAM-A)
- Montgomery Asberg Depression Rating Scale (MADRS)
- Clinical Global Impression Severity and Improvement Scales (CGI)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Inventory of Clinically Significant Upper and Lower GI events (CSULGIE)

Meeting with the psychiatrist will take approximately 1 hour. You will be asked to complete the following self-assessment regarding your level of depression, anxiety, and mood:

- Beck Depression Inventory (BDI)
- Beck Anxiety Inventory (BAI)
- State/Trait Anxiety Inventory (STAI)
- Spielberger Anger Expression Inventory (STAXI)
- International Physical Activity Questionnaire (I-PAQ)
- Quality of Life and Enjoyment Questionnaire (QLES-Q)
- The Short-Form McGill Pain Inventory (MPI)
- Perceived Stress Scale (PSS-14)
- A survey on side effects

You will also provide a saliva sample at the beginning of this visit, after 20 minutes of rest in the exam room. You will also be asked about possible adverse events or side effects from the medication. You will be given a one week supply of study pills at the end of your Week 1 visit. This visit will last approximately 2 hours. You will be scheduled to return to the clinic in 1 week.

Week 2 – Visit 5

At Week 2 (Visit 5), you will complete the same rating scales you completed in Week 1 to assess your condition. You will be asked about possible adverse events from the medication.

You will also provide a saliva sample at the beginning of this visit, after 20 minutes of rest in the exam room. You will be given a one week supply of study pills at the end of your Week 1 visit. This visit will last approximately 2 hours. You will be scheduled to return to the clinic in 2 weeks.

Week 4 – Visit 6
At Week 4 (Visit 6), about 8 teaspoons of blood will be drawn to run clinical labs for safety monitoring and measure drug levels and biomarkers. You will complete the same rating scales you completed in Week 1 to assess your condition. You will also provide a saliva sample at the beginning of this visit, after 20 minutes of rest in the exam room. You will be asked about possible adverse events from the medication and given a refill for your medication. PWA will be performed. You will be scheduled to return to the clinic in 4 weeks. This visit will last approximately 2 hours.

Week 8 – Visit 7
At Week 8 (Visit 7), you will undergo the same SphygmoCor procedures, psychiatric assessments and rating scales that were administered at the Baseline visit.

You will also provide a saliva sample at the beginning of this visit, after 20 minutes of rest in the exam room.

You should be fasting for 12 hours prior to this visit. Up to 11 teaspoons of blood drawn from your arm. The blood will be used to measure drug level, biomarker levels, and routine chemistry analyses. You will be asked about possible adverse events from the medication. This visit will last approximately 3 hours.

Throughout the course of treatment, approximately 25-28 teaspoons of your blood will be taken. This includes blood for routine blood chemistry draws, biomarker draws, and drug level draws. At this point, your study participation will be completed. After your participation in the study is over, our doctor will discuss continuing treatment options with you.

There are certain medicines that you cannot take while participating in this project. Your doctor will discuss them with you before you sign this consent form and you will be given a list of the medicines that you cannot take while participating in this project, upon your request.

For confidentiality reasons, when your data is reviewed outside of the patient-doctor relationship, your identity will not be revealed and all information about you, including your blood samples, will only be known by a code. The code and the key to the code will be kept in a secure and locked location. Your blood will be processed and stored for later testing in our laboratory. Since this is a research study and the clinical meaning of the results we obtain may not be immediately understood or known, neither you nor your doctor will be notified of the results of the research tests.

Your blood will only be used for purposes of this research and will be destroyed when the project is completed. Your blood will not be sold.

At two time points: prior to the Baseline visit, and prior to the Week 8 visit, we will have you collect your saliva at five times during the day: upon awakening, approximately 30 minutes past awakening, before lunch, at approximately 3pm, and before bedtime. You will be required to do this at home and store the samples in your refrigerator until your next visit. You will be provided with a log to document the exact time at which you collected your samples.

RISKS/DISCOMFORTS: Escitalopram (Lexapro) may not help with your depression. The treatment you are randomly assigned to receive may be less effective or may be associated with more problems than the treatment other participants may be randomly assigned to receive in this study.

The most commonly reported side effects of escitalopram (Lexapro) are: nausea, insomnia, problems with ejaculation, sleepiness, increased sweating, fatigue, decreased sexual desire, and anorgasmia (inability to have an orgasm). Much less common side effects have also been reported: headache, nervousness or anxiety, nausea, diarrhea, dry mouth, changes in appetite or weight, sleepiness or insomnia, and decreased sex drive. Most of the side effects experienced by patients taking this medication are mild to moderate and go away with continued treatment, and usually do not cause patients to stop taking escitalopram (Lexapro). If you experience any of these side effects, contact your physician.

Suicidality and Antidepressant Drugs
Depression is associated with increased risk of suicide. Short-term studies have shown that antidepressants like escitalopram (Lexapro) increase the risk of suicidal ideations and behavior in young adults between the ages of 18 and 24 with major depressive disorder, compared to a placebo. Similar studies have shown no such increase in the risk of suicidality with antidepressants in adults beyond age 24, and there is a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Patients of all ages who are started on antidepressant therapy should be monitored closely for clinical worsening, suicidality, or unusual changes in behavior. Families are advised of the need for close observation and communication with the prescriber.

Non-Steroidal Anti-Inflammatory Drugs
Celecoxib (Celebrex) may cause an increased risk of heart attacks and strokes. This can be fatal. All non-steroidal anti-inflammatory drugs (NSAIDs) may have a similar risk. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.

NSAIDs, including celecoxib, cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines. This can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.

Celecoxib (Celebrex) may cause heart or circulation problems, such as chest pain, weakness, shortness of breath, slurred speech, or problems with vision or balance. Celecoxib (Celebrex) can also increase your risk of serious effects on the stomach or intestines, including bleeding or

perforation (forming of a hole). These conditions can be fatal and gastrointestinal effects can occur without warning at any time while you are taking celecoxib (Celebrex). Older adults may have an even greater risk of these serious gastrointestinal side effects.

Blood drawing may be associated with mild and brief lasting pain from the stick. There is also a possibility of bruising and infection. Since we conduct fasting blood draws, you will be asked not to eat or drink anything, except water, after midnight prior to your Baseline visit and Week 8. At these times, you should not drink alcohol or take any medications not previously allowed by the physician for at least 12 hours prior to the blood draw procedure.

Side effects for albuterol include hoarseness, headache, tremors, and palpitations, fast heart rates and nervousness. Some people can be allergic to albuterol. You will be asked if you have had previous exposure to albuterol, and if you have had any problems with it. If you develop any problems due to the albuterol while participating in this research, you will not have any more exposure to albuterol.

You may become uncomfortable or feel bored when completing the questionnaires and rating scales.

In order to meet the goals of the research study, we will collect information on you, your test results, and how you do. The information will be coded to remove information that could be used to identify you and collected by Dr. Halaris, the principal investigator, other physicians, the research nurses, data administrators, and secretaries. This information will then be stored in a locked room, either in locked cabinets or on a locked computer in secure electronic files. However, there is the possibility that there could be a loss of confidentiality regarding your health information.

There could also be unknown risks.

REPRODUCTIVE AND SEXUAL ACTIVITY INFORMATION: The intervention in this study could affect a developing baby. Therefore, you cannot participate in this research project, if you are pregnant or breast feeding. If you are a woman of childbearing potential, a pregnancy test will be done to make certain that you are not pregnant before beginning the study.

Both men and women who are able to have children must use an effective method of preventing pregnancy while participating in this study. You are encouraged to discuss your preferred method with the study doctor. He/she will answer any questions you have regarding effective methods of preventing pregnancy. It is important that you consult with your physician because some study medications may affect the effectiveness of various methods of preventing pregnancy.

If you become pregnant, or suspect that you have become pregnant, or you have fathered a child during the study, notify the study doctor immediately.

BENEFITS: You will not receive additional benefit from participating in this study beyond the benefit that you may receive by taking approved treatments for your depression. The information

we obtain from you may help others.

Loyola University Medical Center may benefit from your participation in this project.

ALTERNATIVE TREATMENTS: You do not have to participate in this research project to receive care and treatment at Loyola University Medical Center. There are approved medicines that you can receive to treat your condition. Your doctor has discussed other treatments with you along with their risks and benefits.

FINANCIAL INFORMATION: There will be no charge to you for any of the research procedures and blood tests. Escitalopram (Lexapro) and celecoxib (Celebrex) will be provided free of charge only while participating in this research project.

You will be compensated a total of $360 for your participation in the study. The IRS requires that we have a W-9 form on file for all participants who receive compensation. You will be asked to complete a W-9 form before your payment can be processed. The payments will be distributed as follows:

Visit	Payment
Screen 1 – Visit 1	$25
Screen 2 – Visit 2	$25
Baseline – Visit 3	$50
Week 1 – Visit 4	$30
Week 2 – Visit 5	$30
Week 4 – Visit 6	$60
Week 8 – Visit 7	$140

You will be paid a total of $360 upon completion of all visits. If you terminate your participation earlier, you will receive prorated compensation according to the completed visits as per the above schedule. If you terminate your participation before completion of the study, it will take at least 4 weeks for your payment to be processed and mailed to you.

If you do not qualify for the study after completing all assessments at Visit 1, you will still be compensated $25. If the psychiatrist determines that you do not qualify for the study at Visit 1 before having completed less than 25% of the psychiatric assessments, we will reimburse you for your travel fare or parking but you will not receive the $25 payment.

RESEARCH RELATED INJURY: In the event that you are injured as a direct result of participating in this research project, your doctor will take necessary steps to diagnose and treat the problem. You will be financially responsible for the cost of care of the problem.

INFORMATION COLLECTED AND WHAT WILL HAPPEN TO IT: In order to meet the goals of the research study (see Purpose of Research section of this consent), we will collect information on you, your test results and how you do. The information will be collected by Dr. Angelos Halaris, the study physician(s), the research nurses, data administrators and secretaries. Information about you will be provided to Loyola University of Chicago and data collection and

study verification agencies and/or government regulatory agencies, such as the Food and Drug Administration.

The information we will collect and send:

X____DEMOGRAPHIC INFORMATION E.G., NAME, ADDRESS, PHONE NUMBER, SOCIAL SECURITY NUMBER
X____MEDICAL RECORD (INCLUDING BUT NOT LIMITED TO HISTORY AND PHYSICAL EXAM NOTES, CONSULTATION REPORTS, LABORATORY TEST RESULTS, OPERATIVE REPORTS)
X____INFORMATION RELATING TO MENTAL OR BEHAVIORAL HEALTH OR PSYCHIATRIC CARE EXCLUDING PSYCHOTHERAPY NOTES
X____BLOOD SAMPLES

We will collect and provide this information about you for as long as you are in the study

Once the information is disclosed outside of LUMC, it may no longer be protected by federal privacy laws.

It is possible that the sponsor, the Stanley Medical Research Institute, ,data collection and/or study verification agencies, data administrators or staff of the Food and Drug Administration may come to Loyola University Medical Center ("LUMC") and view the medical record (see above for description of content) and the research records. They may take notes or copy pages of the medical record.

The results of this research study may be published in a journal for the purpose of advancing medical knowledge. You will not be identified by name or by any other identifying information in any publication or report about this research.

Consent for LUMC to use and disclose your medical information is required in order for you to participate in the study.

WITHDRAWAL OF CONSENT: Your consent to use and disclose your medical information for the purpose of this research study is completely voluntary. You can withdraw your consent for LUMC to use and disclose your information and your consent to participate in this study at any time without affecting your ability to receive care and treatment at LUMC unrelated to the research study. Withdrawal means that all study procedures and follow-up will stop and we will not send any more information about you to the sponsor of this research or its designees. However, information already used and disclosed to the research sponsor prior to the time of your withdrawal from this study may continue to be used and disclosed by LUMC and the sponsor.

For your safety we may ask that you return to clinic one more time for a follow up visit. This will be to assess your wellbeing. We will also ask that you return any unused study medication. If you withdraw from the study, you will need to contact your physician(s) to discuss what other options may be available.

If you withdraw from the study we will ask that you sign the form attached to this consent and send it to Dr. Angelos Halaris MD PhD, or give it to the study staff. Your withdrawal from the study will not have any affect on any actions by LUMC taken before the attached form is received by LUMC.

Your study doctor, the Institutional Review Board, or the regulatory authorities may terminate the study at any time with or without your consent. Your study doctor may choose to take you out of the study because of unexpected or serious side effects, treatment non-compliance or because you are not taking the medication as you were instructed. You may also be removed from the study if your study doctor feels that you are not benefiting from the treatment.

CONSENT

I have fully explained to _____ the nature and purpose of the above described procedure and the risks that are involved in its performance. I have answered and will answer all questions to the best of my ability. I may be reached at 708-216-3752

_____ _____
(Signature of Investigator) Date

Dr. Angelos Halaris, who is the principal investigator for this study or his associates will be available to answer any questions you may have. They can be reached at 708-216-3752.

If you ever feel that you have been injured by participating in this study or if you have any questions concerning your rights as a research participant, you may contact Dr. Kenneth Micetich, Chairman, Institutional Review Board for the Protection of Human Subjects-Medical Center (708-216-4608).

Although you have the right to revoke this authorization except that such revocation will not apply to any uses and disclosures of your information that are described in the Loyola University Health System Notice of Privacy Practices or otherwise allowable under any Federal or State laws.

You will receive a signed copy of this informed consent document.

You have been fully informed of the above-described research program with its possible benefits and risks. Your signature below indicates that you are willing to participate in this research study and agree to the use and disclosure of information about you as described above. You do not give up any of your legal rights by signing this consent document.

_____Date:_____
(Signature: Participant)

_____Date:_____
(Signature: Witness)

PROJECT TITLE: Cyclooxygenase-2-Inhibitor Combination Treatment for Bipolar Depression: Role of Inflammation and Kynurenine Pathway Biomarkers.

REVOCATION OF AUTHORIZATION TO RELEASE PROTECTED HEALTH INFORMATION (PHI)

I, _____, hereby revoke my consent to participate in the study, "Cyclooxygenase-2-Inhibitor Combination Treatment for Bipolar Depression: Role of Inflammation and Kynurenine Pathway Biomarkers", at Loyola University Medical Center ("LUMC"). I also revoke my consent to release information I provided to LUMC that allowed LUMC to use and disclose my medical information to the Stanley Medical Research Institute, as outlined on the consent form, which I signed on _____[INSERT DATE CONSENT WAS SIGNED ORIGINALLY]. I understand that this revocation does not apply to any action LUMC has taken in reliance on the consent I signed earlier.

_____ _____

Signature: Participant Date

Please return this form to:

Dr. Angelos Halaris
c/o Paula Olivieri
Loyola University Medical Center
2160 South First Avenue
Bldg 54 Rm 222
Maywood, Illinois 60153