CAROLINAS HEALTHCARE SYSTEM

SUBJECT INFORMATION AND CONSENT FORM

Name of Research Study: A Double-blind, Placebo Controlled, Randomized, Multicenter Study to Assess the Safety and Clinical Benefit of Rasagiline as an Add on Therapy to Stable Dose of Dopamine Agonists in the Treatment of Early Parkinson's Disease (**ANDANTE: A**dd-O**N** to **D**opamine **A**gonists in early stage patients **N**eeding enhanced **T**reatment **E**fficacy).

Protocol #: TVP-1012/PM103

Sponsor: Teva Neuroscience Inc.

Principal Investigator Name: **Sanjay Iyer, MD**

Research Site Address(es):

Carolina Medical Center/Neuroscience & Spine Institute
1010 Edgehill Rd North
Charlotte NC 28207

Daytime telephone number(s): 704-446-1909

24-hour contact number(s): 704-355-4088 ext 3471

PURPOSE OF THE SUBJECT INFORMATION AND CONSENT FORM

This Subject Information and Consent Form may contain words you do not understand. Please ask the study doctor or the study staff to explain any words or procedures that you do not clearly understand.

The purpose of this form is to give you information about the research study and, if signed, will give your permission to take part in the study. The form describes the purpose, procedures, benefits, risks, discomforts and precautions of the research study. You should take part in the study only if you want to do so. You may refuse to take part or withdraw from this study at any

time without penalty or loss of benefits to which you are otherwise entitled. Please read this Subject Information and Consent Form and ask as many questions as needed. You should not sign this form if you have any questions that have not been answered to your satisfaction.

INTRODUCTION

Dr. Sanjay Iyer and his associate are asking you to participate in this research study of Rasagiline tablet (Azilect®) at the Neuroscience and Spine Institute, Carolinas HealthCare System (CHS). You are being asked to take part because you have Parkinson's disease. Parkinson's disease (PD) is a slowly progressive and worsening disorder of the central nervous system. PD is treatable by taking a dopamine agonist (a medication that starts the release of dopamine). In high doses, however, a dopamine agonist may have side effects that prevent patients with PD from taking the amount needed to control their symptoms. You are being asked to participate because you have PD and are taking a dopamine agonist for treatment of your PD.

Rasagiline tablet (Azilect®) is approved by United State Food and Drug Administration (FDA) for the treatment of PD. Rasagiline works by stopping the reduction of dopamine in the central nervous system. Rasagiline is FDA-approved to use as a single medication for the treatment of PD and also as a medication used in combination with levodopa (another medication that is approved to treat PD). The combination of rasagiline and dopamine agonists, however, is experimental and is not approved by the (FDA).

The purpose of this research study is to test the safety and effectiveness of the experimental use of the study drug, rasagiline, compared to a placebo (inactive ingredient) for treatment of PD, when taken with a dopamine agonist medication.

You will be one of 6- 8 subjects involved at the Neuroscience & Spine Institute, and your participation will last for 18 weeks (5 months). This study will have approximately 360 subjects involved at 55 research centers in the US.

EXCLUSION CRITERIA

- If you have received rasagiline or any other MAO inhibitor (such as: phenelzine, tranylcypromine and selegiline) within 60 days prior to the baseline visit.
- If you have received levodopa for more than 21 consecutive days within 90 days prior to the baseline visit.
- If you experience moderate to severe motor fluctuations (wearing off and on/off effects of medications).
- If you have hepatic (liver) impairment.
- If you have taken any experimental medications (not approved by FDA) within 30 days prior to the baseline visit.
- If you have used a Dopamine agonist more than 5 years prior to baseline.

- If you have major depression, or significant cognitive impairment, or an impulse control disorder (ICD) defined by the study doctor.
- If you are a woman who is pregnant, lactating or planning to become pregnant within the next 18 weeks.
- If you have uncontrolled hypertension (high blood pressure) as defined by the study protocol.
    - Patients with uncontrolled hypertension (systolic blood pressure [BP] ≥ 160, or diastolic BP ≥ 100; US NIH JNC 7 criteria)
    - Hypertensive patients whose BP is controlled with medication to systolic BP < 160 and diastolic BP < 100 are eligible
- If you are currently taking MAO inhibitors or medications contraindicated for use with MAO inhibitors are not allowed (ex. Meperidine – Dextromethorphan, Tramadol - St. John's wort, Methadone, Propoxyphene – Cyclobenzaprine, Cocaine, Ciprofloxacin or other CYP1A2 inhibitors). You will need to carry the sheet of prescription and over the counter medications with you whenever you are getting a new drug, and show it to a doctor or pharmacist before taking any new medications.

HOW THE STUDY WORKS

This study includes approximately three (3) to four (4) study visits to the Neuroscience & Spine Institute. This study will use competitive enrollment. This means that when a target number of subjects have been entered the treatment phase of the study, all further enrollment will be closed. Therefore, it is possible that you could be in the screening phase, ready to enter the treatment phase, and be discontinued without your consent if the target number of subjects has already entered the treatment phase of the study.

If you agree to take part in this study, you will first sign this Subject Information and Consent Form before any study-related procedures are performed. If you agree to be in the study, you would be randomized to one of two study drug administration groups. You will be randomly assigned by chance to receive either rasagiline or placebo (inactive substance). You will have a 50% chance of receiving rasagiline and a 50% chance of receiving placebo. Being randomized means that you are put in a group by a chance process, like flipping a coin. This is a double-blind study, which means neither you nor the study doctor will know to which of these study drug groups you are assigned. We are using this method because it is not clear at the present time which study drug is better.

Although you and your doctor will not know which study drug you are receiving, this information can be determined in the event of an emergency.

The following tests and procedures will be performed to determine if you qualify to take part in this study:

At the Screening/Baseline Visit 1, you will have the following procedures performed:

- Review of your medical history, including your PD history.
- Review of your medication history, including all medications you are taking to treat your PD.
- Physical examination, including measurement of your weight, blood pressure and heart rate.
- Electrocardiogram (ECG – measures the electrical activity of the heart) at Carolinas Medical Center
- Collection of a blood sample (approximately 3½ teaspoons) for safety laboratory testing.
- Collection of a urine sample for:
    - Safety laboratory testing
    - A pregnancy test if you are a woman who is able to become pregnant. The results of the pregnancy test must be negative for you to participate in the study.
- You and your study doctor will complete questionnaires to:
    - Evaluate your memory/thinking abilities
    - Determine if you have any depression or impulsive behavior
    - Rate how much your PD has slowed your movements
    - Determine the severity of your PD
    - Rate your independence since you were diagnosed with PD
    - Determine how often you are sleepy during the day
- You and the study doctor will complete a test to determine how well you can identify different odors.

If, based on the results of the tests and procedures performed at the Screening Visit, you qualify to participate in the study, you will continue to take your prescribed dopamine agonist. In addition, you will be randomly assigned by chance (like the flip of a coin) to one of the following study drug administration groups:

- Rasagiline 1 mg
- Placebo (inactive substance)

You have an equal 50/50 chance of being assigned to either study drug administration group. The placebo will look similar to rasagiline.

You will be instructed to take one tablet of study drug daily. If a dose is missed, the next dose should be taken at the usual time on the following day. Do not double-up the dose of study drug.

This is a double-blind study, which means neither you nor the study doctor will know to which of these study drug groups you are assigned. In case of an emergency, however, the study doctor can get this information.

Because this is a research study, the study drug will be provided by Teva Neuroscience only during this study and not after the study is over. Rasagiline is available by prescription.

You will be:

- Given three (3) bottles of study drug with instructions on how to take the study drug.
- Asked to avoid over the counter cough medications containing dextromethorphan (such as Benylin DM, Delsym and Robitussin DM).
- Asked to contact the study doctor if the symptoms of your PD become worse. The study doctor may ask you to return to the research center for an unscheduled visit.
- Scheduled to return to the study center for Visit 2 in approximately 9 weeks.

At visit 2, you will have the following procedures performed:

- Measurement of your blood pressure and heart rate.
- Review of any changes in your health and medications since your last study visit.
- Return of your three (3) bottles of study drug (even if the bottles are empty). The study doctor or a member of the study staff will count the number of tablets in each bottle and ask you if you missed any doses.
- You will be given three (3) bottles of study drug with instructions on how to take the study drug.
- You and the study doctor will complete questionnaires to:
    - Rate how much PD has slowed your movements
    - Determine the severity of your PD
    - Determine how often you are sleepy during the day
    - Rate whether or not you think the symptoms of your PD are improving
- You and the study doctor will complete a test to determine how well you can identify different odors.
- You will be asked to contact the study doctor if the symptoms of your PD become worse.
- You will be scheduled to return to the study center for your next study visit in approximately 9 weeks.

At Visit 3, you will have the following procedures performed:

- Review of any changes in your health and medications since your last study visit.
- Measurement of your blood pressure and heart rate.
- You will return your bottles of study drug (even if the bottles are empty). The study doctor or a member of the study staff will count the number of tablets in each bottle and ask you if you missed any doses.

- You and the study doctor will complete questionnaires to:
    - Rate how much PD has slowed your movements
    - Determine the severity of your PD
    - Determine how often you are sleepy during the day
    - Rate whether or not you think the symptoms of your PD are improving
- You and the study doctor will complete a test to determine how well you can identify different odors.

Unscheduled Visit

If, at any time after you have been on the study for 30 days, the study doctor determines that your PD is not well controlled, you may be asked to return to the research center for an unscheduled visit. The following tests and procedures will be performed:

- Review of any changes in your health and medications since your last study visit.
- Measurement of your blood pressure and heart rate.
- You will return your bottles of study drug (even if the bottles are empty). The study doctor or a member of the study staff will count the number of tablets in each bottle and ask you if you missed any doses.
- You and the study doctor will complete questionnaires to:
    - Rate how much PD has slowed your movements
    - Determine the severity of your PD
    - Determine how often you are sleepy during the day
    - Rate whether or not you think the symptoms of your PD are improving
- You and the study doctor will complete a test to determine how well you can identify different odors.

If these tests were not performed at a regularly scheduled study visit, the study staff may reschedule your next study visit.

Based on the results of the tests and procedures performed during the unscheduled visit, the study doctor may prescribe levodopa, an FDA-approved medication for the treatment of PD. You will take levodopa in addition to your prescribed dopamine agonist and the study drug.

If you participate in this study, you will be expected to:

- Attend all study visits.
- Take your study drug as instructed.
- Avoid over the counter cough medications containing dextromethorphan.
- Not take any other experimental drugs while you are enrolled in this study.

- Contact the study doctor if you have any changes in your health during the 30 days after you stopped taking the study drug.

RISKS

Your condition may not improve and could even worsen if you take part in this study.

The study has several risks. First, you may be in the placebo group and not receive any additional active medicine for your condition for 18 weeks other than your Dopamine Agonist. Second, it is possible that you will receive rasagiline but do less well than you have been doing. Third, because the use of rasagiline with dopamine agonists is new, we may not yet know all the side effects; something unexpected could happen. The known side effects are:

Risk from rasagiline

Side effects seen with rasagiline alone are headache, joint pain, indigestion, depression, flu syndrome, falls, hallucination and melanoma.

The incidence of melanoma is two to six times greater in patients with Parkinson's Disease for reasons that are unknown.

When rasagiline is taken with levodopa, the following side effects may occur: uncontrolled movements (dyskinesias), accidental injury, weight loss, low blood pressure when standing, vomiting, joint pain, nausea, constipation, dry mouth, rash, and sleepiness.

Risk of ECG

The risk of ECG is skin irritation from either the electrodes or the gel that is used.

Risk of Blood Drawing

Risks associated with blood drawing may include pain, bruising, and infection. Rarely, a person faints.

Unforeseen Risks

There may be risks from participating in this study that are unknown, including an allergic reaction , which if not treated promptly could become life-threatening.

REPRODUCTION RISK

Taking the study drug may involve unknown risks to a pregnant woman or nursing infant. Therefore, if you are pregnant, planning to become pregnant or are breastfeeding a child, you cannot participate in this study.

The effects of rasagiline on a fetus are unknown. If you become pregnant or father a child while on this research study, an injury to the fetus may occur that has not been seen before or is worse than seen before.

In order to reduce the risk of pregnancy, you must agree to use an effective method of birth control while you are participating in this study. If you are already using a method of birth control, the study doctor or study staff will discuss with you whether your current method of birth control is acceptable for use during this study.

If, during this study, you become pregnant, you should notify the study doctor as soon as possible. The study drug will be stopped and your participation in this study will be ended.

Your study doctor will ask that you, or the doctor taking care of you during your pregnancy, provide updates on the progress of your pregnancy and its outcome. The study doctor will make this information available to the study sponsor for safety monitoring follow-up.

NEW FINDINGS

During the course of the study, you will be informed of any important new findings (either good or bad) such as changes in the risks or benefits resulting from participation in the research study or new alternatives to participation in this study that might change your decision to be in the study. You may contact the study doctor at any time after your participation ends to find out if any new information about this study has become available.

BENEFITS

Your Parkinson's disease may or may not improve while participating in this study. Your participation in the study will contribute to information about the study drug and may benefit other patients in the future.

PAYMENT FOR PARTICIPATION

For your participation, you will be paid $50.00 for visit 1, $35.00 for visit 2, and $50.00 for visit 3, for each completed visit for a possible total of up to $135.00. You will receive payment at 3 month intervals.

ALTERNATIVE PROCEDURE/TREATMENT

You do not have to take part in this study to receive treatment for your condition. If you decide not to take part in this study, there are other treatments for Parkinson's Disease, such as Azilect®, levodopa, Eldepryl®, Cogentin®, Stalevo®, Parlodel®, Mirapex® and Requip®. Your doctor will discuss alternative treatments with you.

ADDITIONAL COST

There will be no charge to you for your participation in this study. The study drug, study-related procedures, and study visits will be provided at no charge to you or your insurance company. If you require levodopa therapy, this will be prescribed to you by your doctor. You or your insurance company will need to pay for the levodopa. Your insurance company may not pay for research treatments. You may wish to discuss coverage with your insurance company before agreeing to participate in this research study.

COMPENSATION FOR RESEARCH-RELATED INJURY

In the event that you are harmed as a result of your participation in this study, we will provide or arrange for treatment as necessary. This treatment, as well as other medical expenses, will be billed to you or your insurance company in the usual manner. The Sponsor will cover the medical expenses necessary to treat the injury only to the extent that such costs are not covered by your health insurance policy or by any other third party.

If you are injured during this study, your study doctor will discuss with you the available medical treatment options.

You must follow the directions of the study doctor to be eligible for this coverage.

Neither the Sponsor nor the study doctor has a program in place to provide other compensation in the event of an injury.

LEGAL RIGHTS

The above section does not restrict your right to seek legal assistance. You do not waive any legal rights by signing this Subject Information and Consent Form.

VOLUNTARY PARTICIPATION

Your participation in this study is completely voluntary. You should feel under no pressure to be in the study. If you decide not be in the study, that will not in any way harm your relations with your doctors or with Carolinas HealthCare System. You are free to stop being in the study if you change your mind after entering it. This would not harm your relations with your doctors or Carolinas HealthCare System.

WITHDRAWAL

Your doctor, the sponsor company, or the FDA has the right to stop your participation in the study at any time, with or without your consent, for any of the following reasons:

Your decision to participate in this study is voluntary. You may choose not to participate or you may withdraw from the study for any reason without penalty or loss of benefits to which you are otherwise entitled and without any effect on your future medical care.

The study doctor or the sponsor can stop your participation at any time without your consent for the following reasons:

- If it appears to be medically harmful to you
- If you fail to follow directions for participating in the study;
- If it is discovered that you do not meet the study requirements
- If the study is canceled
- For administrative reasons, including competitive enrollment –the target number of subjects has entered the treatment phase.

If you leave the study for any reason, the study doctor may ask you to have some end-of-study tests for your safety.

CONFIDENTIALITY

The records of this study will be kept private. In any sort of report we might publish, we will not include any information that will make it possible to identify you. Your record for this study may, however, be reviewed and/or photocopied by the drug/device manufacturer, by Carolinas HealthCare System, by Copernicus Group Independent Review Board (IRB), or by representatives of the Food and Drug Administration or other government agencies. To that extent, absolute confidentiality cannot be guaranteed.

Primary Care Physician/Specialist Notification Option

Please indicate below whether you want us to notify your primary care physician or your specialist of your participation in this study by initialing beside your choice below.

_____ **Yes, I want the study doctor to inform my primary care physician/specialist of my participation in this study.**

_____ **No, I do not want the study doctor to inform my primary care physician/ specialist of my participation in this study.**

_____ **I do not have a primary care physician/specialist.**

_____ **The study doctor is my primary care physician/specialist.**

FINANCIAL INTEREST OF INVESTIGATOR

None of the doctors asking you to participate in this study have received or will receive money or other benefits for personal use from the study sponsor. However, the sponsor will give money or other benefits to a research fund, foundation, educational institution, or other organization with which the doctor or study staff is associated.

QUESTIONS

If you have any questions about your participation in this research study or if you feel that you have experienced a research-related injury or reaction to the study drug, contact:

Principal Investigator: **Sanjay Iyer MD**

Daytime telephone number(s): 704-446-1909

24-hour contact number(s): 704-355-4088 ext 3471

If you have questions about your rights as a research subject, you may contact the Copernicus Group IRB at 1-888-303-2224 (toll free). An Independent Review Board is a group of scientific and non-scientific individuals who perform the initial and ongoing ethical review of the research study with the study subject's rights and welfare in mind. Copernicus Group IRB has reviewed and approved the research study described in this Subject Information and Consent Form. If you have study-related comments, complaints or concerns, you should first contact the study investigator. Please call the IRB if you want to talk to someone other than the study investigator or have difficulty reaching the study investigator. For further information regarding the clinical trials process and your role as a research subject, you may visit the Copernicus Group IRB website at www.cgirb.com.

HIPAA AUTHORIZATION

If you wish to take part in this research study, you will be asked to sign this consent and authorization form. It allows the study sponsor and the study investigator to collect, process and pass on to the sponsor organizations any relevant personal health information collected from you during the study. These are activities routinely carried out during all clinical studies.

You have been told that personal information about you (including sensitive personal health information, such as your medical history and your racial/ethnic origin if relevant to the study) will be reviewed, collected on a computer database, stored in electronic or manual files, audited, and/or otherwise processed by:

- the clinical study investigator, **Dr. Sanjay Iyer**, his associates and research staff
- the study sponsor (Teva Neuroscience, Inc.) and/or its associated companies,
- regulatory or other governmental authorities of the United States and other countries,
- other persons authorized by the study sponsor,
- Carolinas HealthCare System employees,
- Copernicus Group IRB
- other persons or agencies as required by law or allowed by federal regulations.

You have been told that your personal data are being collected and processed to:

- check your suitability to take part in the study,
- monitor your treatment with the study medication,
- compare and pool treatment results with those of other subjects in clinical studies,
- support the development of the study medication,
- support the licensing application for regulatory approval of the study medication or device in the world
- support the marketing, distribution, sale and use of the study medication or device anywhere in the world.

You have been told that your personal information may be processed within the U.S. or elsewhere in the world or transferred to or from the U.S. for review, processing and/or storage by an associated company or a carefully selected third-party organization. By signing this document, you explicitly consent to the transfer of your personal information, including sensitive personal information, collected during this clinical study, for review, processing and/or storage. Your personal health information may be further shared by the groups above. If shared by them, the information will no longer be covered by the Privacy Rule. However, these groups are committed to keeping your personal health confidential.

You may refuse this authorization to transfer your personal information. If you choose not to agree to this authorization, you might be ineligible to participate in the study. If you decide not to sign this authorization, that will not harm your relations with your doctors or with Carolinas HealthCare System.

You have the right to inspect your medical record at any time. Your research record may be unavailable until the conclusion of the study. At that point, it will be available. Please speak with the study doctor if you desire to access your record.

You have been told whenever your personal information is processed, it will be kept confidential and secure, to the best of our ability. It will be used only for the purpose for which it was collected.

You have been told that if you withdraw from the study and withdraw your Authorization, no new information will be collected for study purposes unless the information concerns an adverse event (a bad effect) related to the study. If an adverse event occurs, your entire medical record may be reviewed. All information that has already been collected for study purposes, and any new information about an adverse event related to the study, will be sent to the study sponsor.

This Authorization does not have an expiration date. You have been told that according to the guidelines for good clinical practice, the study investigator and sponsor will keep your personal information for at least 6 years. If you do not withdraw this Authorization in writing, it will remain in effect indefinitely. If you wish to revoke authorization to use your personal

information, you will notify the study doctor, **Dr. Sanjay Iyer at 1010 Edgehill Road North, Charlotte, NC 28207**, in writing. Some of the data obtained from your record prior to your revocation may still be used if considered necessary for the study.

SUBJECT'S STATEMENT OF CONSENT

*A Double-blind, Placebo Controlled, Randomized, Multicenter Study to Assess the Safety and Clinical Benefit of Rasagiline as an Add on Therapy to Stable Dose of Dopamine Agonists in the Treatment of Early Parkinson's Disease (**ANDANTE: Add-ON to Dopamine Agonists in early stage patients Needing enhanced Treatment Efficacy**).*

- This is a research study of rasagiline.
- I have been given sufficient opportunity to consider whether to participate in this study.
- My taking part in this research study is voluntary. I may decide not to take part or to withdraw from the research study at any time without penalty or loss of benefits or treatment to which I am entitled.
- If I meet the criteria, I would like to take part in this research study, and my doctor may enroll me in the research study.
- The research study may be stopped at any time without my consent either by the study doctor or by the company sponsoring the research.
- My study doctor will be receiving payment from the sponsor to conduct the research.
- I have had an opportunity to ask my study doctor questions about this research study. My questions so far have been answered to my satisfaction.
- I have been told how long I may be in the research study.
- I have been informed of the procedures and tests that may be performed during the research study.
- I have been told what the possible risks and benefits are from taking part in this research study. I may not benefit or my condition may worsen if I take part in this research study.
- I authorize the use of my personal health information.
- I do not give up my legal rights by signing this form.
- I have been told that prior to any study related procedures being performed, I will be asked to voluntarily sign this Subject Information and Consent Form.
- I will receive a signed and dated copy of this Subject Information and Consent Form.

_____	_____	_____
Subject Print Name	**Date**	**Time**
_____	_____	_____
Subject Signature	**Date**	**Time**

I certify that the information provided was given in language that was understandable to the subject.

_____	_____	_____
Signature of Person Obtaining Consent	**Date**	**Time**
_____	_____	_____
Investigator Signature	**Date**	**Time**