INFORMED CONSENT/ AUTHORIZATION TO USE AND DISCLOSE PERSONAL HEALTH INFORMATION
CONSENT TO TAKE PART IN A RESEARCH STUDY

Title:	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 4 Study to Assess the Effect of Naltrexone Hydrochloride and Bupropion Hydrochloride Extended Release Combination on the Occurrence of Major Adverse Cardiovascular Events in Overweight and Obese Subjects with Cardiovascular Disease
Protocol Number:	NaltrexBuprop-4001
Sponsor:	Takeda Development Center Americas, Inc. One Takeda Parkway Deerfield, IL 60015
Contract Research Organization:	PPD 929 North Front Street Wilmington, NC 28401

Study Doctor Name:

Research Site Address(es):

Daytime Telephone Number(s):

24-hour Contact Number(s):

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INTRODUCTION

You have been invited to take part in this clinical research study because you are overweight or obese and have cardiovascular disease (for example, you have had a heart attack, stroke, peripheral vascular disease, etc.). To help you make an informed decision on whether or not to take part you need to understand what the study is for, what is involved and what benefits, risks and discomforts there may be. This process is called "informed consent."

Please take the time to read the following information carefully and discuss it with others. If there is anything that is not clear, or if you would like more information, please ask your study doctor or nurse.

Once you have decided if you want to take part, you will be asked to sign the informed consent form. You will get a copy of the signed form.

The Sponsor is paying the study clinic and the study doctor to carry out this research study.

PURPOSE OF THIS STUDY

The aim of this study is to learn about the cardiovascular safety of naltrexone and bupropion combination when added to standard medications for overweight or obese people who have cardiovascular disease.

To learn about this drug, there will be two groups of people treated - those who receive study drug and those who receive placebo. A placebo is a tablet that looks like the study drug but has no active ingredient. The study doctor is also doing this study to compare the safety of taking the study drug to placebo when added to your treatment for cardiovascular disease and other medical conditions.

Approximately 8,800 subjects/patients at about 500 sites in the United States will participate in the study. Your participation may last up to 6 years and will include up to 24 visits to the study site. In addition, the study site will contact you by telephone at regular intervals, at least 9 times, to inquire about your health status.

STUDY MEDICATION

If you participate in this study, you will receive "study drug" (placebo or naltrexone HCl/bupropion HCl [NB]). NB is a combination of the active ingredients **n**altrexone HCl (8 mg) and **b**upropion HCl (90 mg) into one extended release tablet. Naltrexone is a medication used for alcohol and opioid addiction. Bupropion is a medication used for mood disorders, like depression, as well as an aid to help stop smoking. The extended release combination of naltrexone HCl and bupropion HCl is approved by the U.S. Food and Drug Administration (FDA) in addition to a reduced-calorie diet and increased physical activity for chronic weight management in adults who are obese or who are overweight and have at least one additional weight-related condition such as high blood pressure, diabetes or high cholesterol. The use of naltrexone HCl 8 mg / bupropion HCl 90 mg extended release tablets in this study is investigational. "Investigational" means that the study drug is currently being tested for the purpose of this study.

STUDY PROCEDURES AND YOUR RESPONSIBILITIES

If you decide to participate in the study, you will first have medical tests and procedures performed to help the study doctor decide if you meet the requirements of the study. This is called the "screening period", and can last up to approximately 28 days. You will be evaluated for your eligibility into the study at your first visit (Visit 1). This visit can be split into 2 visit days, if needed, as you need to be fasting (no food for 10 hours) for the blood draw.

If you meet all study requirements, you will then return to the study center for your second visit (Visit 2). You will receive two bottles (bottle #1 and bottle #2). Each of the bottles will contain only one of the study drugs below but you will not know which bottle contains which drug:

- naltrexone HCl 8 mg and bupropion HCl 90 mg extended release tablet (8/90 NB)
- Placebo - a tablet that has no active ingredients (0/0 placebo)

You will be randomized (assigned by chance, like flipping a coin) to one of the following two sequences below:

Week	Study Drug Daily Dosing Schedule	Total Daily Dose of Study Drug (mg)
1	one tablet each morning from bottle #1	8/90 NB
2	one tablet each morning from bottle #2	0/0 placebo

Or

Week	Study Drug Daily Dosing Schedule	Total Daily Dose of Study Drug (mg)
1	one tablet each morning from bottle #1	0/0 placebo
2	one tablet each morning from bottle #2	8/90 NB

At Visit 2, you will receive instructions on how to take your study drug during the next 2 weeks. Neither you nor your study doctor will know which drug you are taking during Week 1 or Week 2.

In preparation for Visit 3, it is important to bring your study medication and bottles back to the study clinic and DO NOT take the study medication on the day of Visit 3 as you will be given medication in clinic, if you still qualify for the study.

After approximately 2 weeks, if you still qualify for the study, you will be randomized again (assigned by chance, like flipping a coin) at Visit 3, to one of the following 2 treatment groups:

- naltrexone HCl 8 mg and bupropion HCl 90 mg extended release tablet escalated to a maximum daily dose of naltrexone HCl 32 mg and bupropion HCl 360 mg (4 tablets per day) (NB)
  or
- Placebo - a tablet that has no active ingredients and alsoescalated to a maximum amount (4 tablets per day) (placebo)

Your study doctor, and the study staff, will not know which treatment group you are assigned to. However, this information is available to your study doctor if needed in an emergency.

During the first four weeks following Visit 3 (Study Treatment Period), you will start and slowly increase the daily dose of study drug you've been assigned to receive for the remainder of the study as per the following dosing schedule:

Week	Study Drug Daily Dosing Schedule	Total Daily Dose of Study Drug (mg)
1	one tablet each morning	8/90 (NB) or 0/0 (placebo)
2	one tablet each morning, one tablet each evening	16/180 (NB) or 0/0 (placebo)
3	two tablets each morning, one tablet each evening	24/270 (NB) or 0/0 (placebo)
4	two tablets each morning, two tablets each evening	32/360 (NB) or 0/0 (placebo)

After Week 4 of the Study Treatment Period, you will continue to take two tablets of study drug each morning and two tablets each evening until the end of the study.

If you find out during the study that you have kidney or liver disease, the study medication dose may need to be reduced or stopped. You should contact the study doctor right away to inform him/her of this new information and discuss what needs to be done.

The study drug should be stored at room temperature. It does not matter if you take your study drug with or without food, but you should avoid taking your study drug with a meal that is high in fat. Keep study drug out of reach of children. Do not cut, crush or chew the study drug tablets.

If you miss a dose, wait until your next regular time to take the study drug dose. Do not take more than one dose (2 tablets) of study drug at a time. If you stop study drug for more than one week, you will be asked to decrease your dose and then slowly increase it again over the next four weeks as shown in the daily dosing schedule above as you did in Weeks 1 through 4. Please contact your study doctor if you decide to go off study drug.

You should bring your study medication, including empty containers, with you to the study clinic at every on-site visit.

After you have completed Visit 5 (Week 4 Visit), you will return to the study center at Week 8 and Week 12 and then every 3 months until the end of the second year. After you have participated in the study for over 2 years you will come to the study center for visits every 6 months and the study staff will contact you by telephone every 6 months between visits to inquire about your health status. (Thus, you will either come for a visit or receive a phone call every 3 months until the end of the study.) You will come to the study center for a total of up to 24 times over 6 years.

Even if your study drug is temporarily or permanently stopped during the study, you will have study visits with your study doctor until the end of the study. The length of the study is based on an ongoing review of study results. This means the study might finish before you have completed all your visits. Your study doctor will inform you if this happens and what you need to do.

From the time you sign the informed consent through the end of the study, you may not take any prescriptions or FDA-approved over-the-counter medications used to promote weight loss (for example, Contrave, Belviq, Orlistat), any appetite suppressant prescription medications (for example, phentermine, phendimetrazine) or have any investigational procedures for weight loss even if you stop taking study drug during the study. Also, you may not have bariatric surgery or approved devices that may be used as part of the bariatric procedures while you are in this study.

You will be offered access to a healthy lifestyle program in addition to the study medication. It is not mandatory to participate in the healthy lifestyle program. An overview of the program is provided below and additionally, the study doctor can also provide you with more information.

At the following four visits (Visit 1-screening, Visit 8-week 24, End-of-Treatment Visit [for subjects who discontinue study drug during the study], and End of Study Visit) you will be asked to fast (no eating for 10 hours) prior to the visit as blood collected at these visits must be fasting. All blood samples taken from you will be sent to the Sponsor's designated central laboratory at PPD Laboratories, 2 Tesseneer Drive, Highland Heights, KY 41076. They will store the samples and carry out tests that relate to this study. The samples will be labeled with a code and not your name.

After you have signed this consent form at Visit 1, the study doctor or study staff will perform the activities listed in the table below when you come in for study visits. If you would like more information about which tests and procedures will be completed at each study visit, ask the study doctor or study staff. If you are not fasting prior to signing this consent, you will be asked to return to the study center fasting, so fasting blood samples can be taken.

Study Day/Week:	*Screen-ing*	*Week -2*	*Day 1*	*Week 2*	*Week 4*	*Week 8*	*Week 12*	*Weeks 24, 36, 48, 60, 72, 84, 96,104*	*Weeks 130, 156, 182, 208, 234, 260, 286*	***Telephone Visits** Weeks 117,143, 169, 195, 221, 247, 273, 299*	*End-of-Treat-ment Visit*	*End-of-Study Visit*	*Follow-up Tele-phone Visit*
Visit Number:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8-15*	*17, 19, 21, 23, 25, 27, 29*	*16, 18, 20, 22, 24, 26, 28, 30*			
Personal, medical and medication history	X												
Physical exam	X										X	X	
Body temperature, heart rate, blood pressure	X	X	X	X	X	X	X	X	X		X	X	
Weight	X	X	X	X	X	X	X	X	X		X	X	
Height	X												
Medications	X	X	X	X	X	X	X	X	X	X	X	X	
Symptoms	X	X	X	X	X	X	X	X	X	X	X	X	X
Fast prior to blood sample collection	X							X (Week 24 only)			X	X	
Blood sample	X		X					X (Week 24 only)			X	X	
Urine sample			X										
Blood pregnancy test^	X											X	
Urine pregnancy test^			X				X	X	X		X		
Pgx (*)			X										

Study Day/Week:	*Screen-ing*	*Week -2*	*Day 1*	*Week 2*	*Week 4*	*Week 8*	*Week 12*	*Weeks 24, 36, 48, 60, 72, 84, 96,104*	*Weeks 130, 156, 182, 208, 234, 260, 286*	***Telephone Visits*** *Weeks 117,143, 169, 195, 221, 247, 273, 299*	*End-of-Treat-ment Visit*	*End-of-Study Visit*	*Follow-up Tele-phone Visit*
Visit Number:	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8-15*	*17, 19, 21, 23, 25, 27, 29*	*16, 18, 20, 22, 24, 26, 28, 30*			
Biomarker sample (optional)(			X					X (Week 48 only)					
Urine drug screen	X												
ECG~	X												
Contact information	X	X	X	X	X	X	X	X	X	X	X	X	
In-clinic dosing		X	X										
Given Study medication		X	X		X	X	X	X	X				
Study medication return			X	X	X	X	X	X	X		X	X	
Healthy Lifestyle program			X	X	X	X	X	X	X	X	X	X	

^ Females of childbearing potential only

* Pharmacogenomics (PGx) participation is optional. You will be able to choose to participate in collecting a PGx blood sample at Visit 3. See Pharmacogenomics testing section in this informed consent for more information.

~An electrocardiogram (ECG or Heart Tracing) will be done at the Screening visit. Sticky patches will be placed on your skin and connected to a recording device. This device will record a tracing of your heart's electrical activity.

You may also be asked to return to the study clinic at other times not listed above if you have a study-related issue.

This study is recruiting subjects to take part in the study from many different sites in the United States at the same time. When a set number of subjects have started taking the medication being studied, it may be necessary to stop other subjects from starting their study medication. So there is a small chance that even if you meet all entry criteria at the end of the screening phase you will not be able to continue taking part in the study and taking the study medication. Your study doctor should tell you if this could happen to you.

If you are not honest with your study doctor about your medical history and any medicines or supplements you are taking, taking part in this study may harm you.

HEALTHY LIFESTYLE PROGRAM

You have the choice to participate in a healthy lifestyle program starting at Visit 3 which is a comprehensive nutrition and exercise management program during the Study Treatment Period. This program will be free of charge to you during this study.

This program will include weight management goal setting and tracking tools. The nutrition and exercise tracking tools will include meal plans that provide guidance on how many calories to eat and how to follow the plan. The exercise tracking tools will allow you to track the exercise that you do while in this study. You can use trackers to capture the food that you eat and the exercise that you do every day. In addition, you will receive nutrition and exercise communications in the form of emails, text messaging on your phone and/or paper copies, designed to coach you with your weight loss and exercise goals.

This healthy lifestyle program will be delivered through a website or mobile application (that you can use from your phone or tablet) or via paper tools. Prior to beginning the program, you will have the ability to choose the delivery option that works best for you. Whichever version you choose, all materials and information will be similar for all people participating in the study. Licensed dietitians will also be available to speak with you at no cost. Contact with a licensed dietitian will be by telephone, email, or live chat. You will receive at least one phone call from a licensed dietitian after Visit 3 and you will be able to plan how often, how and if you will have further contact moving forward. You will not meet the licensed dieticians in person.

At Visit 3, you will be registered into this healthy lifestyle program by your study coordinator if you choose to participate and, if you decide to use the website, you will receive instructions on how to access the website on your own. The website for this program will work best if you have a current internet browser on your computer (Internet Explorer 7 and higher, Safari 5.1.2, Google Chrome 16.0, or Mozilla Firefox 9.0). The mobile application version of the website will be available on Android or Apple mobile devices. If you discontinue study medication prematurely during the study, you will be encouraged to continue all other study procedures including participation in the healthy lifestyle program until the end of the study. You also have the option to stop using the healthy lifestyle program during the study.

You will be asked to provide identifying information such as your name, phone number, and/or email address. This information will be held on a secure database and will not be shared with anyone other than those in charge of the healthy lifestyle program. Non-personally identifying information you enter into the website or mobile application may be used to assess patterns of use of the website and mobile application and overall study retention. Your self-reported data will not be included in any of the clinical datasets used to analyze the results of the study.

Throughout the study, the licensed dietitians will help you with your weight loss-related questions, but cannot help you with questions about the study, the study drug or your health. ***You will need to contact the study site staff with questions about the study, study drug or your health.***

STUDY DRUG DISCONTINUATION:
If you decide to stop taking the study drug for any duration of time during the study, please inform your study doctor as soon as possible. Because this study collects safety information, you will be asked to continue coming to the study center for evaluations whether or not you are taking study drug. If you discontinue study drug during the study, you will be asked to continue to follow the visit schedule until the end of the study. If you cannot come into the study center for your visits, ask your study doctor for other options to continue in the study. It is important for you to continue in this study because your data is essential to the final results of the study even if you discontinue study drug early.

CARDIOVASCULAR EVENT COLLECTION AND FOLLOW UP:
The main goal of this study is to evaluate the cardiovascular safety of NB and ensure that any safety issues are included in the study results. If you have not attended a planned study visit or maintained telephone contact, and the study doctor or a member of his/her staff is unable to contact you directly for any reason, they may use other ways of trying to determine whether or not you have experienced a serious cardiovascular event. This could involve making contact with your next of kin, your family doctor, or other hospitals/clinics that treat you**.** Your permission to use and share this follow-up health information regarding a serious cardiovascular event will not end unless you withdraw this authorization in writing to the study doctor**.**

Follow-up could also involve attempts to determine your health status via other means available such as national registries/databases, hospital records, your medical records, voter records and third party locator services. This follow-up information will be collected even if you decide to withdraw from the study.

PHARMACOGENOMIC TESTING
Pharmacogenomic (PGx) testing is an optional portion of this main research study. If you do not want to participate in this testing, you will need to indicate that you do not wish to participate in this testing at the end of this informed consent.

The Pharmacogenomic (PGx) study will examine genetic material (DNA) from a blood sample collected from you. Genes control the characteristics that we inherit from our parents, such as the color of our hair or eyes. Some genes are associated with the development of side effects to certain drugs. Understanding the relationship between genes and certain diseases and their treatment(s) requires extensive research efforts focused on genetic testing. This is known as pharmacogenomic (genetic) research.

If you consent to the Pharmacogenomic testing, the study staff will take 1 tube of 6 mL (~1 teaspoon) of blood at Visit 3. This sample will be later analyzed as described below and is not part of your regular medical care or the main study.

Specific research to be conducted in this PGx study includes:

- Identifying genetic reasons why certain people respond differently to the study drug.
- Finding out more information about how the study drug works.
- Generating information needed for research, development, and regulatory approval of tests to predict response to the study drug.

The blood sample may also be used for future testing related to this study, the disease being studied and potentially related treatments.

The main risk of this type of testing is the potential loss of confidentiality of your genetic information. We will protect against this risk as described below and in the Confidentiality section .

The sample will be sent to a central laboratory that processes the blood sample and serves as a secure storage facility. The sample will be initially stored at PPD Central Laboratories in Highland Heights, KY and then transferred to Covance Central Laboratory Services in Greenfield, IN for long-term storage. The Sponsor and researchers working with the Sponsor will have access to the sample collected and any test results. All samples collected during the study will be stored securely with limited access, and the Sponsor will require anyone who works with the samples to agree to hold the research information and any results in confidence.

The sample will be labeled with a unique sample identifier similar to labeling in the main study but using a code that is different from the code attached to the health information and other clinical test results collected in the study. The sample and data are linked to your personal health information with code numbers.

This link means that you may be identified but only indirectly. The code numbers will be kept secure by or on behalf of the Sponsor.

The Sponsor will only share your information and test results with the people identified in this consent form, except as required by law. The results of research performed using the samples collected will not be used in any decision to grant or deny insurance,

employment, mortgage, loan, credit or educational opportunities and should not affect your medical care. You will not have access to these test results unless required by law.

GENETIC INFORMATION NONDISCRIMINATION ACT (GINA)

A federal law called the Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

1. Health insurance companies and group health plans may not request your genetic information that we get from this research or use your genetic information when making decisions regarding your eligibility or premiums.
2. Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Employers with 15 or more employees, health insurance companies, and group health plans must follow this law. This law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

However, all samples collected during the study will be stored securely with limited access and the Sponsor will require anyone who works with the samples to agree to hold the research information and any individual results in confidence. The genetic tests that will be performed are not intended to make determinations about your health or the likelihood you will develop any disease so no test results will be provided to your doctor or put into your medical record.

The blood sample collected from you and the information and results from tests performed with this sample may be used individually or combined with other data. Information gathered or created by the Sponsor will be analyzed, evaluated and/or modified by the Sponsor, and may result in new product(s), new information, discoveries and/or ideas. This new information and any new products, tests, and/or discoveries created by the Sponsor will be owned by the Sponsor. In some cases these may have potential commercial value but you will not share in the financial benefits or get any money for these products, tests or discoveries.

You will also not retain any property rights to the blood collected from you for the PGx study. The blood sample collected from you will only be used for research and will not be sold.

Samples collected will be stored for up to 15 years from the end of the study when the study report is signed or if less, the maximum period permitted under applicable law or until consent is withdrawn. The sample will then be destroyed. If you want to withdraw your consent, please see the "Leaving the study" section.

BIOMARKER TESTING ***<For sites participating in Biomarker testing only>***
You will be asked to provide optional blood samples at Visits 3 and 10. These samples will be processed and stored frozen and used for future analysis for the purpose of examining biomarkers that may predict risks and benefits of treatment with the investigational product and to better understand the relationships between body weight, being overweight or obese, cardiovascular disease and cardiovascular disease risk in people.

The blood samples will be stored for a maximum of 15 years, after the last patient visit for the study, at a facility selected by the sponsor and then destroyed. These samples will be identified by your own patient number but it will not reveal sensitive medical information. If you want to withdraw your consent, please see the "Leaving the study" section.

Please place an "X" in the box below if you do not wish to take part in the optional biomarker portion of this study. LEAVE THE BOX BLANK IF YOU AGREE TO PARTICIPATE:

☐ **Please place an X in this box if you DO NOT consent to take part in the optional biomarker portion of the study**

ALTERNATIVE TREATMENT
You do not have to participate in this study to receive treatment for being overweight or obese. Your study doctor will discuss with you any alternative treatments that may be available to you. If you choose not to participate in this study, you may have other options such as:

- Medications approved for treatment of obesity such as orlistat (Alli™, Xenical®), phentermine (Adipex-P®, Ionamin®), phentermine/topiramate (Qsymia®), lorcaserin (Belviq®), naltrexone/bupropion (Contrave®) and liraglutide (Saxenda®)
- Other weight management programs such as Jenny Craig®, Weight Watchers®, Medifast®, Optifast®, and Nutrisystem®
- Weight loss surgery such as gastric bypass surgery, laparoscopic adjustable gastric banding (Lap-Band®), gastric sleeve, and duodenal switch
- Lifestyle changes such as diet and exercise
- Other clinical research studies for the treatment of obesity

Please refer to your study doctor for further discussion on alternative treatment.

POTENTIAL RISKS AND DISCOMFORT
The most common side effects (greater than or equal to 5%) with NB were nausea, constipation, headache, vomiting, dizziness, trouble sleeping (insomnia), dry mouth, and diarrhea. In addition, a greater percentage of subjects treated with NB (approximately 4%) compared to placebo (approximately 1%) reported anxiety, hot flush, tiredness (fatigue) and tremor as side effects. If you have diabetes, you are more likely to have nausea, vomiting, diarrhea, and high blood pressure than those who do not have diabetes when treated with NB.

Most side effects are mild in severity and do not last long. If you experience severe side effects during the study, your doctor has the option of interrupting or stopping the study drug. If the side effects return after restarting the study drug, your doctor may discontinue you from study drug. The risk of some side effects may increase when your dose of study drug increases. It is important that you never take a higher dose of study drug than instructed. Consumption of alcohol should be minimized or avoided while participating in this study.

Prescribing information is available for doctors for the approved combination of NB. If you would like to know more about the prescribing information, please ask the study doctor.

Antidepressant drugs including bupropion (an active ingredient of NB), may trigger angle closure glaucoma (an eye disorder associated with high eye pressure). You should not be in this study if you have glaucoma without speaking to the study doctor. Also, if you experience any eye symptoms such as eye pain, sudden change in vision, seeing halos around lights or reddening of the eye, you should seek immediate care from an eye doctor.

Vital Signs

On average, subjects taking NB can expect to see a small increase in blood pressure during the first few months of treatment followed by a decrease in blood pressure as they lose weight. However, some patients get high blood pressure or a high pulse rate, sometimes severe, while taking NB. Your blood pressure and heart rate will be monitored at every study visit. The chance of getting high blood pressure may be increased if you smoke or use nicotine replacement such as a nicotine patch.

Seizures

Bupropion, an active ingredient of NB, can cause seizures. The risk of having a seizure with NB is uncommon and is approximately 1 in 1000 patients exposed. Certain conditions make it more likely that you may have a seizure. These include:

- History of head injury, brain tumor or infection, or severe liver damage
- A history of prior seizures
- Using too much alcohol or drugs to be able to sleep or treat pain, using stimulants ("uppers"), or trying to stop using these drugs
- Diabetes that requires taking medicines to lower blood sugar

Tell your doctor if you have any of these conditions.

Gall Bladder

Gall bladder inflammation is more common in subjects taking NB than placebo. Rapid weight loss is associated with gall bladder inflammation.

Liver
Liver problems including hepatitis (inflammation of the liver) have been reported in patients taking naltrexone, an active ingredient of NB, at doses approximately 9 times higher than the maximum dose used in this study. You should notify your study doctor immediately if you develop yellow eyes, dark urine, or severe fatigue.

Suicide
Antidepressant drugs (like bupropion) may increase suicidal thoughts and behavior in patients less than 25 years of age with psychiatric disorders, especially in the first few months of treatment or when the dose is changed. There has been no indication that NB increases the risk of suicidal behavior. You should call your study doctor and get help immediately if you experience thoughts about suicide or dying.

Allergic Reactions
Sometimes people have allergic reactions to medications. Allergic reactions may be mild (rash, itching, hives) to severe (difficulty breathing, loss of consciousness, death). If you think you are having a severe allergic reaction, you should seek emergency medical attention immediately, do not take additional doses of the study drug, and contact the study site staff.

Drug Interactions
Since NB can interact with other drugs, it is important to discuss any new drugs you may be taking with your study doctor. NB interferes with the effects of some pain relievers such as opioids (i.e., codeine, morphine, hydrocodone, and fentanyl). If you have a sudden injury or emergency surgery, the doctor treating you will need to know that you are/may be taking NB as part of a research study. You will be given a card with information about the study to place in your wallet. If you are having elective (non-emergency) surgery, your study doctor should be notified and your study drug must be stopped 1 to 2 days before the surgery. Your study doctor will tell you when to start taking your study drug again after the surgery.

Risk of Driving or Operating Machinery
All drugs may affect your ability to drive or operate heavy machinery. You should be aware of this possibility as you begin treatment and evaluate whether you are affected and should not drive.

Unknown Risks
There may be additional risks that are currently unknown and unanticipated related to taking NB. You might have side effects or discomforts that are not listed in this form. Some side effects may not be known yet. New ones could happen to you. If new risks associated with administration of study drug are identified during the study, you will be told about them.

Blood Draw Risks

Drawing blood may cause some pain and carries a small risk of bleeding, infection, and/or bruising at the puncture site. The total amount of blood planned to be drawn during the study will be approximately **[9 teaspoons (non biomarker sites) or 12 teaspoons (biomarker sites)].** Additional blood may need to be drawn if side effects occur to evaluate them.

Risks Associated with Increased Physical Activity

If you choose to participate in the life style modification program that will be offered, you may be asked to increase your physical activity as part of the healthy lifestyle program during the study. You should discuss with your study doctor whether you are able to participate in increased physical activity. A certain amount of discomfort, such as sore muscles, during or after exercise is normal because you are challenging your body to do more than it is used to doing. Symptoms such as pain or pressure in your chest, feeling dizzy or sick, and an irregular heartbeat may be warning signs that something is wrong. Immediately slow down your exercising, seek help if needed, and notify your study doctor.

Electrocardiogram Risks

Skin irritation is rare but could occur from the electrodes or gel that is used.

POTENTIAL BENEFITS

There is no guarantee that your weight or cardiovascular condition will improve as a result of your participation in this research study. You may receive benefits to your health by participating in this research study in the form of reduced weight or your condition could stay the same or get worse. The medical evaluations including the electrocardiogram, blood and urine tests, and vital sign measurements may be beneficial to you by documenting your current health status. You can request copies of the results to review with your personal doctor or specialist. Your participation in this study may help researchers obtain information on weight loss drugs that may help other people in the future.

NEW FINDINGS

The study doctor or staff will tell you about any significant new findings that develop during this study that may affect your decision to continue taking part in the study. If you decide to stay in the study, you may be asked to sign a new informed consent form.

PREGNANCY, CONTRACEPTION AND BREASTFEEDING

The effects of NB on an unborn child are not known at this time. Therefore, if you are a woman who is sexually active and capable of becoming pregnant, you must use birth control from signing this informed consent through 12 weeks after the last dose of study drug. You should also not donate any eggs or breastfeed from the time of signing this informed consent through 12 weeks after the last dose of study drug. If you have been surgically sterilized or have been through menopause (discuss this with your study doctor), you do not need to meet any contraception or pregnancy test requirements to take part in this study.

In order to enter the study, you must have a pregnancy test to confirm that you are not pregnant. This test will be repeated just before you start taking the study medication and then regularly throughout the study. If a pregnancy test during the study shows that you may be pregnant, treatment with study medication will end, however, you will still be followed during the study period. You have the right to choose whether or not you would like to receive unblinded treatment information and based on this, you should discuss your pregnancy with the study doctor who will be able to advise you.

You must be willing to use any of the following acceptable methods of contraception from signing this informed consent through 12 weeks after the last dose of study drug:

Barrier methods (each time you have intercourse):

- Male condom PLUS spermicide
- Cap (plus spermicidal cream or jelly/gel) PLUS male condom and spermicide
- Diaphragm (plus spermicidal cream or jelly/gel) PLUS male condom and spermicide

Intrauterine devices

- Copper T
- Progesterone T

Hormonal Methods

- Implants
- Hormone Shot/Injection
- Combined Pill
- Minipill
- Patch
- Vaginal Ring PLUS male condom and spermicide

You should notify the study doctor immediately if you believe that you may be pregnant while participating in the study, and study drug should be discontinued immediately. All reported pregnancies will be followed-up to final outcome. You will be asked for the results of any tests and procedures carried out during your pregnancy and up to the birth. You may also be asked for the results from any evaluation of the baby after the birth.

LEAVING THE STUDY

You can stop taking part in this study at any time. If you choose not to take part or you agree to take part but then withdraw from the study, this will not affect your present or future medical care and there will be no penalty or loss of benefits that you may otherwise be entitled to.

Your study doctor can take you out of the study even if you want to continue taking part if:

- the Sponsor, FDA or ethics committee cancels the study;

- the study doctor thinks that removing you from the study is in your best interests;
- you need extra medication that would interfere with the study;
- this is necessary to meet the requirements of the study;
- you are not cooperating or you have not followed the directions given by the study doctor.

If you decide to stop being part of the study you should:

- tell the study doctor immediately;
- see the study doctor to be examined; and
- return all of the unused study medication along with any other study materials with the exception of retention items.

If you stop being part of the study for any reason, the study doctor may continue to use and distribute any information gathered so far in connection with your taking part in the study, as long as this is for the purposes described in the informed consent form.

You also can ask that all samples that are kept which can be identified as coming from you are destroyed to prevent further analyses.

Once you have stopped taking part in the study, the study medication will no longer be provided to you by the Sponsor. The study doctor will talk to you about how best to continue your medical care.

If you choose to withdraw your consent to allow testing on the Pharmacogenomics or Biomarker coded sample collected from you, you must inform the study doctor or (after the study is completed and the study doctor is unavailable) the Sponsor that you want the Sponsor to stop testing, at which point any remaining sample that can be identified as having come from you will be destroyed. The study doctor and Sponsor may continue to use and distribute any information and test results gathered in connection with you taking part in this study prior to your request to stop testing.

COSTS AND EXPENSES
There is no cost to you for participation in this study.

The study medication, study-related procedures and tests, and study visits will be free of charge.

While you are in the study, you will still need to get regular medical care. You (and/or your health care payer) will still have to pay for the costs of your regular medical care that are not a part of this study.

PAYMENTS
You will be reimbursed $XX.00 for completed on-site study visits which includes travel costs and $XX.00 for completed telephone study visits for your participation.

You will be also be reimbursed $25.00 for travel expenses associated with collection and delivery of documentation relating to any Major Cardiovascular (heart or circulation) Events, if this documentation is requested by your study doctor.

INTERNAL NOTE - PI Specific Comp - delete template wording as appropriate

CONFIDENTIALITY

If you take part in the PGx portion of the study, your PGx information (information from the genetic material purified from your blood) can reveal personal things about you. The PGx test results from this study are confidential. The Sponsor will make every effort to ensure that no one gets your test results except those people, organizations and companies that you read about in this consent form.

The below describes how information about your health and treatment may be collected in the main study and then, in coded form with your name removed, used by or sent to the Sponsor and other people, organizations and companies. It also describes the purposes for which this information may be used and transferred. The information related to blood and genetic material collected from you and generated in the optional PGx portion of this study may be combined with some or all of this coded information from the main study and used and shared by the Sponsor and the same people, organizations and companies for the same purposes. However, for samples and test results which are part of the PGx portion of this study, additional safeguards will be put in place to protect your privacy, as described in the Pharmacogenomic testing section above.

If you agree to take part in the study, the study doctor will gather and store personal information about your health and your treatment. This may include information that may be used to identify you, such as your name, address, phone number, date of birth, new and existing medical records, or the types, dates, and results of various tests and procedures, as well as information in your medical record and information created or collected during the study.

All information about you which leaves the study clinic will be identified by a code number and your initials, without your name and address. Confidentiality will be maintained in accessing, keeping, processing and publication of information related to your taking part in the study, i.e. your name will not be disclosed outside the study clinic unless required by law.

Your study doctor is responsible for keeping a list of codes to make it possible to link your code to your name. This list will be kept in a safe place to make sure that in an emergency you can be identified and contacted. The list will be kept for at least 15 years from the end of the study and then for as long as necessary to keep to the legal, regulatory, scientific or other requirements. It will then be destroyed.

Personal information about your health and treatment during the study may be used by or sent to other parties, in other countries, for clinical research and safety-reporting purposes. The parties the information may be passed to include the following:

- The Sponsor and other companies and people acting for or with the Sponsor
- The Sponsor's business partners and licensing partners
- Regulatory agencies and other health authorities including the FDA
- Copernicus Group Independent Review Board (CGIRB)

It is possible that your personal health information may be used by and sent to countries that do not have data protection or privacy laws that offer the same level of protection as the data protection and privacy laws in the United States. However, the Sponsor will do everything possible to keep your personal information confidential, and your name will not be revealed unless this is required by law.

The Sponsor, the Sponsor's representatives, health authorities (FDA) and relevant institutional review boards and ethics committees may inspect your medical records, which may include your name, address and other personal information that identifies you. If necessary, some or all of your medical records may be copied during these inspections. The purpose of these inspections is to make sure that the study is carried out correctly.

The results of this study may be presented at meetings or in publications. However, you will not be personally identified in any presentations or publications.

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.

The personal information collected during this study may also be added to research databases and used in the future by the Sponsor and other companies and people working for or with the Sponsor to:

- develop a better understanding of the safety and effectiveness of the study medication;
- study other therapies for patients;
- develop a better understanding of diseases included in the study; and
- improve the efficiency, design and methods of future studies.

In addition, the Sponsor is committed to responsible sharing of clinical data with the goal of advancing medical science and improving patient care. Qualified independent researchers will be permitted to use data collected from patients during the study to conduct additional scientific research, which may be unrelated to the study drug or your disease. The data provided to external researchers will not include information that identifies you personally.

By signing the informed consent form, you are authorizing the study doctor and Sponsor to use and share personal information about your health and treatment, as specified in the informed consent form. You will not lose any of your legal rights by signing the informed consent form. This consent does not have an end date.

In addition to the hard copy of this consent form that you will receive, you have the option to receive a copy of this consent form sent to you through electronic mail. If you choose to have a copy sent to you through electronic email, you understand that there are certain risks associated with transmission of email through the Internet, including but not limited to, unauthorized access, having other users view your consent form through a shared device, having your personal electronic device (PED) lost, hacked, subject to a search warrant or subpoena. Additionally, e-copies may not be able to be permanently deleted or removed from your PED. You acknowledge and accept the above risks if you choose to have an electronic copy sent to you.

COMPENSATION AND TREATMENT FOR INJURY

If you are harmed as a direct result of a study procedure or using the study medication, you will receive appropriate medical treatment. The Sponsor will pay the costs of such treatment as long as:

- those costs have not been paid by others; and
- you have followed the instructions you were given by the study doctor.

The Sponsor does not provide compensation other than that described above. If you would like more information about compensation for research-related injuries, contact the study doctor.

FURTHER INFORMATION AND CONTACT DETAILS

You should contact the study doctor first if you have questions, complaints, or concerns about the study.

Please call Copernicus Group IRB at 1-888-303-2224 if:

- You want to talk to someone other than the study doctor or study staff.
- You have a hard time reaching the study doctor or study staff.
- You have questions about your rights as a research subject.

Please visit the Copernicus Group IRB website www.cgirb.com for more information about research studies and the role of a research subject.

INFORMED CONSENT FORM
By signing below, you are confirming that you have read this informed consent form and understand it.

I declare the following:

- I have been given enough time to ask questions about the study and my questions have been answered to my satisfaction.
- I understand that I am taking part in this study voluntarily and I can withdraw from the study at any time without penalty or losing any benefits or medical care I am entitled to.
- **Involving your own doctor**
  If you agree, your own doctor or specialist may be:
  - told about you taking part in this study; and
  - asked to provide details of your medical history and any new information about your health during the study.

I agree that my family doctor or specialist be informed about my participation in this study.

☐ Yes ☐ No (check as appropriate)

- I understand that I will not lose any of my legal rights by signing this informed consent form.
- I will receive a fully signed and dated copy of this consent form and I have received a copy of the Experimental Subjects Bill of Rights.***For CA Sites Only***. .

Please place an "X" in the box below if you do not wish to take part in the optional PGx portion of this study. LEAVE THE BOX BLANK IF YOU AGREE TO PARTICIPATE:

☐ **Please place an "X" in this box if you DO NOT consent to take part in the PGx portion of the study**

By signing below, I agree that I would like to take part in the study.

Your Name (print)

Your Signature

__ __ / __ __ / __ __ __ __

[For the State of Indiana, add a line for subject's address, city, state and zip code]

Subject Address City State Zip Code

The information about the study was described to the subject in a language he/she understood.

_____
Printed Name of Authorized Person Obtaining Informed Consent

_____ _____
Signature of Authorized Person Obtaining Informed Consent Date

Time of consent: _____

AUTHORIZATION TO USE AND DISCLOSE PERSONAL HEALTH INFORMATION

A privacy rule has been issued to protect the privacy rights of patients. This rule (the "Privacy Rule") was issued under a law called the Health Insurance Portability and Accountability Act of 1996 (HIPAA). The Privacy Rule is designed to protect the confidentiality of your health information and requires your written permission for your health information to be used in this study. This section, called an "Authorization," explains how your health information will be used and disclosed during this study and describes your rights, including the right to see your health information.

By signing this Authorization, you allow the study doctor to use your Personal Health Information to carry out this study. Your "Personal Health Information" is information about you that could be used to identify you, such as your name, address, telephone number, photograph, date of birth, social security number, new and existing medical records, pharmacogenomics samples and analyses, if applicable, biomarker samples and analysis <<if applicable>>, or the types, dates, and results of various tests and procedures. This may include information in your medical record and information created or collected during the study.

By signing this consent form, you also allow the study doctor to disclose your Personal Health Information to other parties in other countries for clinical research and safety reporting purposes, including to the following: (1) Sponsor, its affiliates and licensing partners; (2) business partners assisting Sponsor, its affiliates and licensing partners; (3) regulatory agencies and other health authorities such as the FDA; and (4) Copernicus Group Independent Review Board (CGIRB).

Your Personal Health Information may no longer be protected by the Privacy Rule once it is disclosed by the study doctor, although other confidentiality safeguards apply. Please refer to the CONFIDENTIALITY section above to see how Sponsor will treat your Personal Health Information confidentially. If you have questions about how your Personal Health Information will be protected, you can ask the study doctor. You have the right to see and copy your Personal Health Information related to the study for as long as this information is held by the study doctor. However, to ensure the scientific integrity of the study, you agree that you may not be able to review some of your records related to the study until after the study has been completed.

You may cancel this Authorization at any time by sending a written notice to the study doctor at his/her address listed on the first page. below. **(Mail Only bookmark below)**

If you cancel this Authorization, the study doctor will no longer use or disclose your Personal Health Information under this Authorization for this study, unless the study doctor needs to use or disclose some of your Personal Health Information to preserve the scientific integrity of the study. Information given to Sponsor before you cancel this Authorization may still be used by Sponsor.

If you do not sign this Authorization, you cannot participate in the study. If you cancel this Authorization in the future, you will no longer be able to participate in the study. For further information regarding cancellation, see the LEAVING THE STUDY section above.

This Authorization does not have an expiration date. If you do not withdraw this Authorization in writing, it will remain in effect indefinitely. ***will expire December 31, 2060, unless you withdraw it in writing before then. (FOR CA, WA, WI, IN SITES)*** ***SPONSOR USE ONLY DOC GEN PLEASE DELETE***

This Authorization Applicable wording from above paragraph will pull over to site-specific ICFs. INTERNAL NOTE FOR DOC GEN **HIPAA EXPIRATION WORDING BOOKMARK**

The study doctor will keep this Authorization for at least 6 years.

AUTHORIZATION
By signing this form, I allow the use or disclosure of my health information. I will receive a signed and dated copy of this Authorization.

		/			/				

Subject Name

Date

Subject Signature

Home **Back** **Submit**