CLINICAL PROTOCOL

A PHASE 4, NON-TREATMENT FOLLOW-UP FOR CARDIAC ASSESSMENTS FOLLOWING USE OF SMOKING CESSATION TREATMENTS IN SUBJECTS WITH AND WITHOUT A HISTORY OF PSYCHIATRIC DISORDERS

Cardiac Assessments after Treatment Study - CATS

Compound: CP-526,555
Compound Name: Varenicline Tartrate
US IND Number: 58,994

European Clinical Trial Database (EudraCT) Number: 2011-005513-37
Protocol Number: A3051148
Phase: Phase 4
Amendment 2 05 June 2012

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The name, title, address and telephone number(s) of the sponsor's medical expert for the trial is documented in the study contact list located in the Study Manual.
### Document History

<table>
<thead>
<tr>
<th>Document</th>
<th>Version Date</th>
<th>Summary of Changes</th>
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| Amendment 2  | 05 June 2012  | This is being amended to incorporate changes based on feedback from the US FDA and to match the most recent protocol template and Pfizer SOPs. The following sections were updated:  
  - Vital signs (PR and BP) are added to all clinic visits.  
  - Section 6 (Study Procedures) is updated to include additional vital signs at every clinic visit.  
  - Section 6.2.1 (Clinic Visits) was updated to add a definition of a visit window.  
  - Section 6.3 (Subject Withdrawal) is updated to include information that all subjects will be followed until final visit unless they withdraw consent.  
  - Section 7.1 (Physical Examination, Vital Signs and Electrocardiogram) is updated to include vital signs at every clinic visit.  
  - Section 7.5 (Cardiovascular Events of Interest) is changed from: Hospitalization for angina pectoris or chest pain to: Hospitalization for unstable angina. Also wording was added to further clarify how events of interest will be identified, reviewed and adjudicated.  
  - Section 8 Updated various Adverse Event sections to match the most recent protocol template and Pfizer SOPs.  
  - Section 9.2 Efficacy Analysis was changed to Exploratory Efficacy Analyses. This was updated to provide clarification to these exploratory statistical analyses.  
  - Section 15 Publication of Study Results updated to match the most recent protocol template and Pfizer SOPs. |
| Amendment 1  | 08 November 2011 | This amendment is to update the study protocol template from the non-interventional template to the interventional template because local regulations in some countries where the study will be conducted consider certain study procedures an intervention (eg, blood draws).  
  
  The contents of the protocol are minimally changed to include language applicable to interventional studies. This amendment will be implemented globally. |
| Original protocol | 04 October 2011 | N/A                                                                                                                                                                                                             |

This amendment incorporates all revisions to date, including amendments made at the request of country Health Authorities, IRB/ERB, etc.
SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to Study Procedures (Section 6) and Assessments (Section 7) for detailed information on each procedure and assessment required for compliance with the protocol.

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* These will be collected at the Week 24 visit of Study A3051123.

b All females unless surgically sterilized or at least 2 years post menopausal.

NOTE: Week designations continue from last planned visit of study A3051123.
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1. INTRODUCTION

1.1. Indication

Aid to smoking cessation treatment.

1.2. Background and Rationale

Smoking is a major modifiable risk factor for cardiovascular disease. Current smokers have a high risk of experiencing an acute myocardial infarction and the risk increases with the number of cigarettes smoked. A residual excess risk has been reported to persist up to 20 or more years after quitting.1

It is well recognized that smoking cessation interventions (including use of pharmacologic and behavioral treatment) are among the most cost-effective disease prevention interventions available.2 The most commonly used aids for smoking cessation are: nicotine replacement therapy, varenicline and bupropion.

On June 16, 2011, the US FDA 3 issued a Drug Safety Communication based on review of study A3051049 of smokers with cardiovascular disease who were treated with varenicline or placebo.4 The Agency notified the public that cardiovascular adverse events in this study were infrequent overall, however, certain events were reported more frequently in patients treated with varenicline than in patients treated with placebo. Study A3051049 conducted between 2006 and 2008 compared the safety and efficacy of varenicline for smoking cessation to placebo in 714 patients with stable cardiovascular disease.4 Patients were treated for 12 weeks and the follow-up lasted 52 weeks. Cardiovascular (CV) adverse events of interest were adjudicated by an independent committee. All patients enrolled in the study had stable cardiovascular disease diagnosed up to 2 months before the screening visit, and in many cases, multiple cardiovascular morbidities.

The results of the study show that patients who received varenicline were more likely to quit and remain abstinent, and the overall benefit-risk balance for varenicline remains positive.5 Common adverse events occurring more frequently among subjects randomized to varenicline were similar to what was previously reported for varenicline (nausea, insomnia, sleep disturbances, vomiting, and constipation). Cardiovascular adverse events occurred infrequently albeit at a higher rate than what was observed in other varenicline studies. However the differences between varenicline and placebo was small, and the modest imbalances in frequency were distributed across multiple diagnosis, and not always suggesting an increase in frequency in the varenicline group. The number of deaths was lower in the varenicline arm compared to the placebo arm for all causes of death (0.6% varenicline vs 1.4% placebo), cardiovascular deaths (0.3% varenicline vs 0.6% placebo) and non cardiovascular deaths (0.3% varenicline vs 0.9% placebo).

The interpretation of the data and the potential role of confounders such as time from drug exposure, progression of already existing subclinical disease, contribution of other co-morbidities, changes in smoking status and use of non-study prescribed aids for smoking cessation are limited due to the relatively small size of the study and the small number of events across different diagnoses. Study A3051123 which will recruit 8,000 subjects equally
randomized to varenicline, bupropion, NRT or placebo offers an opportunity for additional assessments of cardiovascular adverse events.

Study A3051123 is a 24-week multicenter, multinational, randomized, double-blind placebo and NRT controlled trial designed to assess the safety and efficacy of varenicline 1 mg BID and bupropion hydrochloride 150 mg BID for smoking cessation. The objective of study A3051123 is to characterize the neuropsychiatric safety profiles of varenicline and bupropion for subjects with and without a diagnosis of psychiatric disorder. At the request of the US FDA study A3051123 protocol was amended to include additional CV safety data collection and independent adjudication of CV events, including hospitalization for CV and certain pulmonary diagnoses. The A3051148 study is a non-treatment extension to study A3051123, aimed at collecting data on cardiovascular safety for all participants in the A3051123 trial for an additional 28 weeks, allowing for a total of 52 weeks of cardiovascular safety data collection.

The A3051148 study qualifies as a Post-Authorization Safety Study (PASS) and it is a US Post-Marketing Requirement.

The Single Reference Safety Document for varenicline, bupropion and NRT are the respective Core Data Sheets (CDS).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective of the CV safety assessment will be to characterize the cardiovascular safety profiles of varenicline and bupropion compared to placebo.

The secondary objective will be to characterize the cardiovascular safety profiles for the following comparisons:

1. NRT vs. Placebo.
2. Varenicline vs. Bupropion.
3. Varenicline vs. NRT.
4. Bupropion vs. NRT.

2.2. Endpoints

Primary Endpoint:

The primary endpoint for the CV surveillance will be the time to major cardiovascular event (MACE; defined as a cardiovascular death, a non-fatal myocardial infarction or a non-fatal stroke) evaluated during the treatment phase (up to date of last dose of study drug).
Secondary Endpoints:

Time to MACE will also be evaluated (1) up to date of last dose of study drug plus 30 days and (2) until the end of study.

Incidence of each of the following events will be assessed (1) up to date of last dose of study drug, (2) up to date of last dose of study drug plus 30 days, and (3) until end of study:

- MACE;
- MACE + (defined as any MACE or a new onset or worsening peripheral vascular disease (PVD) requiring intervention, a need for coronary revascularization, or hospitalization for unstable angina);
- CV deaths;
- Non fatal MI;
- Non fatal stroke.

Note: All time to event endpoints start at date of first study drug during study A3051123.

Exploratory Endpoints:

Via the Nicotine Use Inventory, abstinence endpoints will be derived with the primary intention to serve as complementary information when discussing SAE cases. These include:

- Nicotine use since last visit;
- Nicotine use since last visit, CO confirmed;
- Nicotine use in the past 7 days;
- Nicotine use in the past 7 days, CO confirmed;
- Continuous abstinence from Week 9 of parent study to Week 52, CO-confirmed.

Additional Safety Endpoint:

- Serious cardiac arrhythmia

3. STUDY DESIGN

This is a 28 week Phase 4 extension to study A3051123 for surveillance of cardiovascular events in subjects who have completed the 24 week study in the parent protocol and who have meet the eligibility requirements outlined in Section 4, Subject Selection. The projected
sample size is dependent upon the completion rates of the parent study. The parent study will involve approximately 8000 subjects and approximately 200 centers globally.

4. SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

The study will be open to all subjects who meet the inclusion and exclusion criteria for enrollment in this study.

4.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator’s study team before subjects are included in the study.

- Evidence of a personally signed and dated informed consent document indicating that the subject (or a legally acceptable representative) has been informed of all pertinent aspects of the study.
- Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
- Randomized to and completed study A3051123.

4.2. Exclusion Criteria

Subjects presenting with any of the following will not be included in the study:

1. Participation in study A3051123 ceased (ie, withdrew, lost to follow-up, etc.) prior to Week 24 final visit.

4.3. Life Style Guidelines

Participants are expected to abstain from the use of tobacco products such as pipe tobacco, cigars, snuff, chewing tobacco, hookah, and the use of marijuana. Subjects will be expected to refrain from using any form of nicotine replacement therapy, bupropion, varenicline and other aids to smoking cessation during this study.

5. STUDY TREATMENTS

5.1. Allocation to Treatment

This is the non treatment extension study of study A3051123. No study drug is provided during the extension phase. The Single Subject Identifier (SSID) will remain the same as in the parent study.
5.2. Concomitant Medication(s)

Any use of the following drugs are prohibited during this study:

- Drugs containing bupropion;
- Varenicline (Chantix®/Champix®);
- Nicotine replacement therapy and other aids to smoking cessation.

6. STUDY PROCEDURES

6.1. Initiation Visit

The initiation visit of this extension study will be the same as the Week 24 visit of the parent study. All subsequent weeks will be numbered from week 24 of the A3051123 study. The following procedures will be performed:

- Obtain written informed consent for this study (if not already previously obtained);
- Review Inclusion/Exclusion Criteria;
- Complete physical examination;
- Record sitting blood pressure, and pulse rate;
- Record a 12-lead electrocardiogram (ECG);
- Collect blood samples for CBC and blood chemistry;
- Perform urine or serum pregnancy test for all females of childbearing potential;
- Measure and record weight*;
- Record adverse events*;
- Record concomitant medications*;
- Complete the Nicotine Use Inventory (NUI)*;
- Measure the end expiratory exhaled carbon monoxide (exhaled CO)*,
- Collect and forward records on cardiovascular events of interest and hospitalizations of interest as defined in Appendix 2 for adjudication, if applicable*.

*Note these activities will be performed during the Week 24 visit of study A3051123.
For reporting purposes, the term baseline visit will refer to the baseline (Week 0) visit of the parent study, A3051123. Data collected at the screening and baseline visits of study A3051123 will be used as the baseline data for this study, including but not limited to: medical history, cardiovascular history, demography, and smoking history.

6.2. Study Period

6.2.1. Clinic Visits (Weeks 28, 32, 36, 40, 44, 48, and 52 or Early Termination ET_{52})

The following procedures will be performed:

- Record sitting blood pressure, and pulse rate;
- Record adverse events;
- Complete the Nicotine Use Inventory (NUI);
- Record concomitant medications;
- Measure the end-expiratory exhaled carbon monoxide (exhaled CO);
- Collect and forward records on cardiovascular events and hospitalizations of interest as defined in Appendix 2 for adjudication, if applicable.
- Perform additional examinations and/or laboratory tests if applicable for the adjudication of the cases as in Appendix 2.

The following procedures will also be performed at Week 52 or Early Termination ET_{52}:

- Complete physical examination;
- Measure and record weight;
- Record a 12-lead electrocardiogram (ECG);
- Collect blood samples for CBC and blood chemistry.

To accommodate unforeseen circumstances a visit window of ±10 days can be allowed throughout the study. The visit window should be used with discretion and all subjects should remain on original visit schedule throughout study participation.

6.2.2. Unplanned Visits

If needed in-between planned clinic visits, an unplanned visit may be performed to collect CV event information if a SAE or AE is reported which may qualify as a CV event.

The following procedures will be performed:
- Complete physical examination;
- Record sitting blood pressure, and pulse rate;
- Record adverse events;
- Record concomitant medications;
- Collect and forward records on cardiovascular events and hospitalizations of interest as defined in Appendix 2 for adjudication, if applicable;
- Perform additional examinations and/or laboratory tests if applicable for the adjudication of the cases as in Appendix 2.

6.3. Subject Withdrawal

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal and follow-up with the subject regarding any unresolved adverse events.

Every effort should be made to keep the subject in the study until the final visit and all planned assessments/evaluations should be performed.

If a subject withdraws from the study, but does not withdraw consent, he/she should be contacted at the end of the trial to assess vital status/cardiovascular events. If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent. All reasonable efforts should be made to contact subjects who are lost to follow up to ascertain their reason(s) for not continuing in the study. A determination needs to be made that they are truly lost to follow up and not withdrawing for another reason (eg, adverse event or lack of efficacy).

7. ASSESSMENTS

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However it is anticipated that from time to time there may be circumstances, outside of the control of the investigator that may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well being of the subject. When a protocol required test can not be performed the investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.
7.1. Physical Examination, Vital Signs and Electrocardiogram

A physical examination will be performed at the initiation visit of study A3051148 and Week 52 or ET$_{52}$. Abnormal changes from the screening visit of study A3051123 deemed clinically significant by the Investigator should be recorded as adverse events.

Body weight will be measured at the initiation visit of study A3051148 and Week 52 or ET$_{52}$. Weight will be measured in indoor clothing without shoes.

Sitting blood pressure and pulse rate will be measured at the initiation visit of study A3051148 and at every clinic visit including Week 52 or Early Termination (ET$_{52}$). Blood pressure will be measured by an appropriate automated/semi-automated or manual sphygmomanometer and recorded to the nearest mmHg. All blood pressure measurements are to be taken in the dominant arm with the appropriate size cuff. Pulse rate will be measured in the brachial/radial artery for at least 30 seconds.

A 12-lead electrocardiogram will be obtained at the initiation visit and Week 52 or ET$_{52}$.

7.2. Nicotine Use Inventory (NUI)

The Nicotine Use Inventory (NUI) Appendix 1 is a questionnaire regarding use of cigarettes and other nicotine-containing products during the treatment period or tobacco products during non-treatment follow-up period. The NUI was designed for and applied in previous varenicline studies. The NUI will be completed monthly at all clinical visits.

7.3. End-Expiratory Exhaled Carbon Monoxide (Exhaled CO)

In order to confirm the smoking abstinence reported in the NUI, an end-expiratory exhaled carbon monoxide (exhaled CO) will be measured at each clinic visit using a breath CO monitor. An exhaled CO $\leq$10 ppm is required to claim successful smoking cessation.

7.4. Laboratory

Blood chemistry, complete blood count with differential and platelet count will be completed at the Initiation Visit and at Week 52/ET$_{52}$. A minimum of an eight hour fast is required prior to the collection of blood for the chemistry panel. Pregnancy test for women of childbearing potential will be completed at the Initiation Visit (Week 24) (dipstick at site or serum).

7.5. Cardiovascular (CV) Events of Interest

Cardiovascular adverse events will be prospectively reviewed and adjudicated by an independent Cardiovascular Event Adjudication Committee. The committee will be blinded to study treatment allocation. The committee will confirm diagnosis for cardiovascular events of interest based on review of documentation provided by investigators. All deaths will be reviewed by the adjudication committee who will make a determination of whether a death is cardiovascular or non-cardiovascular.
Clinically significant cardiac events of interest include:

- Non-fatal myocardial infarction;
- Resuscitated cardiac arrest;
- Need for coronary revascularization;
- Hospitalization for unstable angina;
- Hospitalization for congestive heart failure;
- Fatal, non-fatal stroke or transient ischemic attack (TIA);
- Any new diagnosis of peripheral vascular disease (PVD) in a subject not previously diagnosed as having PVD or any procedure for the treatment of PVD (or any peripheral vascular intervention);
- Cardiovascular death.

In order to ensure that no potential SAEs of interest are missed, in addition to the events above any hospitalization for angina, chest pain, loss of consciousness, cardiac or vascular procedures, respiratory diseases (excluding infections and cancer), and generalized edema will be sent for adjudication as described in Section 9.5. The sponsor will periodically review adverse event lists to identify additional cases for adjudication, irrespective of the diagnosis as described in Section 9.5.

7.5.1. Serious Cardiac Arrhythmias

In addition to cardiac events of interest serious cardiac arrhythmias will be reviewed and adjudicated by the independent adjudication committee. Serious cardiac arrhythmias are defined as the presence of a sustained cardiac rhythm disturbance lasting more than 1 minute which results in either hemodynamic compromise, syncope, cardiac arrest, a cerebral vascular event, or altered mental status, and requires urgent intervention with cardiac monitoring, drug therapy, cardioversion, or placement of a temporary pacemaker.

Examples include:

- Ventricular tachycardia;
- Torsade de Pointes;
- Ventricular fibrillation;
- AICD discharge (must state the underlying initiating rhythm);
- Bradycardia;
- Complete heart block;
- Atrial fibrillation/flutter;
- Supraventricular tachycardia;
- Sick sinus syndrome;
- Second degree heart block (type 2).

7.6. Measures of Abstinence from Smoking

Information for the calculation of abstinence parameters will be obtained at each clinic visit or telephone contact from a set of questions about cigarette and other nicotine use since the last visit/contact (Nicotine Use Inventory). At clinic visits, subject reports of smoking status will be confirmed by measurement of end expiratory exhaled carbon monoxide (CO) concentration, with a result \( \leq 10 \) ppm indicating abstinence.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all adverse events, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to Pfizer or its designated representative. For all adverse events, sufficient information should be obtained by the investigator to determine the causality of the adverse event. The investigator is required to assess causality. Follow up by the Investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious adverse event that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical trial.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject’s participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last
administration of the investigational product. Should an investigator be made aware of any SAE occurring any time after the active reporting period, it must be promptly reported.

- AEs (serious and non-serious) should be recorded on the CRF from the time the subject provides informed consent through last subject visit.

### 8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure via breastfeeding;
- Medication error.
8.4. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.5. Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.
- Lack of efficacy should be reported as an AE when it is associated with an SAE.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.
8.5.1. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (ALT) concurrent with abnormal elevations in total bilirubin that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy’s Law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject’s individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT >3 times the upper limit of normal (X ULN) concurrent with a total bilirubin >2 X ULN with no evidence of hemolysis and an alkaline phosphatase <2 X ULN or not available.

- For subjects with preexisting ALT OR AST OR total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above:
  - For subjects with pre-existing AST or ALT baseline values above the normal range: AST or ALT >2 times the baseline values and >3 X ULN, or >8 X ULN (whichever is smaller).

- Concurrent with
  - For subjects with pre-existing values of total bilirubin above the normal range: Total bilirubin increased by one time the upper limit of normal or ≥3 times the upper limit of normal (whichever is smaller).

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment. In addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/INR and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced subject, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for LFT abnormalities identified at the time should be considered potential Hy’s Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy’s
Law cases should be reported as SAEs. All study drug treatments should be discontinued in these events.

8.6. Hospitalization

AEs reported from studies associated with hospitalization or prolongations of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit).

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Routine emergency room admissions;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment lab abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical exam);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures should be noted in the initiation documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

### 8.7. Severity Assessment

If required on the AE case report forms (CRFs), the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:

<table>
<thead>
<tr>
<th>Intensity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MILD</td>
<td>Does not interfere with subject's usual function.</td>
</tr>
<tr>
<td>MODERATE</td>
<td>Interferes to some extent with subject's usual function.</td>
</tr>
<tr>
<td>SEVERE</td>
<td>Interferes significantly with subject's usual function.</td>
</tr>
</tbody>
</table>

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

### 8.8. Causality Assessment

The investigator’s assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator’s causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as “related to investigational product” for reporting purposes, as defined by the Sponsor (see Section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.
8.9. Exposure During Pregnancy

For investigational products and for marketed products, an exposure during pregnancy (also referred to as exposure in-utero (EIU) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or being exposed (eg, due to treatment or environmental exposure) or after discontinuing or having been directly exposed to the investigational product.

2. A male has been exposed (eg, due to treatment or environmental exposure) to the investigational product prior to or around the time of conception or is exposed during his partner’s pregnancy.

If a study subject or study subject’s partner becomes or is found to be pregnant during the study subject’s treatment with the investigational product, the investigator must submit this information to Pfizer on an EIU Form (this is a specific version of the Serious Adverse Event Form). In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EIU Form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain pregnancy outcome information for all EIU reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination) and notify Pfizer of the outcome as a follow up to the initial EIU Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as serious adverse events when the investigator assesses the neonatal death as related or possibly related to exposure to investigational product

Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis.
(eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the EIU Pregnant Partner Release of Information Form to deliver to his partner. The Investigator must document on the EIU Form that the subject was given this letter to provide to his partner.

8.10. Withdrawal Due to Adverse Events (See Also Section 6.3 Subject Withdrawal)

Withdrawal due to AE should be distinguished from withdrawal due to insufficient response, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws due to an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.11. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs at times indicated in the schedule of activities.

8.12. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.12.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy and exposure via breastfeeding cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.
8.12.2. Non-Serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.12.3. Sponsor Reporting Requirements to Regulatory Authorities

Adverse event reporting, including suspected serious unexpected adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan, which will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

While the objective of the parent study focuses on neuropsychiatric adverse events, the general or standard reporting of cardiovascular adverse events observed during study conduct will be included within its CSR. This extension study will incorporate all necessary data from the parent study in order to properly summarize and report cardiovascular safety, particularly those derived composite endpoints of interest (Section 2.2).

9.1. Sample Size Determination

As this study represents a continued CV surveillance of subjects from the study A3051123, the nominal sample size (8,000 subjects) was determined to meet the primary objective of the parent study. Initially, all subjects enrolled in the parent study are also eligible for this study. The actual sample size realized for this study is dependent on changes in subject disposition, ie, withdrawn consent, discontinuation prior to Week 24, etc.

9.2. Exploratory Efficacy Analyses

Exploratory efficacy analyses will be based on the full analysis set, defined as all subjects randomized into the parent study. Note that imputation rules for efficacy endpoints (ie, abstinence endpoints derived from the NUI) will govern those subjects not transitioning from A3051123 into A3051148.

Summary statistics (frequencies, percents) will be provided. Presentation will consider randomized treatment group, visit and neuropsychiatric cohort (from parent study) as partitioning variables.
9.3. Safety Analysis

Safety analyses will be based on the Safety analysis set, defined as all subjects that receive at least one partial dose of study drug during the parent study.

9.3.1. Primary Safety Analysis

Time to MACE, censored at last study drug dose date (on treatment), is the primary safety endpoint and is evaluated via a stratified (2-level cohort) log-rank test. The hazard ratio and associated 95% confidence interval will be reported for both a varenicline vs. placebo comparison and a bupropion vs. placebo comparison. No multiplicity adjustment will be made.

9.3.2. Secondary Safety Analysis

Secondary analyses involving expanded versions of the primary safety endpoint will be performed. Specifically, time to MACE will also be analyzed via the aforementioned log-rank test by:

- censoring at last randomized dose date + 30 days (treatment emergent) and
- censoring at last study visit (entire study).

A log-rank test will also be conducted for time to MACE (separately for each of the three censoring rules) with respect to each of the remaining pairwise treatment comparisons. Furthermore, analogous analyses will be performed for other time to event endpoints, including such events as:

- MACE+
- CV deaths
- Non fatal MI
- Non fatal stroke

Incidence of event endpoints are also to be evaluated as secondary analyses. For a CV event type (such as MACE, MACE+, CV deaths, non-fatal MI, non-fatal stroke), evaluated separately over three specific time periods (on treatment, treatment emergent and entire study), these secondary analyses will provide model-based estimates and associated 95% confidence intervals for the difference in the incidence of the MACE between varenicline and placebo and between bupropion and placebo for subjects in each cohort. Variables for consideration in the preliminary statistical model include treatment group, cohort and baseline CV risk. A pooled estimate (across cohorts) of the two risk differences and their associated 95% confidence intervals will also be computed. In addition, given the sparseness potential of these endpoints, a non-parametric confirmatory analysis will be performed via
exact conditional logistic regression, with a stratified Mantel-Haenszel analysis provided as another supportive analysis.

As the incorporation of neuropsychiatric diagnosis group (5 levels) will only further accentuate any event sparseness issue, exploratory analyses will replace cohort with neuropsychiatric diagnosis group in the aforementioned analyses.

Additional exploratory analyses will evaluate the CV event components of MACE individually (both in an incidence sense and in a time-to-event sense).

9.3.3. Other Analysis

The association between SAEs and smoking status derived via the Nicotine Use Inventory will be analyzed for:

- Nicotine use since last visit;
- Nicotine use since last visit, CO confirmed;
- Nicotine use in the past 7 days;
- Nicotine use in the past 7 days, CO confirmed;
- Continuous abstinence from Week 9 of parent study to Week 52, CO-confirmed.

Adjudicated serious cardiac arrhythmias will be summarized by treatment group and by smoking status.

9.4. Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) will be established to assess safety data at regular intervals for the duration of the trial and make recommendations to the Executive Steering Committee on whether to continue, modify or stop the study. An IDMC charter authored a priori and governed by the IDMC will be completed.

The committee will be responsible for ongoing monitoring of the safety of subjects in the study. Any recommendation made by the committee to alter the conduct of the study will be forwarded to the Sponsor for final decision. The Sponsor will forward such decisions, which may include summaries of aggregate analyses of safety endpoint events, to regulatory authorities, as appropriate.

9.5. Cardiovascular Event Adjudication Committee (CEAC)

An independent adjudication committee will review documentation provided by investigators during study conduct to identify cardiovascular events of interest (primary and secondary CV safety endpoints). Investigators will collect and submit documentation to the CEAC for all adverse events related to:
- Non-fatal myocardial infarction;
- Any hospital admission for chest pain;
- Hospitalization for angina pectoris/unstable angina;
- Need for coronary revascularization or any cardiac or vascular intervention;
- Resuscitated cardiac arrest;
- Hospitalization for congestive heart failure;
- Fatal, non-fatal stroke or transient ischemic attack (TIA);
- Any diagnosis of peripheral vascular disease (PVD) in a subject not previously diagnosed as having PVD or any procedure for the treatment of PVD;
- Cardiovascular death;
- Death from any cause;
- Hospitalization for loss of consciousness;
- Respiratory diseases (excluding infections and cancer);
- Generalized edema.

To ensure that all possible cardiovascular adverse events of interest (primary and secondary endpoints) are referred to the CEAC for review, a listing of all adverse events (serious and non-serious) from the following SOCs, HLGT, HLT, LLT and PTs will be prepared monthly and sent to the CEAC.

1. All Deaths.

2. SOCs:
   - Cardiac Disorders;
   - General Disorders and Administration Site Conditions;
   - Injury, Poisoning, and Procedural Complications;
   - Investigations;
   - Musculoskeletal and Connective Tissue Disorders;
   - Nervous System Disorders;
- Respiratory, Thoracic, and Mediastinal Disorders;
- Surgical and Medical Procedures;
- Vascular Disorders.

3. HLGT:
   - Tissue disorders NEC.

4. HLT:
   - Necrosis, NEC.

5. LLTs:
   - Cerebral Revascularization Synangiosis (search value: revascularization);
   - Coronary Revascularization (search value: revascularization);
   - Peripheral Revascularization (search value: revascularization);
   - Renal Revascularization (search value: revascularization);
   - Transmyocardial Revascularization (search value: revascularization);
   - Acute myocardial ischemia (search value: myocardial ischemia);
   - ECG signs of myocardial ischemia (search value: myocardial ischemia);
   - Myocardial ischemia (search value: myocardial ischemia);
   - Myocardial ischemia recurrent (search value: myocardial ischemia);
   - Silent myocardial ischemia (search value: myocardial ischemia).

6. PTs:
   - Acute Myocardial Infarction (search value: myocardial infarction);
   - Myocardial Infarction (search value: myocardial infarction);
   - Post Procedural Myocardial Infarction (search value: myocardial infarction);
   - Silent Myocardial Infarction (search value: myocardial infarction);
   - Cell Death.
These searches will be complemented by a quarterly standardized Medra query for other possible CV events that may also require adjudication.

- Myocardial Infarction;
- Ischemic Heart Disease;
- Cardiac Arrhythmias;
- Cardiac Failure;
- Embolic and Thrombotic Events;
- Shock;
- Torsade de pointes/QT prolongation;
- Cerebrovascular Disorders;
- Central Nervous System Haemorrhages and Cerebrovascular Accidents;
- Vasculitis;
- Cardiomyopathy;
- Hemodynamic edema, effusions, and fluid overload;
- Hypertension;
- Pulmonary Hypertension;
- Renovascular Disorders;
- Shock.

The events will be adjudicated using a standard events manual under blinded conditions. The adjudication committee will make the determination of whether a death is cardiac or non-cardiac.

The independent adjudication committee will also review serious cardiac arrhythmias. Serious cardiac arrhythmias are defined as the presence of a sustained cardiac rhythm disturbance lasting more than 1 minute which results in either hemodynamic compromise, syncope, cardiac arrest, a cerebral vascular event, or altered mental status, and requires urgent intervention with cardiac monitoring, drug therapy, cardioversion, or placement of a temporary pacemaker.

Examples include:
• Ventricular tachycardia;
• Torsade de Pointes;
• Ventricular fibrillation;
• AICD discharge (must state the underlying initiating rhythm);
• Bradycardia;
• Complete heart block;
• Atrial fibrillation / flutter;
• Supraventricular tachycardia;
• Sick sinus syndrome;
• Second degree heart block (type 2).

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow Pfizer monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to
third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/ original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator’s site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH), local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.
12. ETHICS

12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 2008). In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

Subject names, address, birth date and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify the trial subject. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data.

The informed consent document must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent document used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Pfizer before use.

The investigator must ensure that each study subject, or his/her legal representative, is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legal representative before any study-specific
activity is performed. The investigator will retain the original of each subject's signed consent document.

12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

End of Trial in all participating countries is defined as last subject’s last visit.

13.1. End of Trial in a Member State

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient subjects have been recruited and completed the study as stated in the regulatory application (ie, Clinical Trial Application (CTA)) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of varenicline at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 7 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of this study on www.clinicaltrials.gov (ClinicalTrials.gov). Pfizer posts the results of all studies that it has registered on ClinicalTrials.gov regardless of the reason for registration.

The results are posted in a tabular format called Basic Results.
For studies involving a Pfizer product, the timing of the posting depends on whether the Pfizer product is approved for marketing in any country at the time the study is completed:

- For studies involving products applicable under the US Food and Drug Administration Amendments Act of 2007 (FDAAA), i.e., FDA-approved products, Pfizer posts results within one year of the primary outcome completion date (PCD).
- For studies involving products approved in any country, but not FDA approved, Pfizer posts results one year from last subject, last visit (LSLV).
- For studies involving products that are not yet approved in any country, Pfizer posts the results of already-completed studies within 30 days of US regulatory approval, or one year after the first ex-US regulatory approval of the product (if only submitted for approval ex-US).
- For studies involving products whose drug development is discontinued before approval, Pfizer posts the results within one year of discontinuation of the program (if there are no plans for outlicensing or within two years if outlicensing plans have not completed).

Primary Completion Date is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.

15.2. Publications by Investigators

Pfizer has no objection to publication by Investigator of any information collected or generated by Investigator, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

Investigator will, on request, remove any previously undisclosed Confidential Information (other than the Study results themselves) before disclosure.

If the Study is part of a multi-centre study, Investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the Study at all participating sites, Investigator is free to publish separately, subject to the other requirements of this Section.
For all publications relating to the Study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - “Ethical Considerations in the Conduct and Reporting of Research” of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.
16. REFERENCES


Appendix 1. Nicotine Use Inventory (NUI)

- Has the subject smoked any cigarettes (even a puff) since the last site visit / telephone contact?

- Has the subject used any other nicotine-containing products* (eg, nicotine patch, nicotine gum, nicotine nasal spray, nicotine inhaler, nicotine lozenge, pipe, cigars, chew, snuff) since the last site visit / telephone contact?

- Has the subject smoked any cigarettes (even a puff) in the last 7 days?

- If the subject smoked in the last 7 days, has the subject had any days on which no cigarettes were smoked, and if so, how many days?

- If the subject smoked in the last 7 days, how many cigarettes did the subject smoke per day, on average for the days on which smoking occurred?

- Has the subject used any other nicotine-containing products* (eg, nicotine patch, nicotine gum, nicotine nasal spray, nicotine inhaler, nicotine lozenge, pipe, cigars, chew, snuff) in the last 7 days?

- Nicotine replacement therapy and/or other smoking cessation medications should be recorded in the concomitant medicine pages in the case report form.
Appendix 2. CV Required Documents

Deaths and cardiovascular events of interest will be reviewed and adjudicated by an independent events committee. The committee will review all pertinent information for each reported case.

Clinical sites will forward all the available records with the appropriate routing form for adjudication.

Any Hospitalization for: loss of consciousness, cardiac or vascular procedures, respiratory diseases (excluding infections and cancer) and generalized edema:

- Admission notes;
- Discharge summary;
- Summary of Event in English (signed by an MD);
- Laboratory, imaging and ancillary examinations.

Hospitalization for Chest Pain or Angina Pectoris/Unstable angina:

- Admission notes;
- Discharge summary;
- ECG tracing(s) (include eRT ECG);
- Stress test or Thallium scan;
- Angiography report;
- Summary of Event in English (signed by an MD);
- Other (for example, MUGA scan, Holter);
- Cardiac enzymes:
  - CK;
  - CK-MB;
  - LDH;
  - Troponin I;
  - Troponin T.
Hospitalization for Congestive Heart Failure:

- Admission notes;
- Physician notes/progress reports supporting typical CHF symptoms and signs or other diagnostic test results;
- Discharge summary;
- Summary of Event in English (signed by an MD);
- Chest x-ray;
- ECG tracings;
- Ejections fraction by echocardiogram, MUGA scans, etc;
- Brain natriuretic peptide (BNP) and NT-proBNP results should be submitted, if available;
- Other.

Coronary Revascularization Procedure (CABG, PTCA, Atherectomy, Transplant, Other)

- Admission notes;
- Physician notes/progress reports;
- Operative report;
- Catheterization report;
- PTCA operative reports;
- Discharge summary;
- Summary of Event in English (signed by an MD);
- Other.

Non-fatal Myocardial Infarction or Resuscitated Cardiac Arrest

- Discharge Summary;
- Clinical Notes;
- Summary of Event in English (signed by an MD);
- Cardiac imaging data (if available);
- ECG tracing(s) (include eRT ECG);
- Cardiac enzymes:
  - CK;
  - CK-MB;
  - LDH Troponin I;
  - Troponin I;
  - Other.

**Non-fatal Stroke, TIA**

- Admission and/or physician progress notes, including neurological exam;
- Discharge summary;
- Summary of Event in English (signed by MD);
- Operative Report;
- CT;
- MRI;
- Angiography Report;
- Spinal Fluid Analysis;
- Other.

**First Diagnosis of PVD or Procedure for PVD**

- Physician Notes;
- Summary of Event in English (signed by an MD);
- Diagnostic Tests (angiograms, Dopplers, etc.);
- PVD procedure;
• Percutaneous Revascularization (ie, atherectomy, PTA);
• Amputation;
• Other.

**Serious Cardiac Arrythmias**

• Physician Notes;
• Summary of Event in English (signed by an MD);
• Diagnostic Tests;
• Admission notes if applicable;
• Discharge summary;
• ECG tracing(s) (include eRT ECG);
• Other (for example, Holter).

**Deaths**

• Physician Notes;
• Summary of Event in English (signed by an MD);
• Admission and/or physician progress notes;
• Diagnostic Tests if applicable;
• Discharge summary if applicable;
• Diagnostic tests if applicable;
• Autopsy Report (if performed);
• Other.