A PHASE 4, MULTI-NATIONAL, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF VARENICLINE COMPARED TO PLACEBO FOR SMOKING CESSATION THROUGH REDUCTION

**Compound:**
CP-526, 555

**Compound Name (if applicable):**
Varenicline Tartrate

**US IND Number (if applicable):**
58, 994

**Protocol Number:**
A3051075

**Phase:**
Phase 4

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## Document History

<table>
<thead>
<tr>
<th>Document</th>
<th>Version Date</th>
<th>Summary of Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amendment 5</td>
<td>05 September 2012</td>
<td><strong>Appendix 2 Neuropsychiatric Adverse Events Interview (NAEI) added</strong> “Have you had times when you felt like you had to be always moving or even pacing?” after question #9.</td>
</tr>
<tr>
<td>Amendment 4</td>
<td>04 June 2012</td>
<td>Removed the word “weekly” to the entry for smoking log in the <strong>Schedule of Activities</strong>.</td>
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<td>Section 5.3.3 Administration –medication error language added.</td>
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<td>Section 6.5 Subject Withdrawal – language added regarding subject compliance with study visits or procedures.</td>
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<td></td>
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<td>Section 7.1.4 Modified cigarette Evaluation Questionnaire (mCEQ) -clarified that the form should be completed if subjects smoked since the last visit or since they last completed the form.</td>
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<tr>
<td></td>
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<td>Section 7.2.5 Laboratory Testing clarified that it will be a urine pregnancy test and added that pregnancy tests could be repeated at the request of IRB/IECs or if required by local regulations.</td>
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</tbody>
</table>


| Amendment 3 | 04 June 2012 | Incorporates all the Changes of Amendment 4 into the Japan specific Amendment 2. |

Section 7.2.6 Other Safety Assessments clarified that the PHQ-9 will be completed at specified clinic visits not all clinic visits.

Section 8 Adverse Event Reporting updated to align with CT3 guidance and FDA final rule.

Section 8.9 Exposure during pregnancy language updated.

Section 11.2 added record retention requirements of 15 years.

Section 15.1 Communication of Results by Pfizer—extensive wording changes to include Basic Results.

Appendix 2 Neuropsychiatric Adverse Events Interview (NAEI) added “extremely anxious” to question #9.

Appendix 3 corrected the answer to Question 3 answer 2 b to “Yes, at one time and really wanted to do it.”

Minor administrative changes and typographical corrections.
<table>
<thead>
<tr>
<th>Amendment</th>
<th>Date (Country-specific: Japan)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amendment 2</td>
<td>05 April 2011</td>
<td>Add Tobacco Dependence Screener (TDS) at the Screening visit. Include only subjects who score 5 or higher on the Tobacco Dependence Screener (TDS).</td>
</tr>
<tr>
<td>Amendment 1</td>
<td>15 March 2011</td>
<td>Change lower age limit in Inclusion Criterion #2 from 18 to 20. Indicate the study is being conducted as a Phase 3 study in Japan.</td>
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<tr>
<td>Original protocol</td>
<td>15 Mar 2011</td>
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This amendment incorporates all revisions to date, including amendments made at the request of country Health Authorities, IRB/ERB, etc.
PROTOCOL SUMMARY

Many smokers express a desire to quit by gradually reducing the number of cigarettes smoked until they stop completely (‘Reduce to Quit’). A US-based population survey reported that 42% of smokers said they wanted to quit smoking completely, of whom 44% (19% of the entire sample) preferred a reduce to quit approach vs. 53% who preferred abrupt cessation (22% of the entire sample; (Shiffman, Hughes et al. 2007). Based on this report, more than half of US smokers motivated to quit wish to utilize a Reduce to Quit approach, which may have considerable efficacy. UK statistics show that few – only 12% of smokers – are ready to stop smoking abruptly (Moore, Aveyard et al. 2009) and 40% of quit attempts involve reducing first (Lindson, Aveyard et al. 2009). A recent meta-analysis by the Cochrane Group determined that reducing prior to quitting and abruptly quitting produced comparable quit rates (RR=0.94, 95% CI: 0.79 to 1.13, main analysis)(Lindson, Aveyard et al. 2010).

The effectiveness of a Reduce to Quit approach using varenicline has not been evaluated in clinical trials. Demonstrating the efficacy and safety of varenicline for smoking cessation in smokers unable to quit abruptly but who are motivated to quit through a reduction approach will provide an important additional approach to achieve abstinence and improve public health by augmenting medical options to treat tobacco dependence.

The primary objective is to compare the efficacy of varenicline to placebo for smoking cessation during the last 10 weeks of treatment in subjects who are not willing/able to make an abrupt quit attempt but are willing to reduce their smoking with the ultimate goal of quitting.

Secondary objectives are the comparison of varenicline to placebo during the last four weeks of treatment and through the longer term follow-up phase to Week 52.

The primary endpoint is the CO confirmed Continuous Abstinence (CA) Weeks 15-24.

Key secondary endpoints are the CO confirmed Continuous Abstinence Weeks 21-24 and 21-52, and other secondary endpoints are the 7 day point prevalence of smoking cessation at Weeks 12, 24, and 52, and the 4 week point prevalence of smoking cessation at Week 52.

This study is a Phase 4, randomized, double-blind, placebo-controlled, parallel group, multicenter study designed to evaluate the efficacy and safety of varenicline in subjects who are not able make an abrupt quit attempt but are willing to reduce their smoking with the ultimate goal of quitting.

It is planned that a total of approximately 1404 subjects will be enrolled into this study at approximately 75 sites; 702 subjects per group. Subjects will enter an initial screening phase of approximately 3-10 days duration, and those subjects meeting the eligibility criteria will then enter the 12 week double-blind reduction phase to receive varenicline 1 mg BID or matching placebo, with a 1:1 randomization ratio. After completion of the 12 week double-blind reduction phase, subjects will enter the abstinence phase for an additional 12 weeks of treatment with either varenicline 1 mg BID or matching placebo (randomization continues into this period). Treatment stops at Week 24 and the subject proceeds into the 28 week post treatment follow-up phase and completes the study at Week 52.
All subjects will be randomized to either varenicline or placebo. Study drug will be titrated to the full dose during the first week in the following manner: varenicline 0.5 mg or matching placebo QD for 3 days, varenicline or matching placebo 0.5 mg BID for 4 days, then varenicline 1 mg BID or matching placebo for the following 23 weeks. Subjects who have difficulties with tolerability may have the blinded dose lowered temporarily or permanently to 0.5 mg BID. Dosing will continue until the Week 24 visit when it is completed. All subjects will be followed for an additional 28 weeks in the post treatment follow-up phase of the protocol, including those who may have stopped treatment in the previous study phase.

A sample size of approximately 1404 subjects randomized to varenicline or placebo in a 1:1 ratio (702 varenicline and 702 placebo) will provide at least 90% power to detect a difference in the primary endpoint of 17.2% and 6.9% for varenicline and placebo, respectively (OR of at least 2.8). This sample size will also provide at least 90% power to detect a difference in the key secondary endpoint CO-confirmed CA rate weeks 21-24 of 23.0% and 8.9% for varenicline and placebo, respectively (OR of at least 3.0). This sample size will also provide 90% power to detect a difference in the long-term key secondary endpoint CO-confirmed CA rate weeks 21-52 of 9.3% and 4.7% for varenicline and placebo, respectively (OR of at least 2.0).

Subject to IRB/EC approval/favorable opinion, this study will include an additional research component involving collection of biological samples for de-identified exploratory pharmacogenomics analysis. The Molecular Profiling Supplement to this protocol provides a description of this additional research. Subjects may participate in this study even if they choose not to participate in the sample banking component.
Table 1. 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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<thead>
<tr>
<th>Protocol Activity</th>
<th>Screening</th>
<th>Baseline Visit</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3 Telephone visit</th>
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- **Informed Consent**: X
- **Medical History**: X
- **Physical Examination**: X X
- **Vital signs with weight**: X X
- **Height**: X
- **Hematology**: X
- **Blood Chemistry**: X
- **Pregnancy Test**: X X
- **Urine drug screen**: X X
- **12 Lead ECG**: X
- **Registration/Randomization**: X
- **Sample Banking for Exploratory Research**: X
- **Smoking history**: X
- **Eggerström Test**: X
- **Exhaled CO**: X X X X X X X X
- **NUI**: X X X X X X X X
- **Concomitant Medications and concomitant non-drug treatments**: X X X X X X X X
- **Concomitant Medications (for smoking cessation)**: X X X X X X X X

*Approved On: 19-Sep-2012 19:08*

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### Protocol Activity

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- a Dipstick at site
- b dipstick at site
- c at site
- d optional and only with signed consent
- e Administered to only those subjects who smoked in the week prior to the visit
- f dispense two weekly smoking logs at Week 2
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Dispense "Clearing the Air" booklet
weekly smoking log

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- Height

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- MNWS

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Final Protocol Amendment 5, 05 September 2012

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1. INTRODUCTION

1.1. Indication

Varenicline tartrate is indicated as an aid to smoking cessation treatment.

1.2. Background and Rationale

Varenicline is the most recently approved medication for smoking cessation treatment acting as a partial agonist at the $\alpha 4\beta 2$ nicotinic receptor. Varenicline (Chantix®/Champix®) was approved as an "aid to smoking cessation treatment" in adults by the FDA in May 2006, and for "smoking cessation in adults" by the EMEA in September 2006. Varenicline is a selective nicotinic acetylcholine receptor (nAChR) partial agonist designed to have specific and potent binding at the $\alpha 4\beta 2$ receptor subtype. The approved dose regimen is 1.0 mg twice daily (1 mg BID) for 12 weeks with a one-week titration period at the commencement of treatment. The majority of varenicline clinical trials have required an abrupt quitting approach in agreement with approved dosage recommendations. The Maintenance of Abstinence study (A3051035, Study 6 in the Chantix® label) has assessed the effect of an additional 12 weeks of therapy on likelihood of long-term abstinence. Based on the results, for patients who have successfully stopped after 12 weeks an additional course of 12 weeks treatment is recommended. The proposed study treatment does not exceed the approved treatment dose or approved treatment duration from the Maintenance of Abstinence study. Additionally, a Pfizer-sponsored Flexible Quit Date study, where patients were allowed to set a quit date between Day 8 and Week 5 of treatment, recently completed and will provide useful information on quitting patterns during the initial month of therapy but will not evaluate phased reduction [ClinicalTrials.gov Identifier: NCT00691483].

Phase 2 and Phase 3 clinical trials demonstrated the efficacy and tolerability of varenicline 1 mg BID in more than 4000 cigarette smokers, increasing the odds of quitting by approximately 4-fold compared with placebo at end of treatment, and by nearly 2-fold compared with bupropion at end of treatment. The most frequently reported treatment-emergent adverse events associated with varenicline were nausea, sleep disturbance, constipation, flatulence and vomiting. Nausea was reported by approximately 30% of subjects treated with varenicline 1 mg BID after an initial week of dose titration compared with 10% in subjects taking placebo. Nausea was generally described as mild or moderate and often transient.

Post Marketing Experience

There have been post-marketing reports of neuropsychiatric symptoms, some serious, including changes in mood, agitation, psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, changes in behavior, anxiety, panic, suicidal ideation, suicide attempt and completed suicide in patients attempting to quit smoking with varenicline. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish causal relationship to drug exposure. Smoking cessation with or without treatment is associated with nicotine withdrawal symptoms and the exacerbation of underlying psychiatric illness. Not all patients had known pre-existing psychiatric illness and not all had discontinued smoking. The role of varenicline in these reports is not known.
There have also been reports of serious skin reactions and hypersensitivity reactions, including angioedema, as well as reports of myocardial infarction and cerebrovascular accident.

Many smokers express a desire to quit by gradually reducing the number of cigarettes smoked until they stop completely (‘Reduce to Quit’). A US-based population survey reported that 42% of smokers said they wanted to quit smoking completely, of whom 44% (19% of the entire sample) preferred a reduce to quit approach vs. 53% who preferred abrupt cessation (22% of the entire sample; (Shiffman, Hughes et al. 2007). Based on this report, more than half of US smokers motivated to quit wish to utilize a Reduce to Quit approach, which may have considerable efficacy UK statistics show that few – only 12% of smokers – are ready to stop smoking abruptly (Moore, Aveyard et al. 2009) and 40% of quit attempts involve reducing first (Lindson, Aveyard et al. 2009). A recent meta-analysis by the Cochrane Group determined that reducing prior to quitting and abruptly quitting produced comparable quit rates (RR=0.94, 95% CI: 0.79 to 1.13, main analysis)(Lindson, Aveyard et al. 2010).

The effectiveness of a Reduce to Quit approach using varenicline has not been evaluated in clinical trials. Demonstrating the efficacy and safety of varenicline for smoking cessation in smokers unable to quit abruptly but who are motivated to quit through a reduction approach will provide an important additional approach to achieve abstinence and improve public health by augmenting medical approaches to treat tobacco dependence.

Complete information for this compound may be found in the Single Reference Safety Document, which for this study is the Core Data Sheet.

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

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective is to compare the efficacy of varenicline to placebo for smoking cessation during the last 10 weeks of treatment in subjects who are not willing/able to make an abrupt quit attempt but are willing to reduce their smoking with the ultimate goal of quitting.

Secondary objectives are the comparison of varenicline to placebo during the last four weeks of treatment and through the longer term follow-up phase to Week 52.

2.2. Efficacy Endpoints

Primary Endpoint:

- CO confirmed Continuous Abstinence (CA) during the last 10 weeks of treatment weeks 15-24.
Secondary Endpoints:

Key secondary endpoints:

- CO confirmed Continuous Abstinence (CA) Weeks 21-24;
- CO confirmed Continuous Abstinence (CA) Weeks 21-52.

Other secondary endpoints:

- 7 day point prevalence of smoking cessation at Weeks 12, 24, and 52;
- 4 week point prevalence of smoking cessation at Week 52.

3. STUDY DESIGN

This study is a Phase 4, randomized, double-blind, placebo-controlled, parallel group, multicenter study designed to evaluate the efficacy and safety of varenicline in subjects who are not able make an abrupt quit attempt but are willing to reduce their smoking with the ultimate goal of quitting.

It is planned that a total of approximately 1404 subjects will be recruited into this study at approximately 75 sites; 702 subjects per arm. Subjects will enter an initial screening phase of approximately 3-10 days duration, and those subjects meeting the eligibility criteria will be randomized on a 1:1 ratio to varenicline 1 mg BID or matching placebo for a 24 week double-blind treatment phase. During the first 12 weeks of treatment the study subjects will reduce the number of cigarettes smoked (reduction phase). An additional 12 weeks of treatment follows the reduction phase. Subjects are expected to be abstinent from smoking during this phase (abstinence phase). Treatment stops at Week 24 and the subject proceeds into the 28 week post treatment follow-up phase and completes the study at Week 52.

Screening Phase (approximately 3-10 days): During this phase, subjects will attend a clinic visit at which they will sign their consent form, screening laboratory tests will be taken, and an ECG will be completed and their eligibility criteria will be evaluated. Results of laboratory tests and 12-lead ECG will be reviewed prior to the baseline visit. Subjects who continue to meet all eligibility criteria for the study at the baseline clinic visit will then be randomized to enter the treatment phase.

12 Week Reduction Phase: During this double-blind treatment phase, subjects will attend the clinic for visits at Weeks 1, 2, 4, 6, 8, and 12. Telephone visits will be conducted at Weeks 3, 5, 7, and 10. There are no visit assessments at Weeks 9 and 11. Efficacy and safety evaluations will be undertaken at the clinic visits, and brief smoking cessation counseling (less than 10 minutes) will be provided at all visits from baseline through to Week 12. Study drug (varenicline 1mg BID or placebo) will be dispensed at clinic visits only. Subjects will be dispensed sufficient medication to last until the next clinic visit.
12 Week Abstinence Phase: Subjects will continue with their same randomization assignment into this additional 12 week treatment phase. During the abstinence phase the subjects will come to the clinic for visits at Weeks 15, 18 and 21-24. A telephone visit will be conducted at Weeks 14 16, and 20. There are no visit assessments at Weeks 13, 17 and 19. Study medication will be dispensed at clinic visits in sufficient quantity to last until the next clinic visit. Subjects are expected to begin abstinence at Week 12 and are encouraged to remain abstinent for the duration of the protocol. If a subject has not made a quit attempt in the reduction phase he should be encouraged to do so in this phase.

28 Week Post Treatment Follow-up Phase (Follow-Up to Week 52): Study drug will be discontinued at Week 24 and subjects will continue into the post -treatment follow-up phase. Clinic visits will take place at Weeks 26, 32, 40, 48 and 52. Telephone contact will be made at Weeks 28, 36 and 44.

Study Diagram:

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.

Only subjects who have no association with the Principal Investigator and his staff or any aspect of the conduct of the study may be included.
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.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Evidence of a personally signed and dated informed consent document indicating that the subject (or a legal representative) has been informed of all pertinent aspects of the study.

2. Male and female cigarette smokers over the age of 18 years who are not willing/able to quit smoking within the next month but who are willing to attempt to reduce their smoking to work toward a quit attempt within the next 3 months.

3. Subjects must have smoked an average of at least 10 cigarettes per day during the past year and during the month prior to the screening visit, with no continuous period of abstinence greater than 3 months in the past year and who have an exhaled carbon monoxide (CO) >10 ppm at screening.

4. Subjects with history of lifetime or current mild to moderate (investigator opinion) major depressive disorder (MDD), depression, depressed mood, anxiety, and anxiety disorders (including general anxiety disorder (GAD), obsessive compulsive disorder (OCD) and phobias such as agoraphobia and social phobia) may be included if their condition is stable. Stability is defined as:
   
   If on medication, on the same dose for the past 6 months;

   No hospitalizations for exacerbations in the past 6 months.

5. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

6. Females who are not of childbearing potential (ie, who are surgically sterilized or at least 2 years postmenopausal) and who are not nursing may be included. Females who are of childbearing potential may be included provided that they are not pregnant, not nursing, and who meet all of the following criteria:

   • Are instructed and agree to avoid pregnancy through 30 days after the last dose of study medication;

   • Have a negative pregnancy test (beta-hCG) at Screening and Baseline and agree to use at least one of the birth control methods listed below:
An oral contraceptive agent, an intrauterine device (IUD), an implantable contraception (eg, Norplant), or an injectable contraceptive (eg, Depo Provera) for at least 1 month prior to entering the study and will continue its use through at least 30 days after the last dose of study medication; or:

- A double barrier method of contraception, (ie, condom plus spermicide in combination with a female condom, diaphragm, cervical cap, or intrauterine device) or sexual abstinence prior to entering into the study and for at least least 30 days after the last dose of study drug.

### 4.2. Exclusion Criteria

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

1. Subjects with a history of a suicide attempt or any suicidal behavior in the past two years as assessed using the C-SSRS and/or the SBQ- R.

   - History of suicidal ideation with intent/plan in the past 6 months ("yes" to Questions 4 and/or 5 on the C-SSRS) or at the screening or baseline visit.

2. Subjects with lifetime or current severe major depressive disorder (MDD), depression, depressed mood, anxiety, or anxiety disorder (including generalized anxiety disorder (GAD), obsessive compulsive disorder (OCD), and phobias such as agoraphobia and social phobia).

3. Subjects with unstable mild to moderate major depressive disorder (MDD), depression, depressed mood, anxiety, or anxiety disorder (including generalized anxiety disorder (GAD), obsessive compulsive disorder (OCD), and phobias) such as agoraphobia and social phobia.

4. Subjects with a lifetime diagnosis or treatment for psychosis, panic disorder, bipolar disorder, post traumatic stress disorder (PTSD), or schizophrenia.

5. Subjects with alcohol or substance abuse or dependence (except nicotine) unless in full remission for at least 12 months.

6. Subjects with a positive urine drug screen (at screening or baseline) for drugs of abuse/potential abuse not prescribed for the treatment of a medical condition.

7. Subjects previously enrolled in a study that included varenicline (CP-526,555) or subject who have previously taken Chantix®/ Champix®. Subjects who have taken a very limited number of prescription doses may be considered pending discussion with the study clinician.

8. Subjects who have participated in other studies within 30 days prior to the screening visit of this study or any time during this study.
9. Subject with an SGOT (AST) or SGPT (ALT) greater than 3 times the upper limit of normal (ULN) or total bilirubin greater than 2 times the ULN at screening.

10. Subjects having clinically significant medical disorders or clinically significant laboratory test abnormalities as determined by the Principal Investigator.

11. Subjects with severe chronic obstructive pulmonary disease (COPD) defined as any subject who fulfills any of the following criteria:
   - History of repeated exacerbations of COPD (greater than or equal to 3 in 3 years).
   - Requires systemic corticosteroid maintenance (eg, oral prednisolone) for management of chronic symptoms.
   - Is maintained on oxygen therapy for management of chronic symptoms.

12. Subjects with a recent (<5 years) history of cancer.Subjects with completely excised carcinoma in situ of the cervix or completely excised melanomas <5 years prior to screening may be considered pending discussion with the study clinician. Subjects with a remote (>5 years) history of cancer may be considered pending discussion with the study clinician.
   - Subjects with cured basal cell or squamous cell carcinoma of the skin are allowed.

13. Subjects with evidence or history of clinically significant allergic reactions to drugs (eg, anaphylaxis or Stevens-Johnson syndrome).

14. Subjects with a clinically significant ECG at the screening visit (as determined by the Principal Investigator or medically appropriate designee).

15. Subjects with clinically significant cardiovascular disease in the past 2 months. Examples of clinically significant cardiovascular disease include:
   - Myocardial infarction;
   - Coronary artery bypass graft (CABG);
   - Percutaneous transluminal coronary angioplasty (PTCA);
   - Severe or unstable angina;
   - Serious arrhythmia;
   - Clinically significant ECG conduction abnormalities;
   - Heart failure.
16. Subjects with clinically significant cerebrovascular disease in the past 2 months. Examples of clinically significant cerebrovascular disease include:

- Cerebrovascular accident (CVA), stroke;
- Documented transient ischemic attack (TIA).

17. Subjects taking a concomitant medication that is prohibited by this protocol (See Section 5.5).

18. Subjects who do not agree to abstain from using non-cigarette tobacco products (including pipe tobacco, cigars, snuff, chewing tobacco, etc.) or marijuana during study participation.

19. Subjects who do not agree to abstain from using nicotine replacement therapy and other aids to smoking cessation during the treatment period.

20. Subjects who intend to donate blood or blood components while receiving study drug or within 1 month of the completion of the treatment phase of the study.

21. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

4.3. Randomization Criteria

Subjects who meet the inclusion and exclusion criteria may be randomized. A computer-generated randomization schedule will be used to assign subjects to treatment. An equal number of subjects will be randomized into the varenicline and placebo treatment groups.

4.4. Life Style Guidelines

Participants are expected to abstain from the use of any tobacco products such as pipe tobacco, cigars, snuff, chewing tobacco, gutka, shiska, and bidis. Participants are also expected to abstain from the use of marijuana and e-cigarettes. Subjects will be expected to refrain from using any form of nicotine replacement therapy during the treatment phase.

Females of childbearing potential (not surgically sterilized or <2 years postmenopausal) must agree to practice a form of effective contraception, such as an oral contraceptive agent, an intrauterine device (IUD), an implantable contraceptive (eg, Norplant), or an injectable contraceptive (eg, Depo provera) for at least 1 month prior to entering the study and will continue its use through at least 30 days after the last dose of study medication. Alternatively they may use double barrier contraception (ie, condom plus spermicide in combination with a female condom, diaphragm, cervical cap or intrauterine device), or sexual abstinence prior to entering into the study and for at least 30 days following the last dose of study drug.
5. STUDY TREATMENTS

All subjects will be randomized to either varenicline or placebo. Study drug will be titrated to the full dose during the first week in the following manner: varenicline 0.5 mg or matching placebo QD for 3 days, varenicline 0.5 mg or matching placebo BID for 4 days, then varenicline 1 mg or matching placebo BID for the following 23 weeks. The subjects who have difficulties with tolerability may have the blinded dose lowered temporarily or permanently to 0.5 mg BID. Dosing will continue until the completion of the treatment phase at the Week 24 visit. All subjects will be followed for an additional 28 weeks in the post treatment follow-up phase of the protocol, including those who may have stopped treatment in the previous study phase.

Smoking cessation counseling, in accordance with Agency for Healthcare Research and Quality (AHRQ) guidelines and/or suggested Cinciripini, et al 1997, Shiffman, et al 2009 (or other) reduction techniques, will be given at each visit during the reduction phase, the abstinence phase, and the post-treatment follow up phase. The counseling will be 1:1 and up to 10 min in duration and should be tailored to the subject’s needs at that point in time. Whenever possible, counseling should be conducted by the same counselor throughout, so that the relationship builds and brings additional value to the sessions.

5.1. Allocation to Treatment

Subjects will be randomized to varenicline or placebo in a 1:1 ratio.

Investigators will obtain subject identification numbers and study drug assignments utilizing a web-based or telephone call-in drug management system as directed by the sponsor. The identification numbers for the subjects will be provided at the screening visit.

5.2. Breaking the Blind

This study will be subject, investigator, and sponsor blind.

At the initiation of the study, the study site will be instructed on the method for breaking the blind. The method will be either a manual or electronic process. Blinding codes should only be broken in emergency situations for reasons of subject safety. The investigator should contact Pfizer before breaking the blind. When the blinding code is broken, the reason must be fully documented and entered on the case report form.

5.3. Drug Supplies

Investigational Product: varenicline tartrate CP-526,555 supplied by Pfizer. One week titration up to final dose 1 mg BID po. 1:1 randomization of approximately 1404 subjects expected to yield 702 subjects with exposure to IP.

Short Title for Labeling of Investigational Product: A3051075.

Additional Investigational Products or Comparators: matching placebo.
Other Information: 10 day varenicline supply in bottles for 24 weeks.

5.3.1. Formulation and Packaging

Tablets (blinded varenicline or placebo) will be supplied in bottles containing sufficient amount of tablets for 10 days. Varenicline will be supplied as 0.5 mg tablets. A new bottle(s) will be dispensed at each weekly clinic visit to provide sufficient study drug until the next scheduled clinic visit.

5.3.2. Preparation and Dispensing

Study drug is to be dispensed to subjects by qualified site study staff at each scheduled clinic visit from the Baseline visit through the Week 23 visit. Subjects will be given their first drug supply in bottles at the Baseline visit and will receive a new bottle(s) at each clinic visit through the Week 23 visit.

5.3.3. Administration

Medication errors may result, in this study, from the administration or consumption of the wrong drug, by the wrong subject, or at a strength of 4mg/day or higher. Such medication errors occurring to a study participant are to be captured on the adverse event (AE) page of the CRFs and on the SAE form when appropriate. In the event of medication dosing error (4 mg/day or higher) the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the product.
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error and, if applicable, any associated adverse event(s) is captured on an adverse event (AE) CRF page (refer to ADVERSE EVENT REPORTING section for further details).

Study drug administration will begin with a titration period. Treatment will begin from the Week 1 drug supply in bottles on the evening of the Baseline visit day. For the first 3 days of the Week 1 dosing period, subjects will take one 0.5 mg tablet per day in the evening. For the next 4 days this will increase to two 0.5 mg tablets per day, 1 in the morning and 1 in the evening. On study Day 8, which should coincide with the Week 1 visit, subjects will increase their dose to two 0.5 mg tablets in the morning. At the Week 1 visit and subsequent clinic visits through the Week 23 visit subjects will receive a new bottle(s) and will take four 0.5 mg tablets daily: 2 in the evening and 2 in the morning.
Dosing should occur with 240 mL of water and it is recommended that subjects eat prior to dosing. It is recommended that there be at least 8 hours between the morning and evening dosing. Subjects who have difficulties with tolerability may have the dose lowered temporarily or permanently to 0.5 mg BID.

5.3.4. Compliance

Subjects will return bottles at each clinic visit. A dosing record and drug accountability form will be completed. Missed doses should be discussed to try to ascertain the reason(s). Reasons for missed doses and/or patterns of missed doses should be incorporated into the smoking cessation counseling. Every effort should be made to ensure proper subject dosing.

5.4. Drug Storage and Drug Accountability

The investigator, or an approved representative (eg, pharmacist), will ensure that all study drug is stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements. Varenicline and matching placebo should be stored at 15-30°C or 59-86°F as indicated on the label and out of reach of children.

To ensure adequate records, all study drug will be accounted for in the case report form and drug accountability inventory forms as instructed by Pfizer. Unless otherwise authorized by Pfizer, at the end of the clinical trial all drug supplies unallocated or unused by the subjects must be returned to Pfizer or its designated agent.

5.5. Concomitant Medication(s)

Female subjects entering the study on concomitant oral or injectable contraceptive medication must continue this medication throughout the study, and for 30 days after discontinuation of study treatment.

The investigator is responsible for obtaining any information about concomitant medication and concurrent diseases at each visit. Any questions regarding concomitant medication use should be referred to the study clinician or his/her designee.

The episodic and chronic use of the following medication is prohibited during the study:

- Any investigational drug not connected to this study;
Nicotine replacement therapy, varenicline, and other aids to smoking cessation and other alternative therapies for smoking cessation including herbal medications (in the treatment phase);

- Bupropion;
- Naltrexone;
- Insulin;
- Nortriptyline;
- Clonidine;
- Oral steroids, including anabolic steroids and parenterally (intravenous/intramuscular) administered steroids, (inhaled and topical steroids, injectable for local intra-articular administration and episodic short term use of oral steroids are permitted);
- Theophylline;
- Warfarin;
- Herbals commonly used for anxiety or depression;
- Over the counter and prescribed stimulants and anorectic agents.

6. STUDY PROCEDURES

6.1. Screening

The Screening visit will occur approximately 3-10 days prior to the baseline/randomization visit. The following procedures will be conducted during screening:

- Obtain informed consent for the clinical trial (must be signed prior to the initiation of any study related activities);
- Record demography, medical history, and smoking history (including questions regarding past attempts to quit smoking and cigarette use) and an assessment of past and present alcohol use);
- Administer the Fagerström Test for Nicotine Dependence (FTND) Appendix 1;
- Measure the end-expiratory exhaled carbon monoxide (exhaled CO);
- Record concomitant medications used within the past 3 months;
- Record non-drug treatment within the past 3 months;
• Measure height and weight;
• Vital signs (blood pressure and pulse rate);
• Physical examination;
• Complete the Columbia Suicide-Severity Rating Scale (C-SSRS) Appendix 5;
• Subject completes the Suicide Behaviours Questionnaire-Revised (SBQ-R) Appendix 3;
• Record a 12-lead electrocardiogram (ECG);
• Collect blood samples for CBC and blood chemistry and send to the central laboratory;
• Collect the optional Molecular Profiling sample and send to central laboratory (if consent signed);
• Perform urine pregnancy test for females of childbearing potential at site;
• Perform urine drug screen at site. (May be repeated at the investigator’s discretion at later visits).

6.2. Reduction Phase

Subjects will be asked to reduce their smoking from the baseline rate by at least 50% at Week 4, with a further 50% reduction in smoking rate from Week 4 to Week 8 with the goal of total abstinence at Wk 12. The last cigarette should have been smoked prior to midnight on the day prior to the Week 12 visit. Subjects may reduce their smoking rate faster if they so desire or may make a quit attempt at any time prior to Week 12 when they are ready. Subjects who reduce faster or quit early will continue dosing and visit participation as originally planned.

6.2.1. Baseline Visit (Randomization)

The following procedures will be conducted at the Baseline visit:
• Record adverse events;
• Record all concomitant medications;
• Record non-drug treatments;
• Vital signs (blood pressure, pulse rate);
• Weight;
• Physical examination;
• Conduct the Neuropsychiatric Adverse Event Interview (NAEI) Appendix 2;
• Complete the Columbia Suicide-Severity Rating Scale (C-SSRS) Appendix 5;
• Subject completes the PHQ-9 Appendix 7;
• Perform urine drug screen at site.
• Perform urine pregnancy test for females of childbearing potential at site.
• Measure the end-expiratory exhaled carbon monoxide (exhaled CO).
• Subject completes the Modified Cigarette Evaluation Questionnaire (mCEQ) Appendix 9;
• Subject completes the Minnesota Nicotine Withdrawal Scale (MNWS) Appendix 8;
• Complete the Nicotine Use Inventory (NUI) Appendix 4;
• Dispense "Clearing the Air-Quit Smoking Today";
• Smoking Cessation counseling 1:1 ≤10 min;
• Re-check Inclusion/Exclusion criteria;
• Randomize to treatment;
• Dispense study drug: Week 1 bottle;
• Dispense smoking log.

6.2.2. Clinic Visits (Weeks 1, 2, 4, 6, 8 and 12 and ET24 Visit)

Approximately one week (3-10 days) after their Baseline visit the subject will return for the Week 1 visit.

Following the Week 1 visit, clinic visits will be conducted at Weeks 2, 4, 6, 8, and 12. Telephone visits will be conducted at Weeks 3, 5, 7, and 10. Every effort should be made to have the subject return on the same day of the week for the clinic visits, thereby keeping visits on time and visits should always be planned referencing the Baseline visit. To accommodate unforeseen circumstances a visit window of ±3 days can be allowed as long as proper dosing is maintained. If an early termination occurs before the end of Week 12, an early termination visit (ET24) will be conducted. At each of these visits, the following procedures will be conducted:
• Record adverse events;

• Record concomitant medications;

• Record non-drug treatment;

• Conduct the Neuropsychiatric Adverse Event Interview (NAEI) Appendix 2;

• Complete the Columbia Suicide-Severity Rating Scale (C-SSRS) Appendix 5;

• Subject completes the PHQ-9 (Weeks 2, 4, 6, 8, 10, 12, and ET<sub>24</sub> Appendix 7;

• Complete the Nicotine Use Inventory (NUI) Appendix 4;

• Measure the end-expiratory exhaled carbon monoxide (exhaled CO);

• Smoking Cessation counseling;

• Count and document drug returns;

• Dispense next week’s bottle(s);

• Dispense smoking log (one log at Week 1 and two logs at Week 2--no logs needed after Week 4);

• **Additional procedures at Weeks 4, 8, and 12;**

• Subject completes the mCEQ (if smoked) and the MNWS.

• **Additional procedures at Week 12 visit or ET<sub>24</sub> visit (if a subject terminates early ET<sub>24</sub> procedures should be followed):**
  
  • Physical examination. (**ET<sub>24</sub> only**) Vital signs with weight;

  • Perform urine pregnancy test for females of childbearing potential at site.

6.2.3. Telephone Visits Weeks 3, 5, 7, and 10

At each of these visits the following procedures will be conducted:

• Complete the Nicotine Use Inventory (NUI) Appendix 4;

• Smoking Cessation counseling;

• Subject answers the PHQ-9 questions (Week 10 only) Appendix 7;
6.3. Abstinence Phase

6.3.1. Clinic Visits at Weeks 15, 18, and 21-24

At the Week 12 visit subjects are expected to be abstinent following a 12 week reduction period (50% reduction from Baseline at Week 4 and a further 50% reduction from the Week 4 level at Week 8). Dosing continues from Week 12 through Week 24. Clinic visits will be conducted at Weeks 15, 18, and 21-24. Telephone visits will be conducted at Weeks 14 and 16, and 20. Every effort should be made to have the subject return on the same day of the week for the clinic visits, thereby keeping visits on time and visits should always be planned referencing the Baseline visit. To accommodate unforeseen circumstances a visit window of ± 3 days can be allowed as long as proper dosing is maintained. If an early termination occurs before the end of Week 24, an early termination visit (ET24) will be conducted. At each of these visits, the following procedures will be conducted:

- Record adverse events;
- Record concomitant medications;
- Record non-drug treatments;
- Conduct the Neuropsychiatric Adverse Event Interview (NAEI) Appendix 2;
- Complete the Columbia Suicide-Severity Rating Scale (C-SSRS) Appendix 5;
- Subject completes the PHQ-9 (Weeks 18, 22, and 24) Appendix 7;
- Complete the Nicotine Use Inventory (NUI) Appendix 4;
- Measure the end-expiratory exhaled carbon monoxide (exhaled CO);
- Smoking Cessation counseling. (not at ET24);
- Count and document drug returns;
- Dispense next week’s bottle(s) (not at Week 24 or ET24);
- **Additional procedures at Weeks 15, 18, and 24;**
- Subject completes the mCEQ (if smoked) and the MNWS;
- **Additional procedures at Week 24 visit or ET24 visit:**(if a subject terminates early ET24 procedures should be followed):
  - Physical examination;
  - Vital signs with weight.
- Perform urine pregnancy test for females of childbearing potential at site.
6.3.2. Telephone visits weeks 14, 16, and 20

At these visits the following procedures will be conducted:

- Subject answers the PHQ-9 questions Appendix 7;
- Complete the Nicotine Use Inventory (NUI) Appendix 4;
- Smoking Cessation counseling.

6.4. Post Treatment Follow-up Phase

6.4.1. Clinic visits Weeks 26, 32, 40, 48, 52, and ET52

Clinic visits will be conducted during the post treatment follow-up phase at Weeks 26, 32, 40, 48 and 52. Telephone visits will be conducted at Weeks 28, 36, and 44. Every effort should be made to have the subject return on the same day of the week for the clinic visits, thereby keeping visits on time and visits should always be planned referencing the Baseline visit. To accommodate unforeseen circumstances a visit window of ± 7 days can be allowed (the visit window for telephone visits is ±3 days). If an early termination occurs before the end of Week 52, an early termination visit (ET52) will be conducted. At each of these visits, the following procedures will be conducted:

- Record adverse events;
- Record concomitant medications;
- Record non-drug treatments;
- Conduct the Neuropsychiatric Adverse Event Interview (NAEI) Appendix 2;
- Complete the Columbia Suicide-Severity Rating Scale (C-SSRS) Appendix 5;
- Subject completes the PHQ-9 Appendix 7;
- Complete the Nicotine Use Inventory (NUI) Appendix 4;
- Measure the end-expiratory exhaled carbon monoxide (exhaled CO);
- Smoking Cessation counseling (not at ET52);
- Additional procedures at Week 26;
- Subject completes the mCEQ (if smoked) and the MNWS.

6.4.2. Telephone visits Weeks 28, 36, and 44

At each of these visits the following procedures will be conducted:
• Complete the Nicotine Use Inventory (NUI) Appendix 4;
• Smoking Cessation counseling.

6.5. Subject Withdrawal

Subjects who discontinue study drug treatment should not be discontinued from the study. They should be encouraged to continue participation in the study. They will be required to maintain the visit schedule and can continue participation through the post treatment follow-up phase of the study.

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 or behavioral reasons or the inability of the subject to comply with the protocol required schedule of study visits or procedures at a given study site. 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, request the subject to return all unused investigational product(s), request the subject to return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events.

Subjects who wish to withdraw from the study will be allowed to do so at any time. The investigator must determine the primary reason for withdrawal and record it on the case report form. Withdrawal due to adverse event should be distinguished from withdrawal due to insufficient response. A discontinuation due to a serious adverse event must be reported to Pfizer immediately. Every effort must be made to complete the early termination visit appropriate to the phase of the study during which the withdrawal occurred.

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).

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.

6.6. Individual Subject Dosing Stopping Criteria

During the course of the study subjects will be monitored for any clinically significant symptomatic changes. Appropriate referrals (eg, Primary Care Physician (PCP), Mental Health Professional (MHP), or treatment facility) must be made promptly to assure subject safety.

The following individual dosing stopping criteria will be followed:

• Dosing must be stopped if the Clinician believes that continuing dosing will be detrimental to the subject’s mental or physical health;
7. ASSESSMENTS

7.1. Efficacy Assessments

7.1.1. Nicotine Use Inventory

Smoking status will be assessed using the Nicotine Use Inventory (NUI). The NUI will be used to collect the information of cigarette or other nicotine use during the study. The NUI will be completed at all post-randomization clinical visits and telephone contacts.

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

In order to confirm the efficacy reported in the NUI, an end-expiratory exhaled carbon monoxide (exhaled CO) will be measured at each clinic visit. Subjects with an exhaled CO >10 ppm will be classified as a smoker regardless of their self-reported abstinence status.

7.1.3. Minnesota Nicotine Withdrawal Scale (MNWS)

The Minnesota Nicotine Withdrawal Scale was developed to assess craving and nicotine withdrawal symptoms in cigarette smokers. It consists of nine items and captures information on the urge to smoke (one item), irritability (one item), anxiety (one item), concentration (one item), restlessness (one item), appetite (one item), depressed mood (one item) and insomnia (two items) using a 5-point Likert scale where scores range from 0 (not at all) to 4 (extreme). This questionnaire was developed to be self-administered and refers to the 24-hour period that immediately precedes the administration of the scale. The MNWS will be first administered at the Baseline Visit and then at Weeks 4, 8, 12, 15, 18, 24, ET24 and 26. Subjects will be instructed to complete this scale based on symptoms over the previous 24 hours.

7.1.4. Modified Cigarette Evaluation Questionnaire (mCEQ)

The rewarding effects associated with smoking will be measured with the Modified Cigarette Evaluation Questionnaire. The mCEQ is a set of 12 self-administered questions using a 7-point rating scale with scores ranging from 1 (not at all) to 7 (extremely). It is administered to only those subjects who smoked since the last visit or since the last time they completed the form, and it requires subjects to refer to the last time they smoked. The mCEQ will be first administered at the Baseline Visit and then at Weeks 4, 8, 12, 15, 18, 24, ET24 and 26.
7.2. Safety Assessments

7.2.1. Physical Examination

Physical examinations will be performed at the screening and baseline visits and at Week 24 visit or at the termination visit before the end of the treatment phase (ET\textsubscript{24}).

7.2.2. Body Weight and Height

Body weight will be measured at the screening and baseline visits and at the Weeks 12 and 24 visits (or ET\textsubscript{24}). Height will be measured at the screening visit. Both will be measured in indoor clothing without shoes.

7.2.3. Blood Pressure and Heart Rate

Sitting blood pressure and heart rate will be recorded at the screening and baseline visits and at the Weeks 12 and 24 visits (or ET\textsubscript{24}). Blood pressure will be measured by using an appropriate sized cuff with a manual or automated/semi-automated sphygmomanometer and recorded to the nearest mmHg. All blood pressure measurements are to be taken in the dominant arm. Heart rate will be measured in the brachial/radial artery for at least 30 seconds.

7.2.4. Electrocardiogram

A 12-lead electrocardiogram will be obtained at the screening visit at the research site. The Principal Investigator is responsible for ECG interpretation and for assignation of clinical significance.

7.2.5. Laboratory Testing

All blood safety tests listed below (hematology and chemistry) will be performed at the screening visit (within 3-10 days prior to randomization). Urine drug screening will be done at the Screening visit and at the Baseline visit at the site and may be performed at other visits at the investigator’s discretion.

**Blood chemistry**: sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, inorganic phosphorus, SGOT (AST), SGPT (ALT), LDH, alkaline phosphatase, total bilirubin, cholesterol, triglycerides, albumin, and total protein.

**Hematology**: hemoglobin, hematocrit, RBC count, WBC count and differential, and platelet count.

**Urine pregnancy test** will be performed for women of childbearing potential at screening and baseline, and Weeks 12 and 24 visits (or ET\textsubscript{24}). Additional pregnancy test will be done whenever one menstrual cycle is missed during treatment or potential pregnancy is otherwise suspected. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.
7.2.6. Other Safety Assessments

At the Screening Visit and at all subsequent clinic visits, the Columbia Suicide-Severity Rating Scale (C-SSRS) Appendix 5 will be administered by trained personnel (training will be provided to site staff) to evaluate suicidal ideation and behavior. Also at the Screening Visit the Suicide Behavior Questionnaire-Revised (SBQ-R) Appendix 3 will be self-administered by the subject to evaluate suicidality and risk of suicide.

The Neuropsychiatric Adverse Event Interview (NAEI) Appendix 2, will actively inquire about the following type of adverse events: aggression, anxiety, agitation, depression, delusions, dissociative states, feeling abnormal, hallucinations, homicidal ideation, hostility, mania, paranoia, panic, and psychosis. The NAEI will be conducted at all clinic visits beginning with the baseline visit.

The PHQ-9 will be completed by the subject at specified clinic visits and answered by the subject at specified telephone visits. The nine questions elicit information about the frequency and severity of events potentially related to depression.

If a subject has a positive response to any item on the C-SSRS, NAEI or PHQ-9 Appendix 7, a determination will be made by the investigator as to whether this meets criteria for an adverse event. If it does meet criteria as an adverse event it will be recorded on the adverse event pages of the Case Report Form.

Appropriate referrals (eg, Primary Care Physician (PCP), Mental Health Professional (MHP), or treatment facility) must be made promptly to assure subject safety.

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 cannot 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.

7.3. Banking Samples

Subject to IRB/IEC approval/favorable opinion, this study will include an additional research component involving collection of biological samples for de-identified exploratory pharmacogenomics analysis. The Molecular Profiling Supplement to this protocol provides a description of this additional research. Subjects may participate in this study even if they choose not to participate in the sample banking component.
8. ADVERSE EVENT REPORTING

For this study, adverse events (serious and non-serious) should be recorded on the CRF from the time the subject provides informed consent to the last subject visit.

8.1. Adverse Events

All observed or volunteered adverse events 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 serious adverse events, 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, i.e., 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.

8.3. Definition of an Adverse Event

An adverse event 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 adverse events 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 breast feeding;
- Medication error.

8.4. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event 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 adverse event by the investigator or sponsor.

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

A serious adverse event or serious adverse drug reaction 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 adverse event when it is associated with a serious adverse event.

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 adverse event 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.

8.6. Hospitalization

Adverse events 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 adverse event is not in itself a serious adverse event. Examples include:

• Admission for treatment of a preexisting condition not associated with the development of a new adverse event 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 adverse event (eg, for elective cosmetic surgery);
• Hospitalization for observation without a medical AE;
• Pre-planned treatments or surgical procedures should be noted in the baseline 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 adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event, and the resulting appendectomy should be recorded as treatment of the adverse event.

8.7. Severity Assessment

Table 2. Severity Assessment

<table>
<thead>
<tr>
<th>Adjective</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 adverse event. A severe event is not necessarily a serious event. 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 adverse events (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 adverse event; 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 a serious adverse event 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 serious adverse event 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 adverse event 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 serious adverse events 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 serious adverse events. 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 6.5 Subject Withdrawal)

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

When a subject withdraws due to a serious adverse event, the serious adverse event 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 adverse events and all adverse events spontaneously reported by the study subject. In addition, each study subject will be questioned about adverse events.
8.11.1. Neuropsychiatric Adverse Events

Anger, frustration, irritability, dysphoria, depressed mood, depression, difficulty concentrating, drowsiness/decreased alertness, impatience, insomnia, sleep disturbances, restlessness, and increased or vivid dreams are among the symptoms that are known to be associated with nicotine withdrawal (Hughes 2007) and as such may be expected to occur in a study of smoking cessation regardless of the type of intervention. These and other symptoms may meet the criteria for adverse events or serious adverse events and should be reported as such, and causality assessments should reflect consideration of study treatments, nicotine withdrawal, or other causes.

Serious neuropsychiatric symptoms have been reported in patients being treated with varenicline in post marketing experience and have been reported to the Pfizer pharmacovigilance group. Some cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking; though some of these symptoms have occurred in patients who continued to smoke. A causal relationship between varenicline and these symptoms has not been established, however, in some reports an association could not be excluded.

8.12. Reporting Requirements

Each adverse event is to be assessed to determine if it meets the criteria for serious adverse events. If a serious adverse event occurs, expedited reporting will follow local and international regulations, as appropriate.

8.12.1. Serious Adverse Event Reporting Requirements

If a serious adverse event occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event. In particular, if the serious adverse event is fatal or life threatening, notification to Pfizer must be made immediately, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event 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 a serious adverse event 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 adverse event.

For all serious adverse events, 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 adverse event case report form. In general, this will include a description of the adverse event 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 adverse events will be reported on the adverse event page(s) of the CRF. It should be noted that the form for collection of serious adverse event information is not the same as the adverse event CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same adverse event term should be used on both forms. Adverse events should be reported using concise medical terminology on the CRFs as well as on the form for collection of serious adverse event 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 (SAP), which will be dated and maintained by the sponsor. This document may modify plans outlined in the protocol; however, any major modifications of the endpoint definitions and/or their analyses will also be reflected in a protocol amendment.

9.1. Sample Size Determination

Though inferences will be model based, the following power/sample size calculations have been derived assuming a comparison of varenicline versus placebo using a two-group continuity-corrected 2-sided Chi-Square test at the 0.05 significance level.

A total of approximately 1404 randomized subjects in a 1:1 ratio (702 in each group) will provide at least 90% power to detect a difference between the varenicline and placebo groups of 10.3% in the primary endpoint of CA from Week 15 to Week 24, assuming a true CAR of 6.9% for placebo and 17.2% for varenicline (odds ratio of at least 2.8). This sample size will also provide at least 90% power to detect a difference in CA from Week 21 through Week 24 assuming a true placebo rate of 8.9% and varenicline rate of 23.0% (odds ratio of at least 3.0). This sample size will also provide 90% power to detect a difference in CA from Week 21 through Week 52 assuming a true placebo rate of 4.7% and varenicline rate of 9.3% (odds ratio of at least 2.0).

Estimates of clinically meaningful varenicline and placebo CA rate from weeks 15 through 24, 4-week CA rate from weeks 21 through 24, and CA rates from weeks 21 through 52 are based on response rates and corresponding 95% odds ratio confidence intervals from bupropion and NRT literature (Hatsukami, 2004 Cochrane, Lindson, 2010)2, 5 and historical varenicline studies in the motivated to quit abruptly population (Cochrane, Cahill, 2008).1
9.2. Efficacy Analysis

The primary efficacy inference of this study is to evaluate the hypothesis that varenicline is superior to placebo for the 10-week CAR from Weeks 15 through Week 24. The primary efficacy endpoint CA for Week 15 through Week 24 will be obtained through reports of cigarette or other nicotine use since the last study visit confirmed by measurement of end-expiratory exhaled CO. If any CO measurement at a particular time point is >10 ppm, the subject will be considered a smoker at that time point.

The key secondary efficacy inference endpoints of CA from smoking are to compare the two treatment groups’ CARs in the last 4 weeks of treatment (Week 21 to Week 24) and the CA from Week 21 through the non-treatment follow-up period (Week 52). These endpoints will be based on subject self-report, confirmed by end-expiratory exhaled CO measurements at clinic visits.

Additional secondary efficacy endpoints will include:

- 7-day point prevalence of smoking cessation at Weeks 12, 24 and 52;
- 4-week point prevalence of smoking cessation at Week 52.

These efficacy endpoints will be based on subject self-report (NUI), confirmed by end-expiratory exhaled CO measurements at clinic visits. Subjects who discontinue the study are assumed to be smokers from the time point of discontinuation through the end of the study.

9.2.1. Analysis of Primary and Secondary Endpoints

The primary efficacy analysis population will be the all randomized subjects.

To support the robustness of the conclusions made on the “All Randomized” population, the primary endpoint and key secondary endpoint analyses will also be performed in the “Completer subjects” population (subset of the all randomized population who have at least 80% treatment compliance as measured by having any dose of study medication for at least 80% of the planned number of days in the trial treatment period).

Data collected at baseline (eg, demographics, smoking history, and baseline nicotine dependence) and other time points will be summarized by treatment group using descriptive statistics. Descriptive statistics, such as the mean, median, standard deviation, and range will be used to summarize continuous variables, and counts and percentages for categorical variables. In addition to tabulated descriptive statistics, graphical data displays may be used.

Logistic regression models will be used in the analyses of primary and key secondary endpoints. The model will include treatment and center as independent variables. Treatment by center interaction will be investigated; however, the reported p-values will be based on the main effects model.
In order to preserve the type I family-wise error rate of 0.05, a step-down procedure will be used for the analysis of the primary and the key secondary endpoints. The hierarchy of comparisons will be:

1. CA for Weeks 15 through 24.
2. 4-week CA for Weeks 21 through 24.
3. CA for Weeks 21 through 52.

Statistical significance will be declared for each hypothesis in the ordered list until a p-value $>0.05$ is obtained, at which point the hypothesis will be declared to not be statistically significant.

Logistic regression will be used for the analyses of other binary secondary endpoints. All other secondary endpoint statistical tests will be two-sided and will use a 0.05 level of significance. P-values will be reported, provided the primary endpoint is met, with no adjustments for the analysis of multiple secondary endpoints.

In addition, subgroup summaries and analyses may be completed, when the number of subjects in the subgroups permits, to evaluate the consistency of the efficacy in the primary and key secondary endpoints over demographic and other baseline characteristics.

Additional analyses may be performed adjusting for baseline covariates as additive terms to the primary model, if necessary. Also, models adjusting for a country or region covariate instead of a center covariate may be explored. Results from any additional analyses will not be used as a substitute for the planned analyses, but may be used as supplemental information for the study report.

9.3. Safety Analysis

Laboratory and other safety data will be subjected to clinical review and summarized, using Pfizer Data Standards, by frequencies of events and mean changes from Baseline.

The following summaries will be used to assess the safety of subjects in this study.

- The incidence and type of AEs;
- The incidence and type of SAEs;
- Change from Baseline in the PHQ-9;
- The change from Baseline in vital signs;
- The incidence of clinically significant vital sign parameters.
All safety analyses will use the population of all subjects who received at least 1 dose of study drug.

Data from the SBQ-R and the C-SSRS will be summarized.

9.4. Interim Analysis

No unblinded interim analysis is planned for this study.

9.5. Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be responsible for the ongoing monitoring of the safety of subjects in the study in accordance with their charter. The DMC will review serious (SAE) and non-serious adverse events (AEs) by treatment assignments periodically or as needed. Any recommendation made by the committee to alter the conduct of the study will be forwarded to Pfizer for final decision.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and 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 case report form (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 forms, copies of all CRFs, serious adverse event 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 ICH, local regulations, or as specified in the Clinical Study Agreement, 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, Molecular Profiling Supplement, informed consent forms, 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 Good Clinical Practice (International Conference on Harmonization 1996), and the Declaration of Helsinki (World Medical Association 2008).

In addition, the study will be conducted in accordance with the protocol, the International Conference on Harmonisation guideline on Good Clinical Practice, 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. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data.

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

The informed consent form 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 form.

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 the Last Subject Last Visit.

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 48 hours. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

Publication of study results is discussed in the Clinical Study Agreement.

15.1. Communication of Results by Pfizer

Pfizer fulfils 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), ie, 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 the discontinuation of the program (if there are no plans for outlicensing or within two years if outlicensing plans have not been 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. Fagerström Test for Nicotine Dependence

<table>
<thead>
<tr>
<th>Questions</th>
<th>Answers</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How soon after you wake up do you smoke your first cigarette?</td>
<td>Within 5 minutes</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>6-30 minutes</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>31-60 minutes</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>After 60 minutes</td>
<td>0</td>
</tr>
<tr>
<td>2. Do you find it difficult to refrain from smoking in places where it is forbidden eg, in church, at the library, in the cinema, etc.?</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>3. Which cigarette would you hate most to give up?</td>
<td>The first one in the morning</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Any other</td>
<td>0</td>
</tr>
<tr>
<td>4. How many cigarettes/day do you smoke?</td>
<td>10 or less</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>11-20</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>21-30</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>31 or more</td>
<td>3</td>
</tr>
<tr>
<td>5. Do you smoke more frequently during the first hours after waking than during the rest of the day?</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>6. Do you smoke if you are so ill that you are in bed most of the day?</td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0</td>
</tr>
</tbody>
</table>
## Appendix 2. Neuropsychiatric Adverse Events Interview (NAEI)

<table>
<thead>
<tr>
<th>Neuropsychiatric Adverse Events Interview Questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you felt depressed (sad, blue, down, empty, as if you didn’t care)?</td>
</tr>
<tr>
<td>Do you find that you have lost interest in things or get less pleasure from things that you used to enjoy?</td>
</tr>
<tr>
<td>Have you cried or felt like crying?</td>
</tr>
<tr>
<td>Have you been worried or scared?</td>
</tr>
<tr>
<td>Have you been nervous or anxious?</td>
</tr>
<tr>
<td>Have you felt panicky at all?</td>
</tr>
<tr>
<td>Some people have panic attacks when they suddenly feel very frightened and have physical symptoms like heart palpitations (your heart is pounding and/or beating rapidly), shortness of breath and chest pains. Have you had this?</td>
</tr>
<tr>
<td>Have you had times when you felt extremely agitated?</td>
</tr>
<tr>
<td>Have you had times when you felt extremely anxious like you had to be always moving or even pacing?</td>
</tr>
<tr>
<td>Have you had times when you felt like you had to be always moving or even pacing?</td>
</tr>
<tr>
<td>Have you felt unusually cheerful, or happy, not just your normal self, so that other people noticed?</td>
</tr>
<tr>
<td>Have you had much more energy than usual to do things?</td>
</tr>
<tr>
<td>Have you needed less sleep than usual to feel rested?</td>
</tr>
<tr>
<td>Have you felt hostile towards others?</td>
</tr>
<tr>
<td>Have you been involved in any serious arguments or fights?</td>
</tr>
<tr>
<td>Have you had the urge to injure or harm someone?</td>
</tr>
<tr>
<td>Have you felt that people have been talking about you?</td>
</tr>
<tr>
<td>Have you felt that someone may be after you, or trying to harm you in some way?</td>
</tr>
<tr>
<td>Has there been anything unusual about the way things look or sound or smell?</td>
</tr>
<tr>
<td>Question</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>• Have you heard things that other people couldn’t hear, like noises or</td>
</tr>
<tr>
<td>voices of people talking when there was no one around?</td>
</tr>
<tr>
<td>• Have you seen things that other people couldn’t see?</td>
</tr>
<tr>
<td>Has your mind been playing tricks on you in any way?</td>
</tr>
<tr>
<td>Have you had any ideas that other people might not understand or might</td>
</tr>
<tr>
<td>find strange?</td>
</tr>
<tr>
<td>Have things seemed unreal to you?</td>
</tr>
<tr>
<td>Have you felt that you are detached from or have trouble connecting with</td>
</tr>
<tr>
<td>other people?</td>
</tr>
<tr>
<td>Have you felt strange or unnatural in any other way?</td>
</tr>
</tbody>
</table>

**Neuropsychiatric Adverse Events Interview (NAEI) Guidelines**

**General Overview & Background on the NAEI**

The NAEI has been designed as a semi-structured interview to systematically assess the presence and severity of specific neuropsychiatric symptoms as part of the adverse event data collection process. The NAEI is used at Baseline to detect symptoms that are present at the time of the subject’s entry into this clinical trial and at follow-up visits to prospectively monitor emergent symptoms. The goal is to facilitate the collection of information relevant to specific neuropsychiatric events of interest in a standardized manner. Standardizing the way in which such information is collected in a clinical trial optimizes reliability and validity across sites and clinicians.

The NAEI is intended to guide the interviewer in determining whether a symptom is present, and then, if it is, clinically significant. In assessing whether a symptom's “clinical significant”, it is important to examine the:

1. Frequency and duration of the symptom.
2. Severity of the symptom.

If the patient responds affirmatively to questions about a specific NAEI symptom, the symptom then must be evaluated by the investigator for clinical presentation and severity and recorded as an adverse event (AE) or serious adverse event (SAE) if warranted. AEs are graded according to their intensity (mild, moderate, or severe) by examining the degree of functional impairment associated with them as per instructions in the protocol. 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. For adverse events with a causal relationship to the investigational product, follow-up by the investigator is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment. Refer to Protocol Section 8 for more information on both AE and SAE reporting.

The determination whether a symptom is an adverse event and therefore warrants an AE report should always be based on the steps outlined in the figure below:

These administration instructions are intended to help interviewers use the NAEI correctly. Sites are responsible for following these guidelines throughout the course of the study. Sites should keep a copy of these guidelines handy to refer to as needed.

A worksheet for the NAEI interview has been developed and made available to sites to facilitate its use. The worksheet is used for both the baseline and follow-up visits. The interviewer should take notes on the worksheet to assist with AE reporting if needed and to refer to during future visits.

**INTERVIEWER QUALIFICATIONS**

The NAEI interview should be conducted by a staff person at the site who has completed training on the NAEI. Only interviewers who have completed the formal training on the NAEI to Pfizer’s standards can administer it for this trial.

If a site needs additional training for a new interviewer, they must contact Pfizer to make arrangements for the necessary training. No interviewer should administer the NAEI without the appropriate training.

Note that where possible, sites are strongly encouraged to have the same individual conduct the volunteered AE collection, the NAEI interview, and the C-SSRS.

Sites should make every effort to keep the same interviewer for each subject over the course of the trial.

**Time Period to be Rated**

At Baseline, symptoms should be assessed for the past two (2) weeks. At follow-up visits, the time period to be rated is since the last clinic visit.

The interviewer should be careful when asking questions to make sure the subject is clear on the time period being rated. It may be helpful to frame questions by frequently reminding the subject of the time frame “In past 2 weeks” (at baseline) or “Since your last visit” (at follow-up) and by probing to make sure the symptoms described did occur during the time period in question (e.g., at baseline asking, “Was that during the past 2 weeks?”).
Materials Needed to Complete the NAEI

The NAEI guidelines should always be available for reference.

In addition, at all visits after the baseline visit, the interviewer should have at hand:

- The subject’s AE log worksheet;
- Previously completed NAEI worksheets.

Order of Assessment

The assessment sequence for this trial should be done in the following order:

1. Volunteered AE report – opening question on how the subject has been feeling in general;
2. Follow up on previously reported AEs that are still ongoing;
3. NAEI;
4. Columbia Suicide Severity Rating Scale.
5. PHQ-9 (if done at that visit)

Volunteered AE report: The collection of volunteered AE reports should follow the site’s usual procedures. Generally this is done by asking the subject how s/he has been feeling in general. During the collection of volunteered AE information, the interviewer should be careful to ask sufficient follow-up questions to determine the clinical significance of the reported event and therefore whether an AE report is warranted.
### Appendix 3. Suicide Behaviors Questionnaire-Revised (SBQ-R)

**Instructions:** Please check the number beside the statement or phrase that best applies to you.

1. **Have you ever thought about or attempted to kill yourself?** (check one only)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Never</td>
</tr>
<tr>
<td>2.</td>
<td>It was just a brief passing thought</td>
</tr>
<tr>
<td>3a.</td>
<td>I have had a plan at least once to kill myself but did not try to do it</td>
</tr>
<tr>
<td>3b.</td>
<td>I have had a plan at least once to kill myself and really wanted to die</td>
</tr>
<tr>
<td>4a.</td>
<td>I have attempted to kill myself, but did not want to die</td>
</tr>
<tr>
<td>4b.</td>
<td>I have attempted to kill myself, and really hoped to die</td>
</tr>
</tbody>
</table>

2. **How often have you thought about killing yourself in the past year?** (check one only)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Never</td>
</tr>
<tr>
<td>2.</td>
<td>Rarely (1 time)</td>
</tr>
<tr>
<td>3.</td>
<td>Sometimes (2 times)</td>
</tr>
<tr>
<td>4.</td>
<td>Often (3-4 times)</td>
</tr>
<tr>
<td>5.</td>
<td>Very Often (5 or more times)</td>
</tr>
</tbody>
</table>

3. **Have you ever told someone that you were going to commit suicide, or that you might do it?** (check one only)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>No</td>
</tr>
<tr>
<td>2a.</td>
<td>Yes, at one time, but did not really want to die</td>
</tr>
<tr>
<td>2b.</td>
<td>Yes, at one time, and really wanted to do it</td>
</tr>
<tr>
<td>3a.</td>
<td>Yes, more than once, but did not want to do it</td>
</tr>
<tr>
<td>3b.</td>
<td>Yes, more than once, and really wanted to do it</td>
</tr>
</tbody>
</table>
4. **How likely is it that you will attempt suicide someday?** (check one only)

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0.</td>
<td>Never</td>
<td>4.</td>
</tr>
<tr>
<td>1.</td>
<td>No chance at all</td>
<td>5.</td>
</tr>
<tr>
<td>2.</td>
<td>Rather unlikely</td>
<td>6.</td>
</tr>
<tr>
<td>3.</td>
<td>Unlikely</td>
<td></td>
</tr>
</tbody>
</table>

Appendix 4. 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?
Appendix 5. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline


Disclaimer: This scale is intended for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of Suicidality depends on clinical judgement.

<table>
<thead>
<tr>
<th>SUICIDAL IDEATION</th>
<th>Lifetime – Time He/She Felt Most Suicidal</th>
</tr>
</thead>
</table>

1. **Wish To Be Dead**

Have you wished you were dead or wished you could go to sleep and not wake up? Frequency of ideation _____

If yes, describe.

2. **Non-Specific Active Suicidal Thoughts**

Have you actually had any thoughts of killing yourself? Frequency of ideation _____

If yes, describe.

3. **Active Suicidal Ideation with Any Methods (not Plan) without Intent to Act**

Have you been thinking about how you might do this? Frequency of ideation _____

If yes, describe.

4. **Active Suicidal Ideation with Some Intent to Act, without Specific Plan**

Have you had these thoughts and had some intention of acting on them? Frequency of ideation _____

If yes, describe.

5. **Active Suicidal Ideation with Specific Plan and Intent**

Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan? Frequency of ideation _____

If yes, describe.
## INTENSITY OF IDEATION

The following features should be rated with respect to both most common and most severe types of ideation. Ask about time he/she was feeling the most suicidal. Only rate most common if most severe and most common are different.

<table>
<thead>
<tr>
<th>Ideation Type</th>
<th>Type # (1-5)</th>
<th>Description of Ideation</th>
<th>Lifetime – Time He/She Felt Most Suicidal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most Common Ideation:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most Severe Ideation:</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Frequency

How many times have you had these thoughts?

1. Less than once a week
2. Once a week
3. 2-5 times in week
4. Daily or almost daily
5. Many times each day

### Duration

When you have the thoughts how long do they last?

1. Fleeting – few seconds or minutes
2. Less than 1 hour/some of the time
3. 1-4 hours/a lot of time
4. 4-8 hours/most of day
5. More than 8 hours/persistent or continuous
**Controllability**

Could/can you stop thinking about killing yourself or wanting to die if you want to?

1. Easily able to control thoughts
2. Can control thoughts with little difficulty
3. Can control thoughts with some difficulty
4. Can control thoughts with a lot of difficulty
5. Unable to control thoughts
0. Does not attempt to control thoughts

**Deterrents**

Are there things – anyone or anything (eg, family, religion, pain of death) – that stopped you from wanting to die or acting on thoughts of committing suicide?

1. Deterrents definitely stopped you from attempting suicide
2. Deterrents probably stopped you
3. Uncertain that deterrents stopped you
4. Deterrents most likely did not stop you
0. Does not apply, wish to die only

**Reasons for Ideation**

What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end pain or stop the way you were feeling (in other words you couldn’t go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?

1. Completely to get attention, revenge or a reaction from others
2. Mostly to get attention, revenge or a reaction from others
3. Equally to get attention, revenge or a reaction from others and to end/stop the pain
4. Mostly to end or stop the pain (you couldn’t go on living with the pain or how you were feeling).
5. Completely to end or stop the pain (you couldn’t go on living with the pain or how you were feeling).
SUICIDAL BEHAVIOR
(Check all that apply, so long as these are separate events; must ask about all types)

Actual Attempt:

Have you made a suicide attempt? Yes/No

Have you done anything to harm yourself?

Have you done anything dangerous where you could have died?

What did you do?

Did you _____ as a way to end your life?

Did you want to die (even a little) when you _____?

Were you trying to end your life when you _____?

Or did you think it was possible you could have died from _____?

Or did you do it purely for other reasons / without any intention of killing your self (like to relieve stress, feel better, get sympathy, or to get something else to happen)? (Self-injurious behavior without suicidal intent)

If yes, describe.

Has the subject engaged in Non-Suicidal Self-Injurious Behavior? Yes/No

Interrupted Attempt:

Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything? Yes/No

If yes, describe.

 aborted _____

Aborted Attempt:

Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything? Yes/No

If yes, describe.

Total # of interrupted _____

Total # of attempts _____
Preparatory Acts or Behavior:

Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?

Yes/No

If yes, describe.

Suicidal Behavior:

Suicidal behavior was present during the assessment period?

Yes/No

If yes, describe.

Completed Suicide:

Yes/No
<table>
<thead>
<tr>
<th>Actual Lethality/Medical Damage:</th>
<th>0. No physical damage or very minor physical damage (eg, surface scratches).</th>
<th>Enter Code</th>
<th>Enter Code</th>
<th>Enter Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Minor physical damage (eg, lethargic speech; first-degree burns; mild bleeding; sprains).</td>
<td>Enter Code</td>
<td>Enter Code</td>
<td>Enter Code</td>
<td></td>
</tr>
<tr>
<td>2. Moderate physical damage; medical attention needed (eg, conscious but sleepy, somewhat responsive; second degree burns; bleeding of major vessel).</td>
<td>Enter Code</td>
<td>Enter Code</td>
<td>Enter Code</td>
<td></td>
</tr>
<tr>
<td>3. Moderately severe physical damage; medical hospitalization and likely intensive care required (eg, comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures).</td>
<td>Enter Code</td>
<td>Enter Code</td>
<td>Enter Code</td>
<td></td>
</tr>
<tr>
<td>4. Severe physical damage; medical hospitalization with intensive care required (eg, comatose without reflexes; third degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area).</td>
<td>Enter Code</td>
<td>Enter Code</td>
<td>Enter Code</td>
<td></td>
</tr>
<tr>
<td>5. Death</td>
<td>Enter Code</td>
<td>Enter Code</td>
<td>Enter Code</td>
<td></td>
</tr>
</tbody>
</table>

**Potential Lethality: Only Answer if Actual Lethality = 0**

0 = Behavior not likely to result in injury

1 = Behavior likely to result in injury but not likely to cause death

2 = Behavior likely to result in death despite available medical care

Definitions of behavioral suicidal events in this scale are based on those used in The Columbia Suicide History Form, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY 10032. (Oquendo M. A.; Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M. B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 – 130, 2003.)

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries contact posnerk@childpsych.columbia.edu.
Appendix 6. COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit


Disclaimer: This scale is intended for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of Suicidality depends on clinical judgement.

**SUICIDAL IDEATION**

<table>
<thead>
<tr>
<th>Since Last Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ask questions 1 and 2. If both are negative, proceed to “Suicidal Behavior” section. If the answer to question 2 is “yes,” ask questions 3, 4 and 5.</strong></td>
</tr>
</tbody>
</table>

1. **Wish To Be Dead**

Have you wished you were dead or wished you could go to sleep and not wake up? Frequency of ideation ______

If yes, describe.

2. **Non-Specific Active Suicidal Thoughts**

Have you actually had any thoughts of killing yourself? Frequency of ideation ______

If yes, describe.

3. **Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act**

Have you been thinking about how you might do this? Frequency of ideation ______

If yes, describe.

4. **Active Suicidal Ideation with Some Intent to Act, without Specific Plan**

Have you had these thoughts and had some intention of acting on them? Frequency of ideation ______

If yes, describe.

5. **Active Suicidal Ideation with Specific Plan and Intent**

Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan? Frequency of ideation ______

If yes, describe.
INTEENSITY OF IDEATION

The following features should be rated with respect to both most common and most severe types of ideation. Ask about time he/she was feeling the most suicidal. Only rate most common if most severe and most common are different.

Since Last Visit

<table>
<thead>
<tr>
<th>Ideation Type</th>
<th>Type # (1-5)</th>
<th>Description of Ideation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most Common Ideation:</td>
<td>________________</td>
<td>Most Common</td>
</tr>
<tr>
<td>Most Severe Ideation:</td>
<td>________________</td>
<td>Most Severe</td>
</tr>
</tbody>
</table>

**Frequency**

How many times have you had these thoughts?

1. Less than once a week
2. Once a week
3. 2-5 times in week
4. Daily or almost daily
5. Many times each day

**Duration**

When you have the thoughts how long do they last?

1. Fleeting – few seconds or minutes
2. Less than 1 hour/some of the time
3. 1-4 hours/a lot of time
4. 4-8 hours/most of day
5. More than 8 hours/persistent or continuous

**Controllability**

Could/can you stop thinking about killing yourself or wanting to die if you want to?

1. Easily able to control thoughts
2. Can control thoughts with little difficulty
3. Can control thoughts with some difficulty

PFIZER CONFIDENTIAL
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4. Can control thoughts with a lot of difficulty
5. Unable to control thoughts
0. Does not attempt to control thoughts

**Deterrents**

Are there things – anyone or anything (eg, family, religion, pain of death) – that stopped you from wanting to die or acting on thoughts of committing suicide?

1. Deterrents definitely stopped you from attempting suicide
2. Deterrents probably stopped you
3. Uncertain that deterrents stopped you
4. Deterrents most likely did not stop you
0. Does not apply, wish to die only

**Reasons for Ideation**

What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end pain or stop the way you were feeling (in other words you couldn’t go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?

1. Completely to get attention, revenge or a reaction from others
2. Mostly to get attention, revenge or a reaction from others
3. Equally to get attention, revenge or a reaction from others and to end/stop the pain
4. Mostly to end or stop the pain (you couldn’t go on living with the pain or how you were feeling).
5. Completely to end or stop the pain (you couldn’t go on living with the pain or how you were feeling).
### SUICIDAL BEHAVIOR

**(Check all that apply, so long as these are separate events; must ask about all types)**

<table>
<thead>
<tr>
<th>Actual Attempt:</th>
<th>Since Last Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you made a suicide attempt?</td>
<td>Yes/No</td>
</tr>
<tr>
<td>Have you done anything to harm yourself?</td>
<td></td>
</tr>
<tr>
<td>Have you done anything dangerous where you could have died?</td>
<td></td>
</tr>
<tr>
<td>What did you do?</td>
<td>Total # of attempts</td>
</tr>
<tr>
<td>Did you _____ as a way to end your life?</td>
<td></td>
</tr>
<tr>
<td>Did you want to die (even a little) when you _____?</td>
<td></td>
</tr>
<tr>
<td>Were you trying to end your life when you _____?</td>
<td></td>
</tr>
<tr>
<td>Or did you think it was possible you could have died from _____?</td>
<td></td>
</tr>
<tr>
<td>Or did you do it purely for other reasons / without any intention of killing your self (like to relieve stress, feel better, get sympathy, or to get something else to happen)? (Self-injurious behavior without suicidal intent)</td>
<td></td>
</tr>
<tr>
<td>If yes, describe.</td>
<td>Yes/No</td>
</tr>
<tr>
<td>Has the subject engaged in Non-Suicidal Self-Injurious Behavior?</td>
<td></td>
</tr>
</tbody>
</table>

| Interrupted Attempt: | |
| Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything? | Total # of interrupted |
| If yes, describe. | |

| Aborted Attempt: | |
| Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything? | Total # of aborted |
| If yes, describe. | |

| Preparatory Acts or Behavior: | |
| Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)? | Yes/No |
| If yes, describe. | |

| Suicidal Behavior: | |
| Suicidal behavior was present during the assessment period? | Yes/No |
| If yes, describe. | |

| Completed Suicide: | |
| Yes/No |
**ANSWER FOR ACTUAL ATTEMPTS ONLY**

<table>
<thead>
<tr>
<th>Actual Lethality/Medical Damage:</th>
<th>Enter Code</th>
<th>Enter Code</th>
<th>Enter Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>0. No physical damage or very minor physical damage (eg, surface scratches).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Minor physical damage (eg, lethargic speech; first-degree burns; mild bleeding; sprains).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Moderate physical damage; medical attention needed (eg, conscious but sleepy, somewhat responsive; second degree burns; bleeding of major vessel).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Moderately severe physical damage; medical hospitalization and likely intensive care required (eg, comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Severe physical damage; medical hospitalization with intensive care required (eg, comatose without reflexes; third degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area).</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Death</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Potential Lethality: Only Answer if Actual Lethality = 0**

<table>
<thead>
<tr>
<th>Potential Lethality</th>
<th>Enter Code</th>
<th>Enter Code</th>
<th>Enter Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 = Behavior not likely to result in injury</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 = Behavior likely to result in injury but not likely to cause death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 = Behavior likely to result in death despite available medical care</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Definitions of behavioral suicidal events in this scale are based on those used in The Columbia Suicide History Form, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY 10032. (Oquendo M. A.; Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M. B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 – 130, 2003.)

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Appendix 7. PATIENT HEALTH QUESTIONNAIRE - 9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? (use ☐ to indicate your answer)

<table>
<thead>
<tr>
<th>Problem</th>
<th>Not at all (0)</th>
<th>Several days (1)</th>
<th>More than half the days (2)</th>
<th>Nearly every day (3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Little interest or pleasure in doing things</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>2. Feeling down, depressed, or hopeless</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>3. Trouble falling or staying asleep, or sleeping too much</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>4. Feeling tired or having little energy</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>5. Poor appetite or overeating</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>7. Trouble concentrating on things, such as reading the newspaper or watching television</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>8. Moving or speaking so slowly that other people could have noticed. Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>9. Thoughts that you would be better off dead, or of hurting yourself in some way</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

<table>
<thead>
<tr>
<th>Difficulty</th>
<th>Not difficult at all</th>
<th>Somewhat difficult</th>
<th>Very difficult</th>
<th>Extremely difficult</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

PHQ-9 is adapted from PRIME MD TODAY, developed by Drs Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke, and colleagues, with an educational grant from Pfizer Inc. For research information, contact Dr Kroenke at kkroenke@regenstrief.org. Use of the PHQ-9 may only be made in accordance with the Terms of Use available of http://www.pfizer.com. Copyright ©1999 Pfizer Inc. All rights reserved. PRIME MD TODAY is a trademark of Pfizer Inc.
## Appendix 8. Minnesota Nicotine Withdrawal Scale

For each of the following, rate yourself on how you have been feeling over the past twenty-four hours. Mark the number that applies to you.

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>Slight</th>
<th>Moderate</th>
<th>Quite a bit</th>
<th>Extreme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urge to smoke</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Depressed mood</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Irritability, frustration, or anger</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Difficulty concentrating</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Restlessness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Difficulty going to sleep</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Difficulty staying asleep</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
Appendix 9. Modified Cigarette Evaluation Questionnaire (mCEQ)

If you have smoked since your last visit (or last completed this form), please mark the number that best represents how smoking made you feel.

1. Was smoking satisfying?
   1-not at all 2-very little 3-a little 4-moderately 5-a lot 6-quite a lot 7-extremely

2. Did cigarettes taste good?
   1-not at all 2-very little 3-a little 4-moderately 5-a lot 6-quite a lot 7-extremely

3. Did you enjoy the sensations in your throat and chest?
   1-not at all 2-very little 3-a little 4-moderately 5-a lot 6-quite a lot 7-extremely

4. Did smoking calm you down?
   1-not at all 2-very little 3-a little 4-moderately 5-a lot 6-quite a lot 7-extremely

5. Did smoking make you feel more awake?
   1-not at all 2-very little 3-a little 4-moderately 5-a lot 6-quite a lot 7-extremely

6. Did smoking make you feel less irritable?
   1-not at all 2-very little 3-a little 4-moderately 5-a lot 6-quite a lot 7-extremely

7. Did smoking help you concentrate?
   1-not at all 2-very little 3-a little 4-moderately 5-a lot 6-quite a lot 7-extremely

8. Did smoking reduce your hunger for food?
   1-not at all 2-very little 3-a little 4-moderately 5-a lot 6-quite a lot 7-extremely

9. Did smoking make you dizzy?
   1-not at all 2-very little 3-a little 4-moderately 5-a lot 6-quite a lot 7-extremely

10. Did smoking make you nauseous?
    1-not at all 2-very little 3-a little 4-moderately 5-a lot 6-quite a lot 7-extremely

11. Did smoking immediately relieve your craving for a cigarette?
    1-not at all 2-very little 3-a little 4-moderately 5-a lot 6-quite a lot 7-extremely

12. Did you enjoy smoking?
    1-not at all 2-very little 3-a little 4-moderately 5-a lot 6-quite a lot 7-extremely.