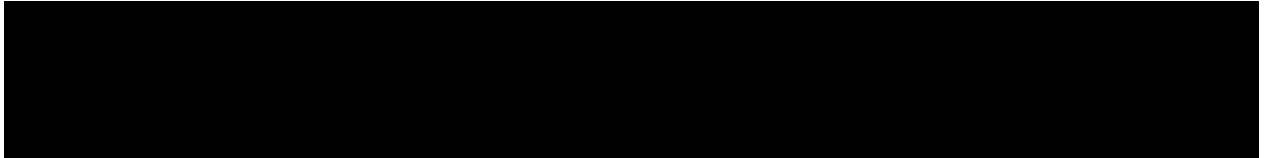




## **CLINICAL PROTOCOL**

### **A TWELVE-WEEK, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, DOSE-RANGING STUDY WITH FOLLOW-UP EVALUATING THE SAFETY AND EFFICACY OF VARENICLINE FOR SMOKING CESSATION IN HEALTHY ADOLESCENT SMOKERS**

<b>Compound:</b>	CP-526,555
<b>Compound Name (if applicable):</b>	Varenicline
<b>US IND Number (if applicable):</b>	58,994
<b>Protocol Number:</b>	A3051073
<b>Phase:</b>	4



### Document History

Version	Version Date	Summary of Changes
Amendment 5	09 July 2012	<p>The protocol was amended to comply with Pfizer's revised template and to include administrative clarifications. There are no changes to study design, visit schedule, procedures, treatments and data collection except as noted below for Section 8.3.</p> <p>Section 4.1 – Inclusion criteria 7 and 8 revised to increase more detailed information regarding women of childbearing potential.</p> <p>Section 5.6 – Medication Errors clarified and added as a potentially reportable adverse event.</p> <p>Section 6.4 – Language revised for clarification on the importance of keeping subjects in the study and to follow up all unresolved AEs.</p> <p>Section 8.1 Language revised to comply with Pfizer protocol template.</p> <p>Section 8.3 Drug dependency and drug abuse added as examples of reportable AEs and removed from signs and symptoms resulting from these. Medication errors added.</p> <p>Section 8.6 Language revised to comply with Pfizer protocol template.</p> <p>Section 9.4 Language revised to comply with Pfizer protocol template.</p> <p>Minor administrative clarifications.</p> <p>Section 15.1 Language revised to clarify disclosure of clinical trial results.</p>
Amendment 4	January 20, 2012	<p>Protocol Summary "Safety Assessments" section wording has been slightly modified to improve quality.</p> <p>Section 2.2 Addition of an exploratory subgroup analysis for each dosing group by weight stratum for the primary efficacy endpoint.</p> <p>Safety assessments language slightly modified to improve quality.</p> <p>Section 5.5 Subject dosing card instructions will be supplied to each patient, and subjects will be asked to read, initial, and date to demonstrate comprehension of sun, moon, and other aspects of dosing instructions.</p> <p>Section 8.10 Language modified to stipulate that if female subjects have a positive pregnancy test, they will be enrolled in a pregnancy registry if a pregnancy registry is ongoing at the time of the</p>

		<p>pregnancy.</p> <p>Section 9.1 Addition of an exploratory subgroup analysis for each dosing group by weight stratum for the primary efficacy endpoint.</p>
Amendment 3	23 November 2011	<p>Modify exclusion criteria to indicate that use of psychoactive or psychotropic drugs in the 6 months prior to screening should be discussed with the sponsor, rather than be prohibited (in order to allow consideration of ADHD subjects on Ritalin or Adderall).</p> <p>Correction of inadvertent symbol error made in Section 5.1 while formatting, which showed incorrect dose allocation.</p> <p>Remove specification for use of the COT-One cotinine testing kit.</p>
Amendment 2	09 August 2011	<p>Modify exclusion criteria to indicate that use of psychoactive or psychotropic drugs in the 6 months prior to screening should be discussed with the sponsor, rather than be prohibited (in order to allow consideration of ADHD subjects on Ritalin or Adderall).</p> <p>Correction of inadvertent symbol error made in Section 5.1 while formatting, which showed incorrect dose allocation.</p>
Amendment 1	11 March 2011	<p>Modification of inconsistency between AE reporting period criteria to make timeframe be “informed consent through last visit”.</p> <p>Change of group counseling (Project Ex) to individual counseling according to modified Public Health Service guidelines.</p> <p>Addition of 24 week endpoints to make consistent with other protocols in program.</p> <p>Clarification of dosing instructions.</p> <p>Addition of lower value for range of BMI.</p> <p>Modification of PK section to modify sample processing.</p> <p>Addition of text to indicate this is a PASS study.</p> <p>Deletion of “drug delivery by courier” option.</p> <p>Additional detail in exclusions vis a vis psychological disorders.</p> <p>Addition of mandatory text to include Hy’s Law.</p> <p>Change to Section 8.2 to correct inconsistency between start of AE collection and AE reporting periods.</p>

		Version update for HADs and NUI.
Original protocol	15 September 2010	

## PROTOCOL SUMMARY

The purpose of this study is to evaluate the efficacy, safety, tolerability, and pharmacokinetics of two doses of varenicline in adolescent smokers (12-19 years) in conjunction with age appropriate cessation counseling. The treatment period will be twelve weeks and subjects' smoking status will then be followed for approximately nine months.

### Background

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 which mediates the behavior reinforcing effects of nicotine. Because of its mixed agonist-antagonist properties, varenicline offers the therapeutic benefit of relieving symptoms of nicotine withdrawal and cigarette craving during abstinence while blocking the reinforcing effects of chronic nicotine. Varenicline (Chantix<sup>®</sup>/Champix<sup>®</sup>) was approved as an "aid to smoking cessation treatment" in adults by the FDA in May 2006, and by the EMEA in September 2006, and is now approved in 98 countries worldwide. The approved dose regimen is 1 mg twice daily (1 mg bid) for 12 weeks starting with a 1-week titration. Post-marketing study commitments required under section 2 of the Pediatric Research Equity Act (PREA) include a study to determine whether varenicline, as part of an overall smoking cessation program, is effective in achieving and maintaining smoking cessation in tobacco-addicted adolescents. The current study is considered to be a post-authorization safety study (PASS) in the adolescent population, an age group not included in the current labeling for varenicline.

Phase 2 and Phase 3 clinical trials demonstrated the efficacy and tolerability of varenicline 1 mg BID in more than 3000 adult cigarette smokers, increasing the odds of quitting approximately 4-fold compared with placebo at end of treatment, and 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.<sup>1</sup> Nausea was reported by approximately 30% of patients treated with varenicline 1 mg BID after an initial week of dose titration compared with 10% in patients taking placebo. In patients taking 0.5 mg BID following initial titration, the incidence was 16% compared with 11% for placebo. Nausea was generally described as mild or moderate and often transient.<sup>1</sup>

### 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.

Additionally there have been reports of hypersensitivity reactions and serious skin reactions.

The Single Reference Safety Document for varenicline, where complete information is available, is the most recent Investigator Brochure (IB).

### **Rationale for this study**

Most adult smokers initiated smoking as adolescents. According to the CDC's 2005 Youth Risk Behavior Survey,<sup>2</sup> 23.0% of students in the United States were current cigarette users (ie, had smoked cigarettes on more than one of the 30 days preceding the survey) and 9.4% of students were current frequent cigarette users (ie, had smoked cigarettes on  $\geq 20$  of the 30 days preceding the survey). Among the students who reported current cigarette use, 10.7% had smoked at least 10 cigarettes/day on the days they smoked during the 30 days preceding the survey and 54.6% had tried to quit smoking cigarettes during the 12 months preceding the survey. Continued smoking increases lifetime risk for various cancers, especially lung cancer, cardiovascular diseases, and respiratory diseases.<sup>3</sup> Objective 27-2 of the US Department of Health and Human Services Healthy People 2010 initiative is to reduce the prevalence of current cigarette use among high school students to  $\leq 16\%$ .<sup>4</sup>

The transition from early smoking to nicotine dependence (ND) in adolescents is not fully understood, but similar to adults, intensity and frequency of cigarette use is associated with ND.<sup>5</sup> Past studies of smoking cessation in adolescents defined their target patient population by intensity, frequency and in some cases, duration of cigarette smoking, in an attempt to identify adolescents who were nicotine dependent. The Fagerström Tolerance Questionnaire (FTQ) was modified and validated for use in adolescents age 12-16.<sup>6</sup> The validation of the FTQ with salivary cotinine in adolescents showed good performance for all questions except for "Do you inhale". As this question did not perform well in either adults or adolescents, the authors recommended abbreviating the scale to six questions. These six questions are the same as the six items included in the Fagerstrom Test for Nicotine Dependence (FTND) (Appendix 2) which will be used in this study as an instrument to identify adolescents likely to be nicotine-dependent.

This study will examine whether varenicline, in conjunction with age-appropriate smoking cessation counseling at each clinic visit and telephone contact will be safe and effective in helping adolescents who smoke on average  $\geq 5$  cigarettes per day, to stop smoking.

### **Primary Objective:**

- To evaluate the efficacy, safety, and tolerability of varenicline compared with placebo in adolescent tobacco smokers (aged 12-19 years).

## Endpoints

### Primary efficacy endpoint:

- The 4-week continuous quit rate (CQR) from Week 9 through Week 12 of treatment for varenicline compared with placebo.

### Secondary efficacy endpoints:

- 7-day point-prevalence of smoking abstinence at Weeks 12, 24, and 52;
- Reduction in number of cigarettes smoked at Weeks 12, 24, and 52;
- Continuous abstinence rate from Week 9 through Week 24;
- Continuous abstinence rate from Week 9 through Week 52.

### Safety Assessments:

- Adverse events spontaneously volunteered or observed, adverse events elicited by the Neuropsychiatric Adverse Event Interview (NAEI) ([Appendix 4](#)), Columbia Suicide Severity Rating Scale (C-SSRS), Hospital Anxiety and Depression Scale (HADS), and adverse events associated with safety laboratory tests, or vital signs.

### PK Assessments:

- Varenicline exposure at steady-state in adolescent smokers.

## Statistical Methods

The primary analysis population will be all subjects who took at least one dose of randomized study medication. All significance tests will be two-sided and will use a 0.05 significance level. No adjustments will be made to the nominal p-values for analysis of the multiple efficacy endpoints. Subjects who discontinue the study will be considered smokers for the remainder of the study regardless of their last smoking status evaluation.

For the binary endpoints with planned inferential treatment comparisons, a logistic regression model will be fitted which will include the main effects of strata, treatment group and center as independent variables. Treatment by center interaction will be investigated by an expanded model; however the reported p-values will be based on the main effects model. Analysis of the change from baseline in mean number of cigarettes smoked per day will use analysis of covariance with baseline value, strata, treatment group and center included in the model. The assumptions of the linear model will be examined and if not satisfied, nonparametric methods will be used. There will be no formal inferential analyses of safety assessments. The standard and additional safety data will be summarized by treatment group using descriptive statistics.

**Table 1. SCHEDULE OF ACTIVITIES**

Protocol Activity	SCR	BL	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	ET 12
Informed consent	X														
Medical history	X														
Physical examination	X														
Body Weight and Height (triplicate)	X	X												X	X
Tobacco use history	X														
Nicotine dependence: FTND	X														
Randomization		X													
Target Quit Date (TQD)			X												
Urine Pregnancy test <sup>a</sup>	X	X			X			X			X			X	X
Urine drug test (dipstick at site)	X	X			X			X			X			X	X
Vital Signs (BP/PR)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Non-drug treatment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology & Chemistry	X				X			X						X	X
Pharmacokinetic samples <sup>b</sup>					X			X						X	X
Dispense Medication		X	X	X	X	X	X	X	X	X	X	X	X		
Dosing Record			X	X	X	X	X	X	X	X	X	X	X	X	X
SBQ-R	X														
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HADS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Event Monitoring		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Neuropsychiatric Adverse Event Interview (NAEI)		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Nicotine Use Inventory		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review/distribute Smoking Diary worksheet	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine cotinine at site	X	X									X	X	X	X	X



<b>Protocol Activity</b>	<b>SCR</b>	<b>BL</b>	<b>Wk 1</b>	<b>Wk 2</b>	<b>Wk 3</b>	<b>Wk 4</b>	<b>Wk 5</b>	<b>Wk 6</b>	<b>Wk 7</b>	<b>Wk 8</b>	<b>Wk 9</b>	<b>Wk 10</b>	<b>Wk 11</b>	<b>Wk 12</b>	<b>ET 12</b>
Smoking cessation counseling (~10 min)		X	X	X	X	X	X	X	X	X	X	X	X	X	X

SCR = screening; BL=baseline; Wk=week; ET=early termination; FTND = Fagerstrom Test for Nicotine Dependence; SBQ-R= Suicidal Behaviors Questionnaire-Revised, C-SSRS = Columbia Suicide-Severity Rating Scale; HADS= Hospital and Anxiety Depression Scale;

- a. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations; subjects with a positive pregnancy test during the treatment period will have study drug discontinued but will be encouraged to remain in the study.
- b. A pharmacokinetic sample will be collected at a random time during the clinic visit. The times of study drug dosing for the prior 2 doses as well as the time of the blood drawing will be recorded at each of these visits on the CRF.

### Non-Treatment Follow-Up Schedule

Protocol Activity	Week 13 (clinic visit)	Week 14 (clinic visit)	Week 15 (clinic visit)	Week 16 (clinic visit)	Week 20 (clinic visit)	Weeks 24, 32, 40 and 48 (phone visits)	Weeks 28,36, and 44 (clinic visits )	Week 52-ET (clinic visit)
Nicotine use Inventory	X	X	X	X	X	X	X	X
Urine cotinine at site	X	X	X	X	X		X	X
Review and/or distribute Smoking Diary worksheet	X	X	X	X	X	X	X	X
C-SSRS	X	X	X	X	X		X	X
HADS	X	X	X	X	X		X	X
Adverse Event Monitoring	X	X	X	X	X		X	X
Neuropsychiatric Adverse Event Interview	X	X	X	X	X		X	X
Concomitant Medications	X	X	X	X	X		X	X
Non-drug treatments	X	X	X	X	X		X	X
Smoking cessation counseling (~10 min)	X	X	X	X	X	X	X	X
Discharge from study								X

ET=early termination.

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## 1. INTRODUCTION

### 1.1. Indication

Aid to smoking cessation treatment in age 12-19 year-old adolescent tobacco smokers.

### 1.2. Background and Rationale

Most adult smokers initiated smoking as adolescents. According to the CDC's 2005 Youth Risk Behavior Survey,<sup>2</sup> 23.0% of students in the United States were current cigarette users (ie, had smoked cigarettes on more than one of the 30 days preceding the survey) and 9.4% of students were current frequent cigarette users (ie, had smoked cigarettes on  $\geq 20$  of the 30 days preceding the survey). Among the students who reported current cigarette use, 10.7% had smoked at least 10 cigarettes/day on the days they smoked during the 30 days preceding the survey and 54.6% had tried to quit smoking cigarettes during the 12 months preceding the survey. Continued smoking increases lifetime risk for various cancers, especially lung cancer, cardiovascular diseases, and respiratory diseases.<sup>3</sup> Objective 27-2 of the US Department of Health and Human Services Healthy People 2010 initiative is to reduce the prevalence of current cigarette use among high school students to  $\leq 16\%$ .<sup>4</sup>

The transition from early smoking to nicotine dependence (ND) in adolescents is not fully understood, but similar to adults, intensity and frequency of cigarette use is associated with ND.<sup>5</sup> Past studies of smoking cessation in adolescents defined their target patient population by intensity, frequency and in some cases duration of cigarette smoking in an attempt to identify adolescents who were nicotine dependent. The Fagerström Tolerance Questionnaire (FTQ) was modified and validated for use in adolescents.<sup>6</sup> The validation of the FTQ with salivary cotinine in adolescents showed good performance for all questions except for "Do you inhale". As this question did not perform well in either adults or adolescents the authors recommended abbreviating the scale to six questions. These six questions are the same as the six items included in the Fagerström Test for Nicotine Dependence (FTND) ([Appendix 2](#)) which will be used in this study as an instrument to identify adolescents likely to be nicotine-dependent.

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 which mediates the behavior reinforcing effects of nicotine. Because of its mixed agonist-antagonist properties, varenicline offers the therapeutic benefit of relieving symptoms of nicotine withdrawal and cigarette craving during abstinence while blocking the reinforcing effects of chronic nicotine.

Varenicline (as Chantix<sup>®</sup>) was approved in the United States in May 2006 as an aid to smoking cessation treatment in adults, and by the EMEA in September 2006, and is now approved in 98 countries worldwide. The approved dose regimen is 1 mg twice daily (1 mg bid) for 12 weeks starting with a 1-week titration. Post-marketing study commitments required under section 2 of the Pediatric Research Equity Act (PREA) include a study to determine whether varenicline, as part of an overall smoking cessation program, is effective in achieving and maintaining smoking cessation in tobacco –addicted adolescents.

Postmarketing study commitments required under Section 2 of the Pediatric Research Equity Act (PREA) include a study to determine whether varenicline, as part of an overall smoking cessation program, is effective in achieving and maintaining smoking cessation in tobacco-addicted adolescents. This study is considered to be a PASS study (post-authorization safety study), and is a regulatory commitment.

### **Efficacy, Safety, Tolerability, and Pharmacokinetics of Varenicline in Adults**

The approved dosing regimen in adults is 1 mg twice daily (BID) for 12 weeks starting with a 1-week titration. Phase 2 and Phase 3 clinical trials demonstrated the efficacy and tolerability of varenicline 1 mg BID in more than 3000 adult cigarette smokers, increasing the odds of quitting approximately 4-fold compared with placebo at end of treatment, and 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 patients treated with varenicline 1 mg BID after an initial week of dose titration compared with 10% in patients taking placebo. In patients taking 0.5 mg BID following initial titration, the incidence was 16% compared with 11% for placebo. Nausea was generally described as mild or moderate and often transient.<sup>1</sup>

### **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.

Additionally there have been reports of hypersensitivity reactions and serious skin reactions.

Complete information for this compound may be found in The Single Reference Safety Document for varenicline, which for this study, is the most recent Investigator Brochure (IB).

### **Safety, Tolerability, and Pharmacokinetics of Varenicline in Adolescents**

A 2-week multiple-dose study (A3051070) examined pharmacokinetics (PK) and tolerability in adolescent smokers, 12-16 years old (see references to report and publication).<sup>19,20</sup> A total of 70 subjects were enrolled in two groups (N=35 each group) according to body weight. In the High Body Weight group (>55 kg) subjects were randomized to varenicline 1 mg BID, 0.5 mg BID or placebo. In the Low Body Weight group (≤55 kg) subjects were randomized to varenicline 0.5 mg BID, 0.5 mg once daily (QD) or placebo. No subjects discontinued treatment or had a dose reduction due to adverse events. Adverse event incidence was higher



in varenicline-treated subjects than in those who received placebo and higher in the Low Body Weight group than the High Body Weight group. The most frequently reported treatment-emergent adverse events associated with varenicline were nausea, headache, vomiting, and dizziness, with incidences tabulated below. Psychiatric adverse events that were considered possibly treatment-related were reported by 3 subjects. In the High Body Weight group receiving 1 mg BID, one male subject had abnormal dreams rated mild, from Days 2-12, and one male subject had anger, rated mild, on Day 10. In the Low Body Weight group receiving 0.5 mg BID, one male subject had abnormal dreams rated mild, on Days 4 and 5. In addition, one female subject in the Low Body Weight group receiving 0.5 mg QD had mood swings rated moderate on Days 10-14 that were considered not treatment-related.

Preferred Term	Low Body Weight (LBW)			High Body Weight (HBW)		
	0.5 mg BID n=14	0.5 mg QD n=15	Placebo n=8	1 mg BID n=14	0.5 mg BID n=14	Placebo n=7
Nausea	5 (36%)	6 (40%)	1 (13%)	2 (14%)	2 (14%)	0
Vomiting	3 (21%)	2 (13%)	0	2 (14%)	1 (7%)	0
Dizziness	2 (14%)	2 (13%)	1 (13%)	0	1 (7%)	0
Headache	3 (21%)	2 (13%)	1 (13%)	1 (7%)	3 (21%)	0

Results from the population pharmacokinetic analysis showed that an open one-compartment model with first-order absorption and elimination best described the multiple-dose pharmacokinetics of varenicline in adolescent smokers. The final population PK parameter estimates (inter-individual variability expressed as %CV) for a typical individual weighing 70 kg were 10.4 L/hr (30%) for oral clearance (CL/F) and 215 L (18%) for volume of distribution (V/F). Body weight was an important predictor of the inter-individual variability in V/F. In adolescents weighing >55, predicted median steady state exposures [AUC(0-24)<sub>ss</sub>] kg were 95.7 ng.h/mL and 197 ng.h/mL for 0.5 mg BID and 1 mg BID, respectively. These exposures were consistent with exposure estimates previously reported at equivalent daily doses in adult smokers (NDA 21-928, 09 November 2005, Sequence # 0000, Module 2.7.2<sup>21, 22</sup> (see references to pop PK in adults). Adolescents from the Low Body Weight group (≤55 kg) tended to have greater varenicline exposures compared to the High Body Weight group. However adjusting the dose to half of that administered to the High Body Weight group, adolescents of smaller body size exhibited exposures within the range of exposures observed in heavier adolescents and in adults. Consistent with the single-dose PK data (Study A3051029<sup>23</sup>), this analysis provided further evidence of dose-proportionality in varenicline systemic exposure in adolescents across the dose range of 0.5 mg to 2 mg daily.

### Dose Selection Rationale

Varenicline doses for this study were selected based on the safety, tolerability, pharmacokinetics, and efficacy information from the clinical trials in adult smokers and the pharmacokinetic and tolerability data from the single-dose (A3051029<sup>23</sup>) and the multiple-dose (A3051070<sup>19, 20</sup>) studies conducted in adolescent smokers 12 to 16 years old.

In clinical trials in adult smokers, both varenicline 1 mg BID and 0.5 mg BID regimens demonstrated efficacy as an aid to smoking cessation, and exposure-response information further indicated that higher systemic exposure to varenicline was associated with greater probability of 4-week smoking cessation. This study proposes to investigate both 1 mg BID and 0.5 mg BID doses compared with placebo in the adolescent population.

Since Study A3051070 demonstrated that varenicline exposure was adequately adjusted by halving the total daily dose of varenicline in subjects at or below the pre-specified weight threshold of 55 kg, adolescent subjects  $\leq 55$  kg will have their randomized dose reduced by half in this study. Those randomized to 1 mg BID will receive 0.5 mg BID and those randomized to 0.5 mg BID will receive 0.5 mg QD. This dosing scheme should provide an adequate range of individual exposures to investigate the exposure-response relationships for selected measures of efficacy and tolerability. All dosing regimens other than 0.5 mg QD will begin with a two week titration period followed by 10 weeks at the target dose.

### **Smoking Cessation Counseling Program**

Smoking cessation attempts are more likely to be successful with counseling and support. All subjects will receive brief age-appropriate smoking cessation counseling in accordance with the Public Health Service (PHS) guidelines<sup>24</sup> at each clinic visit and telephone contact, starting with the baseline visit.

## **2. STUDY OBJECTIVES AND ENDPOINTS**

### **2.1. Primary Objective**

- To evaluate the efficacy, safety, and tolerability of varenicline compared with placebo in adolescent smokers aged 12-19 years.

### **2.2. Endpoints**

#### Primary efficacy endpoint:

- 4-week continuous quit rate (CQR) from Week 9 through Week 12 of treatment for varenicline compared with placebo. An exploratory subgroup analysis for each dosing group by weight stratum will be provided.

#### Secondary efficacy endpoints:

- 7-day point-prevalence of smoking abstinence at Weeks 12, 24, and 52;
- Reduction in number of cigarettes smoked at Weeks 12, 24, and 52;
- Continuous abstinence rate from Week 9 through Week 24;
- Continuous abstinence rate from Week 9 through Week 52.

#### Safety Assessments:

- Adverse events spontaneously volunteered or observed, adverse events elicited by the Neuropsychiatric Adverse Event Inventory (NAEI), Columbia Suicide Severity Rating Scale (CSSRS), Hospital Anxiety and Depression Scale (HADS) and adverse events associated with safety laboratory tests, or vital signs.

#### PK Assessments:

- Varenicline exposure at steady-state in adolescent smokers.

### **3. STUDY DESIGN**

This will be a randomized, double-blind, placebo-controlled, multicenter study to compare two doses of varenicline 1 mg BID and 0.5 mg BID with placebo for smoking cessation in adolescent smokers aged 12-19 years who are motivated to quit. Since varenicline exposure is related to body weight, subjects with a body weight  $\leq 55$  kg will have their varenicline dose reduced by half (those randomized to 1 mg BID will receive 0.5 mg BID and those randomized to 0.5 mg BID will receive 0.5 mg QD).

All subjects and their parents/legal guardians will provide informed consent/assent before any study activities occur. Subjects over the age of 18 may sign their own informed consent. (Parents, guardians, or caregivers need to be actively involved in the assessment and monitoring of these patients). Subject eligibility will be reviewed during a three week screening period.

Those subjects deemed eligible will be randomized and enter the 12-week placebo-controlled treatment period with weekly clinic visits for efficacy and safety assessments and smoking cessation counseling. Varenicline or placebo dosing will begin with two weeks of titration. (Figure 1). All subjects will set a target quit date (TQD) to coincide with the Week 1 visit. The Week 1 visit occurs at the end of the first week of the treatment phase. A visit window of  $\pm 3$  days can be allowed to accommodate unforeseen scheduling issues. Brief age-appropriate smoking cessation counseling, in accordance with Public Health Service (PHS) guidelines, up to 10 minutes duration, will be provided by a trained counselor at each clinic visit and telephone contact beginning at baseline. The primary efficacy endpoint will be complete abstinence from smoking, biochemically verified, during the last 4 weeks of the 12 week dosing period.

#### Follow-up (non-treatment) period:

The primary purpose of the non-treatment follow-up study phase is to assess the long-term smoking abstinence. In addition, during this phase, subjects will be monitored for any neuropsychiatric or suicide-related adverse events.

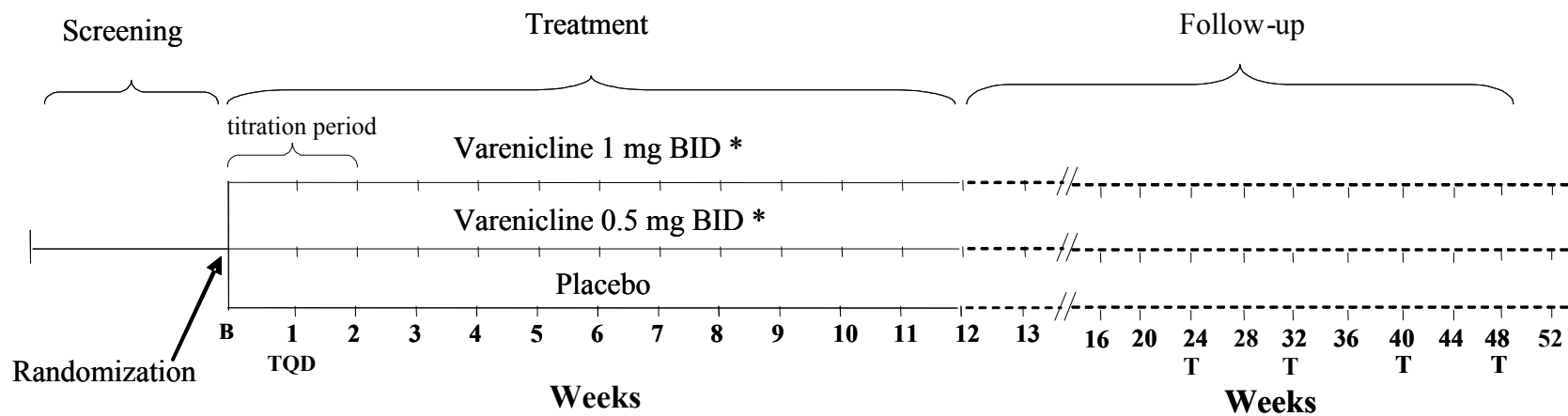
Subjects will be followed to obtain smoking status for 9 months after the end of the 12-week treatment period. Clinic visits will occur at Weeks 13-16 (inclusive), 20, 28, 36, 44, and 52. Telephone contacts are planned for weeks 24, 32, 40, and 48. To accommodate unforeseen

circumstances, a visit window of  $\pm 3$  days can be allowed for week 13 through 20 visits, and a visit window of  $\pm 5$  days can be allowed for week 20 to week 52 visits.

Smoking-cessation counseling up to 10 minutes duration will be provided at each clinic visit and telephone contact for the duration of the study. Whenever possible, counseling should be conducted by the same counselor throughout, so that the relationship builds and brings additional value to the sessions.

Subjects that stop taking study drug during the treatment phase (wks 1-12) are still eligible to remain in the study, provided they continue to comply with remaining visit procedures. All efforts should be made to keep the subjects in the study. If an early termination of the study occurs, the appropriate ET visit should be completed in accordance with the schedule of activities ([Table 1](#)).

**Figure 1. Clinical Trial Design**



**\*Varenicline doses are titrated to target dose over the first weeks of treatment. Subjects whose body weight is  $\leq 55$  kg will have their randomized dose reduced by half.**

BL= Baseline  
T = Telephone

## 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. Subject eligibility should be reviewed and documented by an appropriately qualified member (ie, PI or sub-I) of the investigator's study team before subjects are included in the study.

**All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.** If there is question on the suitability of a potential subject for this trial, the sponsor should be contacted.

### 4.1. Inclusion Criteria

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

1. Healthy male and female subjects between the ages of 12 and 19 years inclusive (at screening), who are motivated to stop smoking.
2. Subjects must be currently smoking at least an average of 5 cigarettes per day during the past 30 days, have a total score of 4 or higher on the Fagerström Test for Nicotine Dependence, (FTND) ([Appendix 2](#)) and must be motivated to stop smoking.
3. Subjects must have had at least one prior failed attempt to quit smoking.
4. Total body weight at screening and randomization  $\geq 35$  kg (77 lbs) and Body Mass Index (BMI) of  $\leq 35$  kg/m<sup>2</sup> and at the lower end, subject should be no more than 2 standard deviations or percentiles from normal BMI for age and stature.
5. For each subject, the parent(s)/legal guardian(s) must provide a signed and dated written informed consent/assent document indicating that the subject and parent (or a legally acceptable representative) have each been informed of all pertinent aspects of the trial and that the adolescent agrees to participate. Parental consent is not required for subjects over the age of 18.
6. Subjects, and if required by local/site regulations their parent(s) /legal guardian(s) must be willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other trial procedures as indicated in the protocol.
7. Male and female subjects of childbearing potential must agree to use a highly effective method of contraception throughout the study and for at least 28 days after the last dose of assigned treatment. A subject is of childbearing potential if, in the opinion of the investigator, he/she is biologically capable of having children and is sexually active.

8. Female subjects who are not of childbearing potential (ie, meet at least one of the following criteria):
  - Have undergone hysterectomy of bilateral oophorectomy;
  - Have medically confirmed ovarian failure; or
  - Are medically confirmed to be post-menopausal (cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; laboratory confirmation may be indicated).

#### 4.2. Exclusion Criteria

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

1. Female subjects with a positive urine pregnancy test (all female subjects are required to have pregnancy testing).
2. Pregnant or nursing female subjects; females of childbearing potential who are unwilling or unable to use an acceptable method of contraception from at least 14 days prior to study medication administration until 30 days after the last dose of study medication. Acceptable methods of contraception are: abstinence; any form of hormonal contraception such as Depo-Provera, daily oral contraceptive, transdermal patch, or Nuva-ring; intra-uterine device, sterilization; or double barrier contraception which is a combination of any two of the following methods: condoms, spermicide, diaphragm. (Note, subjects with a positive pregnancy test during the treatment period will have study drug discontinued but will be encouraged to remain in the study).
3. Subjects with a prior suicide attempt, subjects hospitalized within the past twelve months due to suicidal ideation or suicidal behavior, or subjects considered to have had serious suicidal ideation or suicidal behavior within the past twelve months.
4. Subjects with active suicidal ideation or behavior identified at the screening or baseline visits.
5. Subjects with a score of  $>7$  on the Suicide Behaviors Questionnaire-Revised (SBQ-R) at the Screening visit.
6. Subjects with current evidence or history of clinically significant psychiatric disease, including, but not limited to Axis 2 disorders; major depression disorder, anxiety disorders, panic disorder, hostility or aggression disorder, perceptual/thinking disturbances, mania, psychosis, (including schizophrenia), bipolar disorder, personality disorder, severe emotional problems (in the past year prior to screening), or eating disorder (eg, bulimia or anorexia nervosa). Investigator judgment should be used to assess whether a prospective subject is appropriate for participation in the study.

**Assessment of any evidence or history of clinically significant psychiatric or neurologic disease, *and* the assessment for suicidality must be done by a Mental Health Professional (MHP). A MHP must be a pediatric/adolescent psychiatrist or a licensed PhD level clinical pediatric/adolescent psychologist.**

7. Subjects who require use of medications prescribed for mania or psychosis.
8. Subjects with a score  $\geq 8$  for *either* depression or anxiety on the Hospital Anxiety and Depression Rating Scale (HADS) ([Appendix 3](#)).
9. Subjects with evidence or history of clinically significant neurological, hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, or allergic disease (including serious drug allergies). (Subjects who have seasonal allergies, asthma, or acne may be allowed to enroll in the study).
10. Use of prescription or nonprescription drugs within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study medication should be discussed with the sponsor and recorded on the CRF. Use of ibuprofen, acetaminophen at doses of  $\leq 2$  g/day, antihistamines, asthma medications, bronchodilators, migraine medications and topical medications is permitted.
11. Use of psychotropic or psychoactive drugs in the 6 months prior to screening should be discussed with the sponsor prior to enrolling the subject. Use of Adderal or Ritalin may be allowed for treatment of those subjects with ADHD who are otherwise deemed appropriate for this study.
12. Evidence of alcohol and substance abuse/dependence (other than nicotine) within 3 months prior to screening deemed severe enough to compromise the subject's ability to comply with the study requirements, as determined by the investigator's clinical judgment, OR consecutive positive urine drug screens during **screening and baseline**. If question remains as to the suitability of the subject, contact the sponsor, or use DSM IV guidance to assess potential for substance abuse.
13. Treatment with an investigational drug within 30 days or 5 half-lives (whichever is longer) preceding the first dose of study medication.
14. History of prior use of or sensitivity to varenicline/Chantix®/Champix®.
15. Subjects who plan to move out of the area in the next year.
16. Subjects who are unwilling or unable to comply with the [Life Style Guidelines](#).
17. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with trial participation or investigational product administration or may interfere with the interpretation of trial results and, in the judgment of the investigator, would make the subject inappropriate for entry into this trial.



18. Subjects who are investigational site staff members or subjects who are Pfizer employees directly involved in the conduct of the trial or family members of such employees.

19. Participation in other studies within 30 days before the current study begins and /or during study participation.

#### 4.3. Randomization Criteria

Subjects who meet inclusion and exclusion criteria and have no clinically significant abnormalities on laboratory test results or physical examination may be randomized. A computer-generated randomization schedule will be used to assign subjects to treatment.

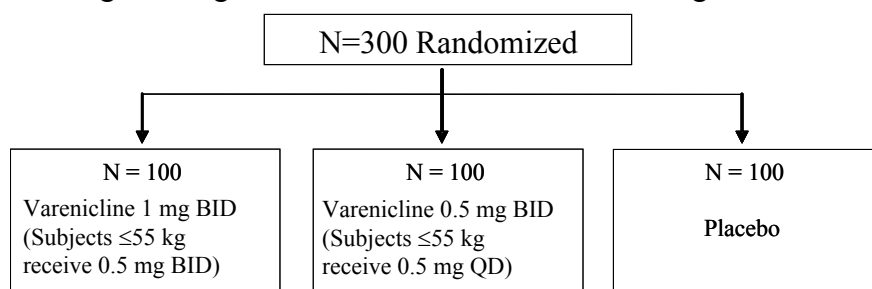
#### 4.4. Life Style Guidelines

Participants are expected to abstain from the use of tobacco products such as pipe tobacco, cigars, snuff, and chewing tobacco, and the use of marijuana. If any of these products are used, they should be recorded with the concomitant medications section of the CRF. Subjects will also be expected to refrain from using any form of nicotine replacement therapy during the treatment phase, however, if any of these products are used, they should be listed as concomitant drug therapy.

### 5. STUDY TREATMENTS

#### 5.1. Allocation to Treatment

This is a 52 week, double-blind, parallel group study. Subjects will be randomized to receive 12 weeks of varenicline 1 mg BID, varenicline 0.5 mg BID or placebo in a 1:1:1 ratio using a block randomization within each site. Within each randomized treatment group, subjects who weigh  $\leq 55$  kg at baseline will receive half the assigned dose strength.



Randomization will be stratified by age group (12-16 vs 17-19). In order to ensure a sufficient number of subjects in the 12-16 year old stratum, the 17-19 year old stratum will be capped at a maximum of 90 subjects.

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 web-based or telephone call-in drug management system will provide identification numbers

for the subjects at the screening visit. The web-based or telephone call-in drug management system will also coordinate drug dispensation to subjects at each clinic visit.

## **5.2. Breaking the Blind**

The study will be subject, investigator, and sponsor blinded.

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.

## **5.3. Drug Supplies**

Varenicline doses will consist of one or two 0.5 mg tablets of the clinical image formulation. Matching placebo tablets will be provided to maintain the blind. Study drug will be supplied in blister packs.

## **5.4. Formulation and Packaging**

Varenicline will be supplied as 0.5 mg tablets of the Immediate Release formulation. Tablets (blinded varenicline or placebo) will be supplied in blister packs containing sufficient tablets for 10 days. A new blister pack will be dispensed after each weekly clinic visit to provide sufficient study drug until the next scheduled clinic visit.

## **5.5. Preparation and Dispensing**

Study drug is to be dispensed to subjects by qualified site study staff at (or after) each scheduled clinic visit from the Baseline visit to the Week 11 visit (according to the study flowchart). Site personnel should provide instructions for study drug dosing to each subject, and request that the subject read for understanding. Once reading is complete, the subject will be asked to initial and date the instructions indicating they comprehend the meaning of the sun (am) and moon (pm) and other aspects of the dosing card instructions. If the child is a minor, the parent should date and sign to indicate their understanding as well. The discussion should be documented in source as well. Subjects will receive their first blister pack at (or after) the Baseline visit and will receive a new blister pack at (or after) each weekly clinic visit through the Week 11 visit. Upon receipt of each new drug package the used package will be returned. Subjects will be instructed to store the study drug at room temperature and out of the reach of small children.

## **5.6. Administration**

To maintain the blind the administration of study medication will use a double-dummy strategy so that all subjects will take two morning tablets and two evening tablets throughout the 12-week dosing period. Tablets will be active drug or placebo as outlined below.

**Study drug administration will begin with a two-week titration period.**

Treatment will begin from the Week 1 blister card as soon as possible, the earliest being the morning after the Baseline visit day. The blister cards are set up in 2 columns; sun, (am), and moon, (pm) to accommodate BID dosing schedule. Each subject will be instructed to take two pills from each column each day starting with the top of the blister card (in the direction of the arrow printed on the card). It is important that this order is followed. The blister cards have been created such that dosing instructions (2 tablets in the morning, 2 tablets in the evening) remain the same throughout the study. After the subjects are instructed on proper dosing, the subjects should repeat these directions, and initial and date to document comprehension of these instructions. If subject is a minor, the parent should initial and date as well.

Dosing should occur with a full glass (240 ml) of water and it is recommended that subjects eat prior to dosing. At least 8 hours is recommended between the morning and evening dosing.

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 4 mg/day or higher. Such medication errors occurring to a study participant are to be captured on the adverse event (AE) page of the CRF 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:

- 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).

The following table shows the dosing scheme for each randomized group with respective adjustments for the low bodyweight subjects.

Treatment Group	Dosing		
	Titration period		Target Dose
	Week 1	Week 2	Weeks 3-12
Varenicline 1 mg BID			
subjects >55 kg	0.5 mg QD	0.5 mg BID	1 mg BID
subjects ≤55 kg	0.5 mg QD	0.5 mg QD	0.5 mg BID
Varenicline 0.5 mg BID			
subjects >55 kg	0.5 mg QD	0.5 mg QD	0.5 mg BID
subjects ≤55 kg	0.5 mg QD	0.5 mg QD	0.5 mg QD
Placebo			
subjects >55 kg	Placebo	Placebo	Placebo
subjects ≤55 kg	Placebo	Placebo	Placebo

### 5.7. Dosing Compliance

Subjects will return blister packs at (or after) each visit. A dosing record and drug accountability form will be completed. Reasons for missed doses should be ascertained and patterns of missed doses should be discussed in detail. Subjects may be considered non-compliant if weekly compliance is less than 80%.

### 5.8. 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.

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.

### 5.9. Concomitant Medication(s)

Any use of psychotropic or psychoactive drugs by a potential subject in the past 6 months prior to screening should be discussed with the sponsor. Use of Adderall or Ritalin may be allowed for treatment of those subjects with ADHD who are otherwise deemed appropriate for this study. Use of prescription or nonprescription drugs within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study medication should be discussed with the sponsor, and documented in the CRF. Acetaminophen and ibuprofen may be used intermittently throughout the trial, but should not exceed 2 g/day on two consecutive days, unless greater quantities are deemed necessary by the investigator. Antihistamines, asthma medications, bronchodilators, migraine medications and topical medications may be permitted during the course of the study. If there is any question about whether a concomitant medication is appropriate for use in subjects while they are participating in this trial, please contact the sponsor.

All concomitant medication taken during the trial must be recorded with indication and start and stop dates of administration. All subjects will be questioned about concomitant medication at each clinic visit through Week 52.

Medications taken within 3 months before the first dose of trial medication will be documented as a prior medication. Medications taken after the first dose of trial medication will be documented as concomitant medications.

## 6. STUDY PROCEDURES

### 6.1. Screening

Subjects will be screened within 3 weeks prior to administration of the trial medication to allow for the return and evaluation of screening results to confirm that they meet the subject inclusion/exclusion criteria for the trial. Informed consent for the clinical trial must be signed prior to the initiation of any study related activities. In the case of adolescents  $\leq 18$  years old, informed consent of the parent/legal guardian and subject assent are both required.

The following procedures will be obtained:

- Obtain informed consent/assent;
- Record demography, medical history and assessment of past and present alcohol/drug use;
- Record concomitant medications as well as prescription medications and non-drug treatment/procedures in the past 3 months;
- Subject self administers the Suicidal Behaviors Questionnaire-Revised (SBQ-R) and the Hospital and Depression Scale (HADS) ([Appendix 3](#));
- Complete Columbia Suicide-Severity Rating Scale (C-SSRS) and record suicide related adverse events;
- Record tobacco use history, including number of cigarettes per day, number of years smoked, number of prior attempts to quit smoking;
- Complete and score the Fagerström Test for Nicotine Dependence (FTND) ([Appendix 2](#));
- Physical examination which should include measurement of height and weight, sitting blood pressure and orthostatic[BP] and resting sitting, supine and standing pulse rate.
- Collect blood specimens for safety laboratory tests in addition to the following:
  - Urine **pregnancy** test for all females;

- Urine **drug** test (dipstick at site ) for all subjects;
- Urine cotinine at site;
- Verify trial eligibility by checking [Inclusion Criteria/Exclusion Criteria](#);
- To prepare for trial participation, subjects will be instructed on the use of [Life Style Guidelines](#) and [Concomitant Medication\(s\)](#) and will be provided with a smoking diary worksheet;
- Subject agrees to a Target Quit date (TQD) which will be planned to coincide with the Week 1 visit. Arrange appointment for the baseline visit (which should be ~7 days prior to the Week 1 visit/Target Quit date). Baseline visit can be cancelled if the inclusion/exclusion criteria, including laboratory results, are not met prior to the Baseline visit.

## 6.2. Study Period

### 6.2.1. Baseline Visit (Randomization)

- Assess baseline symptoms by spontaneous reporting of symptoms and by asking the subjects to respond to a non-leading question such as “How do you feel?” Record adverse events;
- Record height and weight and orthostatic vital signs (sitting, supine, and standing);
- Have Subject self-administer the HADS ([Appendix 3](#));
- Conduct Neuropsychiatric Adverse Event Interview (NAEI) ([Appendix 4](#)) and record solicited adverse events;
- Complete the Columbia Suicide-Severity Rating Scale (C-SSRS) and record any suicide-related adverse events;
- Collect urine for **pregnancy** test from females;
- Perform urine **drug** test on all subjects;
- Urine cotinine at site;
- Record concomitant medications;
- Record any non-drug treatments/procedures;
- Review previous week’s Smoking Diary Worksheet with subject and distribute the following week’s; Complete the Nicotine Use Inventory (NUI) based on subject responses ([Appendix 1](#));

- Provide up to 10 minutes of smoking cessation counseling;
- Re-check [Inclusion Criteria/Exclusion Criteria](#);
- Randomize to treatment;
- Dispense study medication, Week 1 blister pack, for self administration and provide dosing instructions.

#### **6.2.2. Treatment Phase Clinic Visits (Weeks 1 through 12 and ET<sub>12</sub>)**

Following the Baseline visit, clinic visits will be conducted weekly for 12 weeks. All subjects should have set a target quit date (TQD) to coincide with the Week 1 visit. The Week 1 visit occurs at the end of the first week of the treatment phase. Smoking cessation counseling up to 10 minutes duration will be provided at each clinic visit beginning at Baseline. Whenever possible, counseling should be conducted by the same counselor throughout, so that the relationship builds and brings additional value to the sessions. 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. To accommodate unforeseen circumstances a visit window of  $\pm 3$  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 (ET<sub>12</sub>) will be conducted. At each of these visits, the following procedures will be conducted:

- Record spontaneously reported adverse events after asking the subjects to respond to a non-leading question such as “How do you feel?”
- Measure and record sitting and orthostatic blood pressure (BP) and sitting, supine and standing pulse rate;
- Have Subject self-administer the HADS ([Appendix 3](#));
- Conduct Neuropsychiatric Adverse Event Interview (NAEI) ([Appendix 4](#)) and record solicited adverse events;
- Complete the Columbia Suicide-Severity Rating Scale (C-SSRS) and record any suicide-related adverse events;
- Record concomitant medications;
- Record any non-drug treatments;
- Review previous week’s Smoking Diary Worksheet with subject and distribute the following week’s; Complete the Nicotine Use Inventory (NUI) based on subject responses ([Appendix 1](#));
- Provide up to 10 minutes of smoking cessation counseling;

- Count and document drug returns;
- Dispense next week's blister pack (except at Week 12 or ET);

The following additional activities will be conducted at Visit Weeks **3, 6, 12**, and early termination:

- Obtain blood samples for safety laboratory tests (week 3, Week 6, and Week 12 or ET);
- Perform urine **pregnancy** test for females (also at **Week 9**);
- Perform urine **drug** test (dipstick at site) (also at **Week 9**);
- Collect blood samples for pharmacokinetic analysis (Week 3, Week 6, and Week 12 or ET);
- Ask subject to recall the times of last 2 doses of trial medications and record this information in the dosing log;
- At Week 12 or ET12 only, record height and weight;

The following additional activity will be conducted at Visit Weeks 9-12, and at Early Termination:

- Urine cotinine test at site;

### **6.3. Non-Treatment Follow-up Period (Weeks 13-52)**

Following completion of the week 12 visit, subjects will continue in the non-treatment follow-up phase of the protocol. Clinic visits occur weeks 13-16, 20, 28, 36, 44, and 52/ET. Subjects will be contacted by phone at weeks 24, 32, 40, and 48. During the non-treatment phase, smoking cessation counseling up to 10 minutes duration will be provided at each visit and telephone contact. To accommodate unforeseen circumstances, a visit window of  $\pm 3$  days can be allowed for weeks 13 through 20 visits, and a visit window of +5 days can be allowed for week 20 to week 52 visits.

#### **6.3.1. Clinic Visits: Weeks 13-16, 20, 28, 36, 44, and 52/ET**

- Record spontaneously reported adverse events by asking the subjects to respond to a non-leading question such as "How do you feel?"
- Subject self administers the HADS ([Appendix 3](#));
- Conduct Neuropsychiatric Adverse Event Interview (NAEI) ([Appendix 4](#)) and record solicited adverse events;



- Complete the Columbia Suicide-Severity Rating Scale (C-SSRS) and record any suicide-related adverse events;
- Record concomitant medications;
- Record any non-drug treatments;
- Review previous week's Smoking Diary Worksheet with subject and distribute the following week(s); Complete the Nicotine Use Inventory (NUI) based on subject responses ([Appendix 1](#));
- Urine cotinine test at site;
- Provide up to 10 minutes of smoking cessation counseling.

#### **6.3.2. Telephone Contacts: Weeks 24, 32, 40, and 48**

- Review Smoking Diary responses with subject;
- Complete the Nicotine Use Inventory (NUI) based on subject responses ([Appendix 1](#));
- Provide up to 10 minutes of smoking cessation counseling.

Discharge from study at Week 52 or early termination only. If a subject has any clinically significant and trial-related abnormalities at the conclusion of a scheduled visit of the trial, the Pfizer medical monitor (or designated representative) should be notified and the follow-up evaluations will be performed until the abnormalities return to the normal/baseline condition. The investigator should make every effort to arrange follow-up evaluations at appropriate intervals to document the course of the abnormalities.

#### **6.4. Early Permanent Discontinuation of Study Drug**

Subjects who wish to withdraw from the study will be allowed to do so at any time without prejudice, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral, or the inability of the subject to comply with the protocol required schedule of study visits or procedures at a given study site. Subjects should be discontinued if they cannot be contacted for drug monitoring or do not return for subsequent scheduled visits. The investigator should inquire about the reason for withdrawal, request the subject to return all unused investigational product(s), request the subject return for a final visit, if applicable and follow-up with the subject regarding any unresolved adverse events (AEs). Diligent attempts will be made by telephone and certified letter to determine the circumstances for subjects who are lost to follow-up as this may be related to the study drug.

Early permanent withdrawal of study drug use may occur at any phase of the study. Possible reasons for early permanent withdrawal of study drug use include:

- Adverse event: The subject develops an adverse event, which in the opinion of the subject or lead investigator, institutional principal investigator or sub-investigator warrants termination of study drug use.
- Personal reason: A subject may withdraw from study drug use at any time.
- Pregnancy.

In the event of study treatment discontinuation, subjects should be encouraged to continue to attend clinic and telephone visits, and complete study procedures.

The investigator must determine the primary reason for withdrawal of study drug and record it on the case report form. Withdrawal of study drug due to an adverse event should be distinguished from withdrawal of study drug due to insufficient response. A treatment or study discontinuation due to a serious adverse event must be reported to Pfizer immediately.

Return to smoking is not a basis for withdrawing a subject from the study. Subjects who return to smoking should be encouraged to make further quit attempts and to continue their participation with the counseling and protocol-specified visits and procedures.

Female subjects who have a positive pregnancy test during the treatment period will discontinue study medication but should continue study participation. Pregnant subjects must be followed to the outcome of the pregnancy and an Exposure in Utero Form (EIU) must be submitted.

Any subjects who discontinue treatment for any reason may continue participation in the study and should be encouraged to do so. They will be required to maintain the visit schedule and can continue participation through the non-treatment follow-up phase of the study.

Subjects should be encouraged to complete the study even if they stop study medication. 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.

In post marketing safety surveillance there have been some reports of depressed mood, agitation, changes in behavior, psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, anxiety, panic, and suicidal ideation (suicidal thoughts) and suicide in patients attempting to quit smoking while taking 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. The role of varenicline in these reports is not known. A subject who experiences such events should stop dosing and immediately report any such symptoms to the study staff.

**Each clinical research site will have an Emergency Response Plan in place to properly care for subjects who report events of a serious nature that require immediate or very**

**prompt attention. This plan will include having a pediatric/adolescent psychiatrist available at all times.**

At all clinic visits, the investigator will be proactively monitoring for anxiety, panic, hostility, aggression, abnormal thinking, hallucinations, suicidality and depressed mood through the use of the C-SSRS, HADS ([Appendix 3](#)), and the NAEI ([Appendix 4](#)). These evaluations should be conducted by an adolescent or pediatric psychiatrist. A subject must be discontinued from study medication and referred for appropriate medical or psychiatric evaluation and follow-up if there is:

- A positive response to any question on the C-SSRS;
- A score  $\geq 15$  for anxiety or  $>15$  for depression on the HADS ([Appendix 3](#));
- Moderate or severe adverse event as elicited through the use of the Neuropsychiatric Adverse Event Interview.

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, behavioural, or administrative reasons. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request the subject to return all unused investigational product(s), request the subject return for a final visit, if applicable, and follow-up with the subject regarding any unresolved adverse events.

## **7. ASSESSMENTS**

### **7.1. Efficacy**

#### **7.1.1. Smoking Status**

Smoking status will be assessed using a standard series of questions referred to as the Nicotine Use Inventory (NUI) ([Appendix 1](#)). The subject responds Yes or No to questions about cigarette or other nicotine/tobacco use since the last visit or during the past 7 days. The NUI is completed at each clinic visit and/or phone contact during the treatment period and the follow-up period by research staff based on subjects' responses.

All subjects will be provided with Smoking Diary Worksheets to use as a tool to record how many cigarettes they have smoked each day. The Smoking Diary itself will not be data-based.

#### **7.1.2. Urine Cotinine Testing**

In order to confirm the self-reported abstinence from smoking urine cotinine testing will be done at the site at Weeks 9-12 during the treatment phase and all clinic visits during the

follow-up phase. The test indicates a positive result when the cotinine in the urine exceeds 200 ng/mL.

### 7.1.3. Fagerström Test for Nicotine Dependence

The Fagerström Test for Nicotine Dependence provides a short, self-reported measure of dependency on nicotine. This test will be completed at screening only. The test's questions and scale are shown in (Appendix 2). This should be scored and reviewed by the PI prior to randomization.

## 7.2. Safety

### 7.2.1. Laboratory

The following safety laboratory tests will be performed at protocol-specified time points (details in Table 1 Schedule of Activities). Where practical, subjects should be fasted, however, if not appropriate designation should be made on the laboratory requisition.

Hematology	Chemistry	Other
Hemoglobin	BUN and Creatinine	Urine Pregnancy
Hematocrit	Glucose	Test
RBC count	Ca <sup>++</sup>	Urine cotinine
Platelet count	Na <sup>+</sup> , K <sup>+</sup> , Cl <sup>-</sup>	Urine drug test
WBC count	Total CO <sub>2</sub>	
Total neutrophils	(Bicarbonate)	
(Abs)	AST, ALT	
Eosinophils (Abs)	Total bilirubin	
Monocytes (Abs)	Alkaline phosphatase	
Basophils (Abs)	Uric acid	
Lymphocytes (Abs)	Albumin	
	Total protein	

- Results of the screening and baseline urine pregnancy tests must be negative in order for a female subject of childbearing potential to receive study medication at baseline. Female subjects with a positive pregnancy test during the treatment period must discontinue study medications but should be encouraged to remain in the study. Pregnancy tests may be repeated for confirmation, as per request of IRB/IECs, or if required by local regulations.
- Safety laboratory tests from Screening must have no clinically significant findings, as judged by the investigator, in order for a subject to be dosed at baseline.

Additional safety measurements may be obtained if deemed necessary by appropriate study personnel.

#### 7.2.1.1. Blood Volume

Total blood sampling volume for the individual adolescent subject is approximately 69 mL.

**Table 2. Blood Volume**

Sample Type	Sample Volume (mL)	Number of Sampling Times			Total Volume (mL)
		Screening	Treatment Period	Follow-Up	
Safety Labs	15	1	3	0	60
PK	3	0	3	0	9
TOTAL					69

This total volume does not include discarded blood from pre-draws used to remove fluid from flushed catheters. The discarded volume is not expected to exceed 14 mL of blood

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#### **7.2.1.2. Shipment of Laboratory Samples**

The shipment address and contact information will be provided to the investigator sites prior to initiation of the trial.

#### **7.2.2. Blood Pressure and Pulse Rate**

Blood pressure and pulse rate will be recorded after subjects have rested in a sitting position for approximately 5 minutes. Sitting blood pressure and pulse rate will be measured with the subject's arm supported at the level of the heart, and recorded to the nearest mm Hg. The same arm (preferably the dominant arm) will be used throughout the trial. In addition to these first measurements, blood pressure and pulse rate will be recorded after subjects have been supine for approximately 5 minutes, and then orthostatic blood pressure will immediately be recorded when the subject is asked to stand. The pulse should also be recorded at the times that the BP is recorded.

The same size blood pressure cuff, which has been properly sized and calibrated, will be used to measure blood pressure each time. The use of automated devices for measuring blood pressure and pulse rate are acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. The blood pressure and pulse rate should be obtained prior to the blood collection.

Blood pressure and pulse rate will be measured at screening, baseline, and weekly visits during the 12-week treatment period.

#### **7.2.3. Physical Examinations**

A physical examination including height and weight will be performed at screening visit by trained medical personnel. Height and weight will be collected again at Baseline and at the Week 12 end-of-treatment visit or early termination if prior to Week 12. Height and weight must be measured at least three times. Weight should be obtained with a calibrated scale and height should be measured with a stadiometer.

CDC growth charts will be provided to investigators to record height and weight.

#### **7.2.4. SBQ-R**

The Suicidal Behaviors Questionnaire-Revised, a brief self-report measure of past suicidal behavior,<sup>15</sup> will be completed by subjects at the Screening visit.

#### **7.2.5. Columbia Suicide Severity Rating Scale (CSSRS)**

The Columbia suicide Severity Rating Scale (CSSRS)<sup>16</sup> is a set of suggested questions designed to elicit information about passive and active suicidal ideation, active suicidal intent, and self injurious behavior.

The C-SSRS will be completed by a mental health professional (adolescent psychiatrist or PhD psychologist), at screening and at each subsequent clinic visit up to and including Week 52.

#### **7.2.6. Actively Solicited Neuropsychiatric Adverse Events (Appendix 4)**

The NAEI will be conducted at every clinic visit from baseline through Week 52. The Neuropsychiatric Adverse Event Interview (NAEI) must be conducted by a qualified mental health professional, who will actively inquire about the following type of adverse events: depression, anxiety, delusions, hallucinations, paranoia, psychosis, mania, panic, agitation, dissociative states, feeling abnormal, hostility, aggression and homicidal ideation. If a subject has a positive response to any item on the NAEI, 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. Dosing must be stopped if an adverse event moderate or severe in nature is elicited through this interview.

Hospital Anxiety and Depression Scale (HADS) (Appendix 3).

The Hospital Anxiety and Depression Scale (HADS) measures anxiety and depression in hospital and community settings and has also been validated in the adolescent outpatient population.<sup>17</sup> It is a patient completed questionnaire that establishes the presence and severity of both anxiety (7 questions) and depression (7 questions) (Appendix 3).

The HADS is a self-report scale and contains 14 items rated on 4-point Likert-type scales. Two subscales assess depression and anxiety. The HADS will be completed by the subject at every clinic visit through Week 52. Dosing must be stopped if the HADS score for either depression or anxiety is  $\geq 15$ .

Subjects' self-report via the HADS is aimed to more fully characterize potential depression and anxiety related events. These additional measurements will be collected and evaluated in a different manner than the observed or volunteered adverse events. No attempt will be made to resolve any apparent discrepancies between observed or volunteered adverse events and the additional data collected from subjects using the HADS self-report. These additional data will be presented in separate tables, separate figures, and separate data listings, and will be reviewed in the final study report.

Adverse event incidence rates will not be calculated from the self-reported HADS data but rather from the spontaneously reported information, the NAEI and the CSSRS data described above, recorded on the adverse event pages from the Case Report Form (CRF).

### **7.3. Pharmacokinetics (PK)**

#### **7.3.1. Plasma for Analysis of Varenicline:**

Blood samples (3 mL) sufficient to provide a minimum of 1 mL of plasma for pharmacokinetic analysis will be collected at protocol specified time-points (see [Table 1](#) Schedule of Activities) into appropriately labeled tubes containing sodium heparin. These PK samples should not all be collected at the same time after dosing. A distribution of sampling should be encouraged, possibly through randomly scheduling sampling throughout the visit day. The times of study drug dosing for the prior 2 doses as well as the time of the blood drawing will be recorded at each of these visits on the source document and data collection tool (eg, CRF).

The samples should be cooled on ice or in a refrigerator at -2-8°C (this procedure is meant to minimize hemolysis and maximize plasma yield from the whole blood), then centrifuged for about 10 minutes at 1400-1700 x g. Plasma is to be transferred to appropriately labeled screw-capped polypropylene tubes provided by the Central Laboratory. The tubes with plasma samples should then be stored at -20°C within one hour of blood collection. Samples will be analyzed using a validated analytical method in compliance with Pfizer standard operating procedures.

#### **7.3.2. Shipment of PK Samples**

The shipment address and contact information will be provided to the investigator site prior to initiation of the trial.

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 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 preventative 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.

## **8. ADVERSE EVENT REPORTING**

### **8.1. Adverse Events**

The adolescent subjects will be instructed to tell the study doctor immediately if they experience any side effects, injury, symptoms or complaints. They will be provided a 24 -hour telephone contact number to reach the research site staff.

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 review 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, (SAEs), the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through the last subject visit. Should an investigator be made aware of any serious adverse event occurring any time after the active reporting period, it must be promptly reported if a causal relationship to investigational product is suspected.

- Adverse events (serious and non-serious) should be recorded on the CRF from the time the subject/legal guardian provides informed consent/assent through last subject visit.

## **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 (in Utero);
- 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 should be 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 and/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. Potential Cases of Drug-Induced Liver Injury**

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

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

- a. Subjects with *AST or ALT baseline values within the normal range* who subsequently present with AST or ALT  $\geq 3$  times the upper limit of normal concurrent with a total bilirubin  $\geq 2$  times the upper limit of normal with no evidence of hemolysis and an alkaline phosphatase  $\leq 2$  times the upper limit of normal or not available.
- For subjects with preexisting *ALT OR AST OR total bilirubin values above the upper limit of normal*, the following threshold values should be used in the definition mentioned above:

- For subjects with pre-existing AST or ALT baseline values above the normal range: AST or ALT  $\geq 2$  times the baseline values and  $\geq 3$  X ULN, or  $\geq 8$  X ULN (whichever is smaller).
- Concurrent with:
  - For subjects with pre-existing values of total bilirubin above the normal range: Total bilirubin increased by one time the upper limit of normal or  $\geq 3$  times the upper limit of normal (whichever is smaller).

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

### **8.7. 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.

### 8.8. Severity Assessment

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

MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

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

### 8.9. 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.

#### **8.10. Exposure During Pregnancy (Also Referred to as Exposure In Utero)**

For investigational products and for marketed products, an exposure in-utero (EIU) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been directly exposed to (eg, environmental exposure) the investigational product, or the female becomes, or is found to be, pregnant after discontinuing and/or being directly exposed to the investigational product (maternal exposure);
2. A male has been exposed, either due to treatment or environmental, to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy (paternal exposure).

If any 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 Exposure in Utero Form. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the Exposure in Utero Form. This must be done irrespective of whether an adverse event has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of delivery (see below for information related to induced termination of pregnancy). If at any time a study subject becomes or is found to be pregnant and a pregnancy registry is ongoing, the subject will be enrolled in the pregnancy registry.

Follow-up is conducted to obtain pregnancy outcome information on all Exposure in Utero reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination (ie, induced abortion) and then notify Pfizer of the outcome. The investigator will provide this information as a follow up to the initial Exposure in Utero Form. The reason(s) for an induced abortion should be specified. An EIU report is not created when an ectopic pregnancy report is received since this pregnancy is not usually viable. Rather, a serious adverse event case is created with the event of ectopic pregnancy.

If the outcome of the pregnancy meets the criteria for immediate classification as a serious adverse event (ie, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus, stillbirth or neonatal death]), the investigator should follow the procedures for reporting serious adverse events.

In the case of a live birth, the “normality” of the newborn can be assessed at the time of birth (ie, no minimum follow-up period of a presumably normal infant is required before an Exposure in Utero Form can be completed). The “normality” of an aborted fetus can be assessed by gross visual inspection, unless pre-abortion test findings are suggestive of a congenital anomaly.

Additional information about pregnancy outcomes that are classified as serious adverse events follows:

- “Spontaneous abortion” includes miscarriage and missed abortion.
- All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as serious adverse events. In addition, any infant death after 1 month that the investigator assesses as possibly related to the exposure in utero to the investigational medication should be reported.

Additional information regarding the exposure in utero 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 must obtain permission from the subject’s partner in order to conduct any follow-up or collect any information.

#### **8.11. Withdrawal Due to Adverse Events**

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.

#### **8.12. 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.

#### **8.13. 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.

### **8.13.1. 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 by the investigator. 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 in Utero 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 may be 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.

### **8.13.2. 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.

### **8.13.3. 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 trial will be documented in the Statistical Analysis Plan (SAP) and the Statistical Rulebook, which will be dated and maintained by the sponsor, before the time of database release. The reasons for any departure from the planned method of analysis will be fully documented.

## 9.1. Sample Size Determination

Although analysis for the primary efficacy endpoint will be model based, the sample size calculation is based on a two-sided Chi-Square test with a 0.05 significance level and a 1:1:1 randomization ratio of varenicline 1 mg BID to varenicline 0.5 mg BID to placebo. The study is powered at 80% or greater to detect varenicline (1 mg BID or 0.5 mg BID dose) vs. placebo differences in the CQR from Weeks 9 through 12. The sample size is based on CQR of 9% and 24% for placebo and varenicline respectively, or an odds ratio of 3.2.

A sample size of 300 subjects randomized to varenicline or placebo in a 1:1:1 (100 to varenicline 1 mg BID, 100 to varenicline 0.5 mg BID, 100 to placebo) will provide approximately 80% power to detect a difference in the primary endpoint between varenicline and placebo groups, assuming a true Week 9-12 CQR of 9% and 24% for placebo and varenicline respectively.

Enrollment will be stratified by age group (12-16 vs. 17-19) and sufficient subjects will be enrolled in the 12-16 year old age group to detect a difference in the primary endpoint between varenicline and placebo groups, assuming a true Week 9-12 CQR of 9% and 29% for placebo and varenicline respectively.

In order to ensure sufficient subjects are enrolled in the 12-16 year old stratum, the 17-19 year old stratum will be capped at a maximum of 90 subjects, leaving at least 210 subjects (approximately 70 subjects per treatment group) in the 12-16 year old stratum.

## Efficacy Analysis

The primary efficacy inference for the study is a comparison of varenicline to placebo for the CQR for Weeks 9 through 12. This measure will be obtained through reports of cigarette or other nicotine use since the last study visit confirmed by urine cotinine. An exploratory subgroup analysis for each dosing group by weight stratum for the primary endpoint will be provided.

All efficacy analyses will be performed overall as well as on the subgroup of patients who are 12-16 years of age.

Secondary efficacy endpoints are listed in Section [2.2](#).

These efficacy endpoints will be based on subject self-report, with abstinence confirmed by cotinine.

To assess the comparability of subjects across treatment groups, demographic, smoking history, and baseline nicotine dependence and other baseline characteristics will be summarized by treatment group. 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.



Data collected at baseline 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 to summarize the data.

### **9.1.1. Analysis of Primary Endpoint**

Logistic regression models will be used in the analyses of primary endpoint. The model will include strata, treatment, and center as independent variables. Treatment by center interaction will be investigated. If the treatment by center interaction is significant in the model containing treatment, center, and treatment by center interaction, then exploratory analyses will be undertaken to explain the nature and source of the interaction. However, the reported p-values will be based on the main effects model.

Additional analyses may be performed adjusting for baseline covariates as additive terms to the primary model, if necessary. 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.

Statistical hypotheses for the primary endpoint will be tested in an ordered fashion to preserve overall Type I Error. The 1 mg BID group will be tested against placebo, and if a statistically significant difference is observed, the 0.5 mg BID group will be tested against placebo. A p-value of 0.05 will be considered statistically significant in both tests. Both tests will be presented regardless of the p-value obtained.

The primary efficacy analysis population will be all subjects who took at least 1 dose of randomized study medication (Full Analysis set). Subjects who discontinue the study are assumed to be smokers for the time point of discontinuation through the end of the study. In computing responder rates, subjects who discontinue the study will be included in the denominator but not in the numerator, regardless of their last smoking status evaluation.

### **9.1.2. Analysis of Secondary Endpoints**

#### **9.1.2.1. Efficacy Endpoints**

There are several secondary smoking abstinence endpoints for this study, as indicated in Section 2.2. Each of these binary secondary endpoints will be analyzed using procedures similar to that described above for the primary efficacy endpoint. All statistical tests will be two-sided and at a 0.05 level of significance. P-values will be reported with no adjustments for the analysis of multiple secondary endpoints.

The number of cigarettes smoked over the past seven days will be collected by completion of the NUI at each visit. The reduction in the number of the cigarettes smoked will be calculated at each visit by subtracting the reported number of cigarettes smoked in the past 7 days at each visit from the number of cigarettes smoked in the past 7 days reported at the baseline visit. Longitudinal repeated measures models including strata, treatment, center,

and baseline number of cigarettes smoked will be used to assess the effect of treatment on the reduction in the number of cigarettes smoked.

### **Pharmacokinetic Endpoints**

The plasma concentration-time data collected in this study will be analyzed via nonlinear mixed effects (NONMEM software) to describe the population pharmacokinetics (PK) of varenicline including an assessment of covariate effects in adolescent smokers.

Varenicline exposure data derived from the individual Bayesian estimates of the pharmacokinetic parameters will be subsequently utilized to characterize the population exposure-response relationships for selected measures of efficacy and safety/tolerability of varenicline in this pediatric population. Model development may require the use of data from previous clinical studies. An analysis plan describing the details of the model building, covariate assessment and model validation will be provided separately before the unblinding of the data.

### **9.2. Safety Analysis**

All safety analyses will be performed overall as well as on the subgroup of patients who are 12-16 years of age. 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:

- Incidence and type of AEs;
- Incidence and type of SAEs;
- Change from baseline in laboratory parameters;
- Incidence of clinically significant laboratory parameters;
- Change from baseline in vital signs;
- Incidence of clinically significant vital sign parameters;
- Frequency and percent of subjects endorsing suicidal ideation or behavior.

All safety analyses will use the population of all subjects who received at least 1 dose of study drug.

In addition to the standard safety summaries for the vital signs data collected at each visit, the change from Baseline in BMI at Week 12 will be summarized by treatment group. Change from Baseline in BMI and any other safety endpoints of interest may be summarized for subgroups of interest if the number of subjects in the subgroup permits.

### **9.3. Interim Analysis**

Not planned.

### **9.4. Data Monitoring Committee**

An external Independent Data Monitoring Committee (IDMC) will be established to review data during the course of the study for safety monitoring and assessing risk benefit. Based on their review the IDMC will make a recommendation to continue, modify or stop the study.

The IDMC members will be selected from a pool of experts including one statistician, a psychiatrist and an expert in pediatric studies. The IDMC will meet before study start to discuss and finalize the charter.

The frequency of meetings will be dependent upon subject enrollment. It is suggested that the first data review will take place after 30 subjects complete 12 weeks of treatment. Subsequently data reviews will take place in increments of 50 subjects completing the 12 week treatment period, and as subjects complete the 9 month follow-up period; or at a minimum of two times a year. Serious adverse event (SAE) reports will be provided to the IDMC on a real- time basis. The frequency of meetings will be adjusted by the IDMC chair as she/he considers appropriate to fulfill the IDMC's responsibilities.

Details will be outlined in the IDMC charter.

The DMC will be responsible for ongoing monitoring of the efficacy and safety of subjects in the study according to the Charter. The recommendations made by the DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data which are not endpoints, to regulatory authorities, as appropriate. In this instance, such disease-related efficacy endpoints are not reported individually as SAEs.

## **10. QUALITY CONTROL AND QUALITY ASSURANCE**

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

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

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

## **11. DATA HANDLING AND RECORD KEEPING**

### **11.1. Case Report Forms/Electronic Data Record**

As used in this protocol, the term 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 accuracy, authenticity, and timely collection and reporting of all clinical, safety, laboratory data entered on the CRFs and any other data collection forms. 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 party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations. The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

## **12. ETHICS**

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

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent 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).

### **12.3. Subject Information and Consent**

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. Subject names, address, birth date and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify the trial subject. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data.

The informed consent 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 legally acceptable 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 legally acceptable representative before any study-specific activity is performed. Direct assent of the adolescent subject must also be obtained. Parental consent is not required for subjects over the age of 18. These subjects must sign their own informed consent document. The investigator will retain the original of each subject's signed consent/ assent form.

## **12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH Good Clinical Practice (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**

### **13.1. End of Trial in all Participating Countries**

End of Trial in all participating countries is defined as last subject's 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 7 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

## **15. PUBLICATION OF STUDY RESULTS**

- 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 the results of studies through posting the results of this study on [www.clinicaltrials.gov](http://www.clinicaltrials.gov). Pfizer posts the results of 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 FDAAA of 2007, 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 within one year after study completion, defined as 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 after such discontinuation of the program (if there are not plans for outlicensing or within two years if outlicensing plans have not completed).

## **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.

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## **Appendix 1. Nicotine Use Inventory**

### Asked at the Week 1 visit through the Week 12 visit

- Has the subject smoked any cigarettes (even a puff) since the last study visit?
- 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 study visit?
- 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?

### Asked at the Week 13 visit through the Week 52 visit

- Has the subject smoked any cigarettes (even a puff) since the last contact?
- Has the subject used any other tobacco products (eg, pipe, cigars, chew, snuff) since the last 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 tobacco products (eg, pipe, cigars, chew, snuff) in the last 7 days?

### Additionally Asked on the Week 52 visit

- Has the subject smoked any cigarettes (even a puff) in the last 4 weeks?
- Has the subject used any other tobacco products (eg, pipe, cigars, chew, snuff) in the last 4 weeks?
- Nicotine replacement therapy and/or other smoking cessation medications should be recorded in the concomitant medicine pages in the case report form.

## Appendix 2. Fagerström Test for Nicotine Dependence

Questions	Answers	Points
1. How soon after you wake up do you smoke your first cigarette?	Within 5 minutes	3
	6-30 minutes	2
	31-60 minutes	1
	After 60 minutes	0
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.?	Yes	1
	No	0
3. Which cigarette would you hate most to give up?	The first one in the morning	1
	Any other	0
4. How many cigarettes/day do you smoke?	10 or less	0
	11-20	1
	21-30	2
	31 or more	3
5. Do you smoke more frequently during the first hours after waking than during the rest of the day?	Yes	1
	No	0
6. Do you smoke if you are so ill that you are in bed most of the day?	Yes	1
	No	0

### Appendix 3. Hospital Anxiety and Depression Scale (HADS)

This questionnaire is designed to help your clinician to know how you feel. Read each item below and ✓ the reply which comes closest to how you have been feeling in the past week. Ignore the numbers printed next to the replies.

Don't take too long over you replies, your immediate reaction to each item will probably be more accurate than a long thought out response.

<b>1. I feel tense or 'wound up'</b> <input type="checkbox"/> 3 Most of the time <input type="checkbox"/> 2 A lot of the time <input type="checkbox"/> 1 From time to time, occasionally <input type="checkbox"/> 0 Not at all	<b>8. I feel as if I am slowed down</b> <input type="checkbox"/> 3 Nearly all the time <input type="checkbox"/> 2 Very often <input type="checkbox"/> 1 Sometimes <input type="checkbox"/> 0 Not at all
<b>2. I still enjoy things I used to enjoy</b> <input type="checkbox"/> 0 Definitely as much <input type="checkbox"/> 1 Not quite as much <input type="checkbox"/> 2 Only a little <input type="checkbox"/> 3 Hardly at all	<b>9. I get a sort of frightened feeling like 'butterflies' in my stomach</b> <input type="checkbox"/> 0 Not at all <input type="checkbox"/> 1 Occasionally <input type="checkbox"/> 2 Quite often <input type="checkbox"/> 3 Very often
<b>3. I get a sort of frightened feeling as if something awful is about to happen</b> <input type="checkbox"/> 3 Very definitely and quite badly <input type="checkbox"/> 2 Yes, but not too badly <input type="checkbox"/> 1 A little, but it doesn't worry me <input type="checkbox"/> 0 Not at all	<b>10. I have lost interest in my appearance</b> <input type="checkbox"/> 3 Definitely <input type="checkbox"/> 2 I don't take as much care as I should <input type="checkbox"/> 1 I may not take quite as much care <input type="checkbox"/> 0 I take just as much care as ever
<b>4. I can laugh and see the funny side of things</b> <input type="checkbox"/> 0 As much as I always could <input type="checkbox"/> 1 Not quite so much now <input type="checkbox"/> 2 Definitely not so much now <input type="checkbox"/> 3 Not at all	<b>11. I feel restless as if I have to be on the move</b> <input type="checkbox"/> 3 Very much indeed <input type="checkbox"/> 2 Quite a lot <input type="checkbox"/> 1 Not very much <input type="checkbox"/> 0 Not at all
<b>5. Worrying thoughts go through my mind</b> <input type="checkbox"/> 3 A great deal of the time <input type="checkbox"/> 2 A lot of the time <input type="checkbox"/> 1 Not too often <input type="checkbox"/> 0 Very little	<b>12. I look forward with enjoyment to things</b> <input type="checkbox"/> 0 As much as I ever did <input type="checkbox"/> 1 Rather less than I used to <input type="checkbox"/> 2 Definitely less than I used to <input type="checkbox"/> 3 Hardly at all
<b>6. I feel cheerful</b> <input type="checkbox"/> 3 Never <input type="checkbox"/> 2 Not often <input type="checkbox"/> 1 Sometimes <input type="checkbox"/> 0 Most of the time	<b>13. I get sudden feelings of panic</b> <input type="checkbox"/> 3 Very often indeed <input type="checkbox"/> 2 Quite often <input type="checkbox"/> 1 Not very often <input type="checkbox"/> 0 Not at all
<b>7. I can sit at ease and feel relaxed</b> <input type="checkbox"/> 0 Definitely <input type="checkbox"/> 1 Usually <input type="checkbox"/> 2 Not often <input type="checkbox"/> 3 Not at all	<b>14. I can enjoy a good book or radio or television program</b> <input type="checkbox"/> 0 Often <input type="checkbox"/> 1 Sometimes <input type="checkbox"/> 2 Not often <input type="checkbox"/> 3 Very seldom

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#### **Appendix 4. Neuropsychiatric Adverse Event Interview (NAEI)**

	<u>Adverse Event</u>
Have you felt depressed (sad, blue, down, empty, as if you didn't care)?  Do you find that you have lost interest in things or get less pleasure from things that you used to enjoy?  Have you cried or felt like crying?	Depression
Have you been worried, or scared?  Have you been nervous or anxious?  Have you felt panicky at all?  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?	Anxiety, Panic
Have you had times when you felt extremely anxious and you had to be always moving, even pacing?  Have you had times when you felt extremely agitated?	Agitation
Have you been feeling unusually cheerful, or happy, not just your normal self, so that other people noticed?  Have you had much more energy than usual to do things?  Have you needed less sleep than usual to feel rested?	Mania
Have you felt hostile towards others?  Have you been involved in any serious arguments or fights?	Hostility

Have you had the urge to injure or harm someone?	
Have you felt that someone may be after you, or trying to harm you in some way?	Paranoia
Has there been anything unusual about the way things look or sound or smell?  Have you heard things that other people couldn't hear, like noises or voices of people talking when there was no one around?  Have you seen things that other people couldn't see?	Hallucinations
Has your mind been playing tricks on you in any way?  Have you had any ideas that other people might not understand or might find strange?	Delusions
Have things seemed unreal to you?  Have you felt that you are detached from or have trouble connecting with other people?  Have you been feeling strange or odd in any other way?	Dissociative states  Feeling abnormal