Protocol A3051073

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

Statistical Analysis Plan (SAP)

Version: 3.0

Author: PPD (GPD Statistics - Groton)

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[redacted]

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LIST OF FIGURES

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APPENDICES

[redacted]

1. AMENDMENTS FROM PREVIOUS VERSION(S)

1.1. Version 1.1

- Updated per protocol amendment.
- Added definition of compliance and compliance summary table.
- Added summaries of volunteered adverse events.
- Added listings of Physical Examination and Suicide Behavior Questionnaire (SBQ-R) data from the screening visit.
- Updated Section 4.1 to state hypotheses in terms of odds ratios.
- Updated Section 6.1 to clarify that some visits are telephone visits and quit rates based on these data do not require chemical confirmation.
- Updated Section 6.3 to remove upper end to final visit window.
- Updated Section 8.2.6.2 to include box plots.

1.2. Version 1.2

- Added frequency table for post-treatment non-study smoking cessation aid use by treatment group.

1.3. Version 1.3

- Revised the alternative hypothesis from H_1: OR ≥ 1 to H_1: OR $\neq 1$ and included additional details regarding two sets of hypotheses and the odds ratio - Section 4.1.
- Corrected the statement of significance level from "p-value of 0.05 or larger" to "p-value of 0.05 or smaller" - Section 4.2.
- The primary efficacy analysis population will be the Full Analysis Set, defined as all subjects who were randomized – Section 5.1.
- To be consistent with other recent Varenicline studies, the term "continuous abstinence" is used instead of "continuous quit" for efficacy endpoints. For the primary efficacy endpoint, changed "continuous quit rate (CQR) from Week 9 through Week 12" to "continuous abstinence (CA) from Week 9 through Week 12 ". See Section 6.1.1. Note: This term change will not impact the definition of the endpoints or the analyses. The change is only within this SAP, not the protocol.
- Defined visit windows for weeks 14 and 15 - Section 6.3.
- Revised the section for "Pooling of Sites" to be consistent with current methods, which take into consideration of multiple countries - Section 6.4.

[redacted]

- Added sensitivity analysis to assess the impact of excluding 16 randomized subjects with possibly unreliable data who were randomized at investigational site PPD - Section 8.1.1.2.
- CCI [redacted]

1.4. Version 1.4

- Added sensitivity analysis based on imputation.
- Added shift tables for HADS subscores.
- Removed efficacy analysis by body weight group.

1.5. Version 2.0

- Added body weight strata to statistical models.
- Added summary tables by strata.
- Added efficacy figures.
- Added change from baseline summary tables for HADS.
- Added clarifying language to definition of treatment emergent responses on the C-SSRS.
- Removed box plots for laboratory values.
- Removed plots for Tier 1 and Tier 2 adverse events.
- Added additional terms to Appendix 2.
- Removed angioedema specific adverse event summaries.
- Removed CCI [redacted]
- Updated terms in Appendix 4 CCI [redacted]

1.6. Version 3.0

- Corrected body weight strata inequalities.
- Updated study design to align with language in the protocol.
- Indicated pooling of small centers will be based on the 12-16 year old, ≤55 kg stratum.

[redacted]

- Corrected 'including' to 'excluding' in Section 8.1.1.2 referencing a sensitivity analysis of site PPD.

2. INTRODUCTION

Note: in this document any text taken directly from the protocol is ***italicised***.

Most adult smokers initiated smoking as adolescents. According to the CDC's 2005 Youth Risk Behavior Survey, 23.0% of students in the United States were current cigarette users (i.e. had smoked cigarettes on more than one of the 30 days preceding the survey) and 9.4% of students were current frequent cigarette users (i.e. had smoked cigarettes on ≥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. 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 ≤16%.

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®) was approved in the United States in May 2006 as an aid to smoking cessation treatment in adults. 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.

The purpose of this statistical analysis plan is to outline the proposed statistical analysis methods. This analysis plan provides additional details concerning the statistical analyses that were originally outlined in the study protocol A3051073.

2.1. 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 ≤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).

Randomization will be stratified by age group (12-16 vs 17-19) and body weight. *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.*

[redacted]

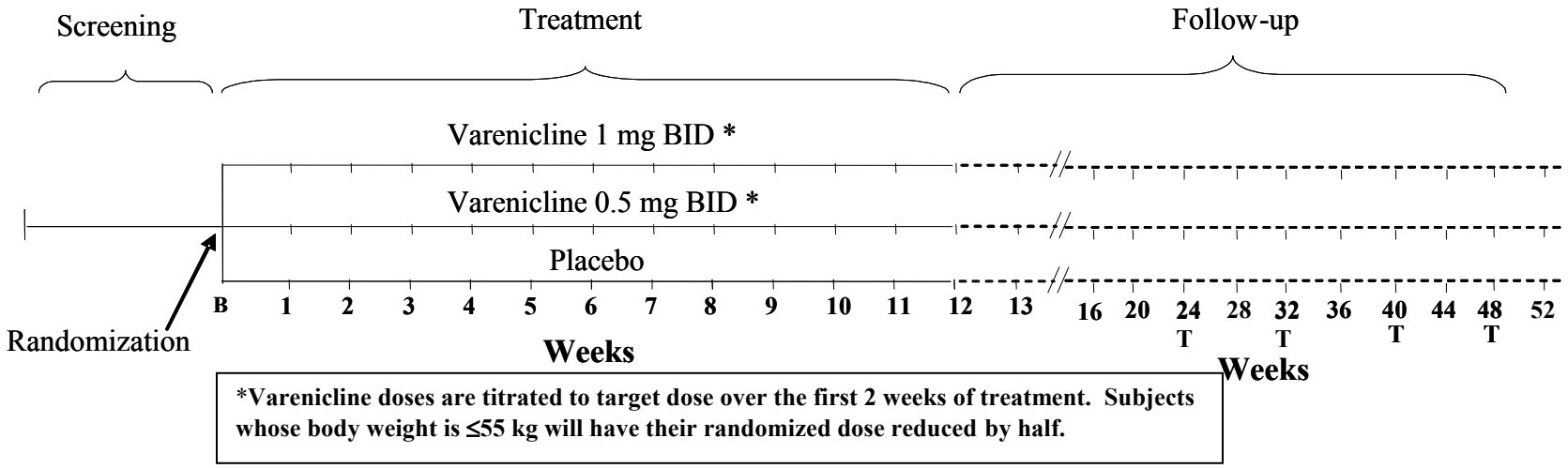
Those subjects deemed eligible will be randomized and enter the 12-week placebo-controlled treatment period with weekly clinic visits for efficacy and safety assessments and smoking cessation counseling. Varenicline or placebo dosing will begin with two weeks of titration. (Figure 1). All subjects will 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. 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 period: 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 visits are planned for Weeks 24, 32, 40, and 48.

The clinical trial is illustrated in Figure 1.

[redacted]

Figure 1. Study A3051073 Trial Diagram



BL = Baseline; T = Telephone contact

[redacted]

2.2. Study Objective

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

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

No interim analyses are planned for this study. The final analysis will be first performed at database release.

A Data Monitoring Committee will be used to monitor unblinded safety data in an ongoing manner.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

The primary hypotheses of interest are designed to assess the efficacy objective of this study, and are as follows;

1 mg BID group vs. placebo

$$H_0 : OR = 1$$
$$H_1 : OR \neq 1$$

0.5 mg BID group vs. placebo

$$H_0 : OR = 1$$
$$H_1 : OR \neq 1$$

where OR is the odds ratio (relative to placebo) of continuous abstinence from Week 9 to Week 12 (the last 4 weeks of treatment). The OR will be evaluated using a logistic regression model based on the predicted Week 9-12 continuous abstinence rate (CAR).

4.2. Statistical Decision Rules

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 or smaller will be considered statistically significant in both tests. Both tests will be presented regardless of the p-value obtained.

P-values will be reported with no adjustments for the analysis of multiple secondary endpoints or analyses by strata.

[redacted]

5. ANALYSIS SETS

In each of the following efficacy populations, subjects who discontinue the study are assumed to be smokers from 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.

5.1. Full Analysis Set

The primary efficacy analysis population will be the Full Analysis Set, defined as all subjects who were randomized.

5.2. Completer Subjects Analysis Set

The Completer Subjects population is defined as the subset of the Full Analysis Set who have at least 80% treatment compliance, as measured by having any dose of study medication for 80% of the planned number of days in the trial treatment period.

5.3. Safety Analysis Set

The Safety Analysis population will be all subjects who took at least 1 dose of randomized study medication, including partial doses.

5.4. Treatment Misallocations

Errors in treatment allocation will be handled in the following way:

If a subject was:

- Randomized but not treated, are excluded from all safety analyses as actual treatment is missing but will be included in the Full Analysis Set for the primary efficacy analysis.

- Treated but not randomized, will be excluded from the efficacy analyses since randomized treatment is missing, but will be reported under the treatment they actually received for all safety analyses.

- Randomized but took incorrect treatment, will be reported under their randomized treatment group for all efficacy analyses, but will be reported under the treatment they actually received for all safety analyses.

5.5. Protocol Deviations

The definitions of the Full Analysis Set and Completer populations are based only on patient treatment compliance as described in Sections 5.1 through 5.2. Violations of the protocol inclusion or exclusion criteria or other protocol violations or deviations will not exclude subjects from the defined analysis populations.

A summary by treatment group as well as a list of all clinically important protocol deviations will be included in the study report.

5.6. Compliance

The definition of compliance for the purpose of assessing the extent to which patients are complying with the prescribed dosing for the entire trial treatment period is as follows:

$$\text{Compliance} = \frac{Actual\ number\ of\ tablets\ taken}{Expected\ number\ of\ tablets\ to\ be\ taken}, \text{ where}$$

Actual number of tablets taken is as per the dosing log in the CRF and expected number of tablets taken is the number of tablets prescribed.

Note that this is not the definition of compliance as used for the Completers Population, which requires only that patients take any amount of study drug for 80% of the planned number of days in the trial treatment period.

6. ENDPOINTS AND COVARIATES

6.1. Efficacy Endpoint(s)

Efficacy assessments will include measurement of smoking cessation and reduction obtained from the Nicotine Use Inventory (NUI) and urine cotinine measurements. The Week 24, 32, 40, and 48 visits are telephone visits, and therefore do not include collection of urine cotinine. Abstinence rates based on or including these visits do not require chemical confirmation. Urine cotinine is collected at all in-person clinic visits, and all abstinence rates based on in-clinic visits utilize urine cotinine to confirm abstinence. The reduction in the number of cigarettes smoked is based solely on the reported number of cigarettes on the NUI at baseline and the post-baseline visit of interest. The endpoints derived from these include:

6.1.1. Primary Efficacy Endpoint

- *4-week continuous abstinence rate (CA) from Week 9 through Week 12 of treatment for varenicline compared with placebo.*

6.1.2. 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.*

6.2. Safety Endpoints

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

[redacted]

6.3. Windowing and Time Point Assignments

No windows will be used to determine planned weeks and days for this study. All analyses will be based on nominal day and week as recorded on the CRF. The exception will be the early termination visit. This visit will be assigned a nominal week according to the following windowing algorithm. (Note: The count of days starts from the first day of dosing and all intervals below are inclusive of the end days):

Week 1: day 2 through 10
Week 2: day 11 through 17
Week 3: day 18 through 24
Week 4: day 25 through 31
Week 5: day 32 through 38
Week 6: day 39 through 45
Week 7: day 46 through 52
Week 8: day 53 through 59
Week 9: day 60 through 66
Week 10: day 67 through 73
Week 11: day 74 through 80
Week 12: day 81 through 87
Week 13: day 88 through 94
Week 14: day 95 through 101
Week 15: day 102 through 108
Week 16: day 109 through 126
Week 20: day 127 through 147
Week 22: day 148 through 161
Week 24: day 162 through 182
Week 28: day 190 through 210
Week 32: day 218 through 238
Week 36: day 246 through 266
Week 40: day 274 through 294
Week 44: day 302 through 322
Week 48: day 330 through 350
Week 52: day 358 on

In the event of ties, the non “early termination” visit (i.e. the earlier visit) will be selected as the representative visit.

Day will be computed by subtracting the date of the first dose of study medication from the date of the evaluation. In order that the first day of dosing be defined as Day 1, one day will be added to this difference.

Baseline will be defined as the latest evaluation performed prior to the first dose of study medication.

[redacted]

6.4. Pooling of Small Sites

Pooling of sites will be performed only once prior to any efficacy statistical analysis.

Any investigator center having less than 2 subjects in any given treatment group or efficacy outcome category within each age group strata will be defined as a 'small' center. The pooling of small centers will be based on the total number of subjects randomized at each center. Small centers will be pooled to large centers within the same country. When there are only small centers within a given country, small centers will be pooled to large centers within the same region.

Small centers will be pooled with other similar small centers using the following process:

Part A: Pool centers based on frequency in binary efficacy endpoints in the 12-16 year old stratum and the ≤55 kg stratum.

1. For the completer subjects population, create a center by CAR 9-52 frequency table (say Table 1).

2. Identify small centers from Table 1 (small center defined as a center with a 0 count in any column of Table 1).

3. Identify the country for each small center.

4. Within each country, independently order the small centers and the non-small centers (those with non-zero cells) based on the total number of subjects in the center.

5. Within each country, pool the smallest small (zero-cell) center to the largest nonsmall (non-zero cell). Then pool the next smallest small center to the next largest non-small center, and so on, until all small centers have being pooled with a nonsmall center. At this point the center by CAR 9-52 frequency table should not have any cell with zero frequency.

6. Renumber the pooled centers after the last two centers are pooled.

7. Repeat Steps 1 to 6 for each of the other efficacy endpoints to ensure there are no zero frequency cells in the frequency table of pooled center by any binary endpoint.

Part B: Pool centers based on frequency in each treatment group. Repeat 'Part A' by replacing the binary endpoint with treatment group data.

After applying 'Part A' and 'Part B', check the convergence of the CAR 9-52 model that includes treatment groups and centers (pooled centers) on the Completers population:

- If model converges, check the convergence of all other logistic models specified in this SAP.

[redacted]

- If model does not converge (unlikely) apply 'Part C' described below.

Part C:

Repeat 'Part A' and 'Part B' with small center defined as a center with a count of 1 in any column of Table 1.

Notes:

a. If two centers have same frequency, select the one with the smallest center number.

b. If for a given country, there is only one center, replace country by region in Steps 3 to 6 above (only for the given country, for other countries do as specified above).

The final pooled centers will be used in the analysis for the rest of the efficacy endpoints.

6.5. Covariates

Age Strata, body weight strata, and center will be included in statistical models as fixed effects. The additional effects of treatment by center interaction, treatment by age, and treatment by body weight may be included in exploratory models.

7. HANDLING OF MISSING VALUES

Subjects who discontinue the study will be considered smokers for the remainder of the study regardless of their last smoking status evaluation. This implies that subjects who discontinue will continue to be represented in the denominator but not in the numerator regardless of smoking status at the time of discontinuation. This can be considered a worst case carried forward analysis and represents a conservative approach to imputation of missing data.

For the HADS-A and HADS-D, if more than one question within a domain (anxiety or depression) is missing, the score will be set to missing. If only one question is missing, the missing response will be imputed with the domain-specific mean based on the remaining questions.

8. STATISTICAL METHODOLOGY AND STATISTCAL ANALYSES

8.1. Statistical METHODS

All PK/PD analyses will be performed by the Pfizer Pharmacometrics/Clin Pharm groups. An analysis plan providing details of these analyses will be provided separately.

No adjustment for multiple comparisons will be made.

8.1.1. Analyses for Categorical Data

8.1.1.1. Descriptive Statistics

Categorical data will be summarized by presenting the counts and percentages with the denominator being the number of subjects in the analysis set in the particular treatment group with non-missing data.

[redacted]

8.1.1.2. Efficacy Analysis

Logistic regression models will be used in the analyses of primary endpoint, as well as several secondary endpoints. *The model will include strata, and* pooled *center as independent variables. Treatment by center*, treatment by age stratum, and treatment by body weight stratum *interaction will be investigated.* If interactions are significant*, 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.

In addition, a sensitivity analysis excluding 16 subjects from investigative site PPD will be performed on the primary endpoint – Continuous Abstinence Rate from Week 9 through 12 – using the primary analysis model.

This sensitivity analysis will be performed for the following groups:

- Overall study.
- 12-16 year old age stratum.

8.1.2. Analyses for Continuous Data

8.1.2.1. Descriptive Statistics

Continuous variables for baseline demographic and smoking history data will be summarized (n, mean, standard deviation, median, minimum and maximum) by treatment group.

8.1.2.2. Efficacy Analysis

Analysis of the continuous endpoints will be performed by using longitudinal repeated measures models including treatment, visit, age strata, body weight strata, pooled study center, and baseline measure.

SAS PROC MIXED will be used, with an unstructured covariance structure. If the unstructured covariance does not converge, compound symmetric variance structure will be used.

8.2. Statistical Analyses

All efficacy analyses will be based on the Full Analysis Set as described in Section 5.1. Efficacy analyses will also be performed on the Completer Set as described in Section 5.2. Missing values will be handled as explained in Section 7.

All analyses will be performed overall as well as on the age stratum of patients who are 12-16 years of age (with corresponding removal of age strata terms from analysis models).

[redacted]

Subjects in this adolescent study will be considered smokers, regardless of the self reported smoking status, if the urine cotinine test is positive.

8.2.1. Baseline Demographics and Other Baseline Characteristics

Height, weight, BMI, and age at screening will be summarized as continuous measures as described in Section 8.1.1.1. Age group and race will be summarized as categorical measures as described in Section 8.1.2.1. Smoking history information and the Fagerstrom Test for Nicotine Dependence will be summarized as described in Sections 8.1.1.1 and 8.1.2.1.

These will be summarized for the following groups:

- Overall study.
- 12-16 year old age stratum.
- 12-16 year old age stratum, ≤55 kg weight stratum.
- 12-16 year old age stratum, >55 kg weight stratum.
- 17-19 year old age stratum.

8.2.2. Compliance

Compliance will be calculated overall as well as by visit as described in Section 5.6. Compliance will be summarized by visit as well as overall. Early termination visits will be windowed as indicated in Section 6.3.

These will be summarized for the following groups:

- Overall study.
- 12-16 year old age stratum.
- 12-16 year old age stratum, ≤55 kg weight stratum.
- 12-16 year old age stratum, >55 kg weight stratum.
- 17-19 year old age stratum.

8.2.3. Primary Efficacy Analysis

The primary efficacy analysis will be analysis of *the 4-week continuous abstinence rate (CAR) from Week 9 through Week 12 of treatment for each varenicline treatment group compared with placebo.*

The 4-week CAR will be summarized by treatment group using descriptive statistics and bar charts.

[redacted]

This will be summarized for the following groups:

- Overall study.
- 12-16 year old age stratum.
- 12-16 year old age stratum, ≤55 kg weight stratum.
- 12-16 year old age stratum, >55 kg weight stratum.
- 17-19 year old age stratum.

The 4-week CAR will be analyzed using a logistic regression model as described in Section 8.1.1.2. Odds ratios and 95% confidence intervals will be shown in plots.

These will be analysed for the following groups:

- Overall study.
- 12-16 year old age stratum (without age strata covariate).
- 12-16 year old age stratum, ≤55 kg weight stratum (without age strata or body weight strata covariates).
- 12-16 year old age stratum, >55 kg weight stratum (without age strata or body weight strata covariates).

While the analysis will be performed for sets listed above, the primary analysis of the primary efficacy endpoint is the overall study.

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.

A sensitivity analysis excluding site PPD will be performed based on the primary analysis of the primary endpoint. This site was terminated based on concerns regarding GCP non-compliance.

As a sensitivity analysis of the primary endpoint, multiple imputation methods will be used to evaluate the impact of missing data. Subjects who discontinue the study due to insufficient clinical response, adverse event, or death will be imputed based upon the observed placebo distribution, regardless of randomized treatment assignment. Imputation will be based on age stratum, body weight stratum, pooled study center, and baseline number of cigarettes smoked. Subjects who discontinue the study for other reasons, or who complete the study but have a missing Week 9-12 CAR, will be imputed based on observed subjects in the same treatment group. Imputation will be based on treatment, age stratum, body weight stratum, pooled study center, and baseline number of cigarettes smoked.

[redacted]

A final sensitivity analysis will be performed based on discontinuation from treatment, regardless of study completion status.

8.2.4. Secondary Efficacy Analyses

8.2.4.1. The 7-day Point-prevalence of Smoking Abstinence at Weeks 12, 24, and 52

The 7-day point prevalence of abstinence will be summarized by treatment group and visit from Week 3 through Week 52 using descriptive statistics and bar charts.

These will be summarized for the following groups:

- Overall study.
- 12-16 year old age stratum.
- 12-16 year old age stratum, ≤55 kg weight stratum.
- 12-16 year old age stratum, >55 kg weight stratum.
- 17-19 year old age stratum.

The 7-day point prevalence of abstinence at Weeks 12, 24, and 52 will be analyzed using separate logistic regression models as described in Section 8.1.1.2. Odds ratios and 95% confidence intervals will be shown in plots.

These will be analysed for the following groups:

- Overall study.
- 12-16 year old age stratum (without age strata covariate).
- 12-16 year old age stratum, ≤55 kg weight stratum (without age strata or body weight strata covariates).
- 12-16 year old age stratum, >55 kg weight stratum (without age strata or body weight strata covariates).

8.2.4.2. The Reduction in Number of Cigarettes Smoked at Weeks 12, 24, and 52

The reduction in the number of the cigarettes smoked will be calculated at each visit by subtracting the reported average number of cigarettes smoked per day in the past 7 days at each visit from the average number of cigarettes smoked per day in the past 7 days reported at the baseline visit.

The reduction in the mean number of cigarettes smoked per day over the past 7 days will be summarized by treatment group and visit using descriptive statistics.

[redacted]

These will be summarized for the following groups:

- Overall study.
- 12-16 year old age stratum.
- 12-16 year old age stratum, ≤55 kg weight stratum.
- 12-16 year old age stratum, >55 kg weight stratum.
- 17-19 year old age stratum.

The reduction in the mean number of cigarettes smoked per day will be analyzed using longitudinal repeated measures models as described in Section 8.1.2.2. In addition to treatment and visit, baseline number of cigarettes smoked, pooled study center, age strata, and body weight strata will be included as covariates. A treatment by visit interaction will be included for estimation purposes. Least square means and 95% confidence intervals will be shown in plots.

These will be analysed for the following groups:

- Overall study.
- 12-16 year old age stratum (without age strata covariate).
- 12-16 year old age stratum, ≤55 kg weight stratum (without age strata or body weight strata covariates).
- 12-16 year old age stratum, >55 kg weight stratum (without age strata or body weight strata covariates).

8.2.4.3. The Continuous Abstinence Rate from Week 9 through Week 24 and Week 52

The continuous abstinence rate at a given time point will be defined as the proportion of subjects who remained abstinent from Week 9 through the time point being summarized.

The continuous abstinence rates from Week 9 through Week 24 and Week 9 through Week 52 will be summarized by treatment group using descriptive statistics and bar charts.

These will be summarized for the following groups:

- Overall study.
- 12-16 year old age stratum.
- 12-16 year old age stratum, ≤55 kg weight stratum.
- 12-16 year old age stratum, >55 kg weight stratum.

[redacted]

- 17-19 year old age stratum.

The continuous abstinence from Week 9 through Week 24 and from Week 9 through Week 52 endpoints will be analyzed using separate logistic regression models as described in Section 8.1.1.2. Odds ratios and 95% confidence intervals will be shown in plots.

These will be analysed for the following groups:

- Overall study.
- 12-16 year old age stratum (without age strata covariate).
- 12-16 year old age stratum, ≤55 kg weight stratum (without age strata or body weight strata covariates).
- 12-16 year old age stratum, >55 kg weight stratum (without age strata or body weight strata covariates).

8.2.5. Additional Efficacy Analysis

Subjects who reported using any non-study smoking cessation aids during the non-treatment follow-up period will be displayed in a table described in Section 8.1.1.1. Additionally, this subset of concomitant medication use will be listed in a separate listing.

8.2.6. Safety Analysis

All subjects who received at least one dose of study medication will be included in the safety analyses and presentations. All safety data as described in Section 6.2 will be subjected to clinical review and summarized descriptively by treatment group as frequencies of events and mean changes from Baseline, as appropriate.

These will be summarized for the following groups:

- Overall study.
- 12-16 year old age stratum.
- 12-16 year old age stratum, ≤55 kg weight stratum.
- 12-16 year old age stratum, >55 kg weight stratum.
- 17-19 year old age stratum.

8.2.6.1. Adverse Events

The Neuropsychiatric Adverse Event Interview (NAEI) 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

[redacted]

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.

All adverse events will be reported using the MedDRA dictionary. The incidence of treatment emergent AEs will be summarized by treatment group and system organ class, higher level group term, and preferred term. Additionally, the incidence of treatment emergent Neuropsychiatric AEs (Appendix 1) and serious skin adverse events (Appendix 2), will be summarized by treatment group in separate tables.

Adverse events will be reported according to Pfizer Data Standards (PDS) without consideration of reporting status (volunteered or solicited via the NAEI). Additionally, adverse events will be summarized including only volunteered events. The lag period for this study will be set at 30 days.

CCI [redacted]

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an adverse event or a group of adverse events. Except for select events in unique situations, studies do not employ formal adjudication procedures for the purpose of event classification. CCI [redacted]

CCI [redacted]

All adverse event summaries will be produced for the following groups:

- Overall study
- 12-16 year old age stratum
- 12-16 year old age stratum, ≤55 kg weight stratum
- 12-16 year old age stratum, >55 kg weight stratum
- 17-19 year old age stratum

8.2.6.2. Clinical Laboratory Measures

Laboratory abnormalities will be summarized by treatment group according to the following three baseline statuses: Normal Baseline, Abnormal Baseline, and Without Regard to Baseline. Median change from baseline to final observed laboratory data will also be summarized by treatment group. Shift tables from baseline to each assessment will be provided by treatment group.

[redacted]

These will be summarized for the following groups:

- Overall study
- 12-16 year old age stratum
- 12-16 year old age stratum, ≤55 kg weight stratum
- 12-16 year old age stratum, >55 kg weight stratum
- 17-19 year old age stratum

8.2.6.3. Vital Signs

Descriptive statistics will be presented by treatment group for pulse, systolic blood pressure, and diastolic blood pressure at baseline and each available visit. Multiple measurements repeated at a given visit will be summarized by the mean of the repeated values. Median changes from baseline in blood pressure and pulse rate will also be presented. Shift tables from baseline to each assessment will be provided by treatment group.

These will be summarized for the following groups:

- Overall study
- 12-16 year old age stratum
- 12-16 year old age stratum, ≤55 kg weight stratum
- 12-16 year old age stratum, >55 kg weight stratum
- 17-19 year old age stratum

8.2.6.4. Height and Weight

As this is a study of adolescents who may still be growing, height will be measured at baseline and Week 12 (or end of treatment) in addition to weight. Descriptive statistics will be presented by treatment group and for height, weight, and body mass index (BMI) at baseline and Week 12. In addition, summary statistics for change from baseline to Week 12 will be displayed for each measure. Multiple measurements repeated at a given visit will be summarized by the mean of the repeated values.

These will be summarized for the following groups:

- Overall study
- 12-16 year old age stratum
- 12-16 year old age stratum, ≤55 kg weight stratum

[redacted]

- 12-16 year old age stratum, >55 kg weight stratum
- 17-19 year old age stratum

8.2.6.5. Physical Examination

A physical examination including height and weight will be performed at screening visit by trained medical personnel. Physical examination data will be included in a listing.

8.2.6.6. Suicide Behavior Questionnaire - Revised

The Suicidal Behaviors Questionnaire-Revised (SBQ-R), *a brief self-report measure of past suicidal behavior, will be completed by subjects at the Screening visit*. SBQ-R data will be included in a listing.

8.2.6.7. Hospital Anxiety and Depression Scale

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. It is a patient completed questionnaire that establishes the presence and severity of both anxiety (7 questions) and depression (7 questions).

The baseline anxiety total score and depression total score as well as change from baseline at each visit will be summarized by treatment group as described in Section 8.1.2.1. In addition the maximum increase in the anxiety total score and depression total score per subject while on treatment will be summarized by treatment group.

Shift tables for HADs Depression subscore and HADS Anxiety Subscore will be produced by treatment and stratum, as well as overall. The shift will be from baseline to the worst score post-baseline. Both baseline and post-baseline will be categorized to 0-7, 8-10, and 11+. The number and percent of patients who increased to a higher category will be tabulated as well.

If more than one question within a domain (anxiety or depression) is missing, the score will be set to missing. If only one question is missing, the missing response will be imputed with the domain-specific mean based on the remaining questions.

These will be summarized for the following groups:

- Overall study
- 12-16 year old age stratum
- 12-16 year old age stratum, ≤55 kg weight stratum
- 12-16 year old age stratum, >55 kg weight stratum
- 17-19 year old age stratum

[redacted]

8.2.6.8. Columbia Suicide Severity Rating Scale (C-SSRS)

The Columbia Suicide Severity Rating Scale (CSSR-S) is a set of suggested questions designed to elicit information about passive or active suicidal ideation, active suicidal intent, and self-injurious behavior.

Frequency counts and percents for the C-CASA categories will be displayed in figures as well as tables for screening (Lifetime), baseline, treatment emergent, and follow up findings by treatment group. Treatment emergent responses are those between the date of first dose of study medication and the date of last dose plus 30 days. If last dose plus 30 days falls within the look back period for the 'since the last visit' administration of the C-SSRS, the responses are considered treatment emergent. Follow Up is all responses more than 30 days after the date of last dose. Listings will include both C-SSRS observed data as well as C-CASA categories.

These will be summarized for the following groups:

- Overall study
- 12-16 year old age stratum
- 12-16 year old age stratum, ≤55 kg weight stratum
- 12-16 year old age stratum, >55 kg weight stratum
- 17-19 year old age stratum

[redacted]

Appendix 1. Neuropsychiatric Adverse Events

Neuropsychiatric adverse events will be the MedDRA preferred terms included below.

Anxiety:

HLT Name	PT Name
Adjustment disorders	Adjustment disorder with anxiety
Anxiety disorders NEC	Anxiety disorder Anxiety disorder due to a general medical condition Generalised anxiety disorder Neurosis
Anxiety symptoms	Activation syndrome Anticipatory anxiety Anxiety Nervousness Stress Tension
Fear symptoms and phobic disorders (incl social phobia)	Autophobia
Impulse control disorders	Impulse-control disorder Impulsive behaviour Pyromania Trichotillomania
Obsessive-compulsive disorders and symptoms	Compulsions Obsessive thoughts Obsessive-compulsive disorder
Panic attacks and disorders	Limited symptom panic attack
Stress disorders	Acute stress disorder Burnout syndrome Post-traumatic stress disorder
Behaviour and socialisation disturbances	Impatience
Anxiety symptoms	Somatoform disorder cardiovascular

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[redacted]

Anxiety:

HLT Name	PT Name
Fear symptoms and phobic disorders (incl social phobia)	Acrophobia Agoraphobia Animal phobia Arachnophobia Claustrophobia Dysmorphophobia Fear Fear of animals Fear of closed spaces Fear of crowded places Fear of death Fear of disease Fear of eating Fear of falling Fear of injection Fear of open spaces Fear of pregnancy Fear of weight gain Haphephobia Hydrophobia Noctiphobia Nocturnal fear Nosophobia Ochlophobia Osmophobia Paruresis Performance fear Phagophobia Phobia Phobia of driving Phobia of exams Phobia of flying Phobic avoidance Phonophobia Photaugiaphobia Social fear Social phobia Thanatophobia

[redacted]

Depression:

HLT Name	PT Name
Adjustment disorders	Adjustment disorder with depressed mood Adjustment disorder with mixed anxiety and depressed mood
Behaviour and socialisation disturbances	Asocial behaviour Social avoidant behaviour
Depressive disorders	Agitated depression Depression Dysthymic disorder Major depression Menopausal depression Postpartum depression
Mood alterations with depressive symptoms	Anhedonia Decreased interest Depressed mood Depressive symptom Feeling guilty Feeling of despair Feelings of worthlessness Morose Negative thoughts Psychomotor retardation Tearfulness
Mood disorders NEC	Apathy Boredom Laziness Mood disorder due to a general medical condition Seasonal affective disorder
Personality disorders NEC	Self esteem decreased
Abnormal behaviour NEC	Regressive behaviour
General signs and symptoms NEC	Crying

[redacted]

Feeling Abnormal:

HLT Name	PT Name
Abnormal behaviour NEC	Abnormal behavior
Mental disorders NEC	Mental disorder Mental status changes Dyslogia
Confusion and disorientation	Confusional state Disorientation
Emotional and mood disturbances NEC	Emotional disorder Emotional distress
Behaviour and socialisation disturbances	Personality change
Mental impairment (excl dementia and memory loss)	Mental impairment
Psychiatric symptoms NEC	Psychiatric symptom Trance
Nervous system disorders NEC	Nervous system disorder
Feelings and sensations NEC	Feeling drunk Feeling abnormal
Disability issues	Activities of daily living impaired Impaired driving ability Impaired work ability Bedridden Disability
General signs and symptoms NEC	Performance status decreased Impaired self-care
Decreased physical activity levels	Catatonia
Dementia NEC	Pseudodementia
Dissociative states	Depersonalisation Dissociation Dissociative amnesia Dissociative disorder Dissociative fugue Dissociative identity disorder
Perception disturbances	Derealisation
Parasomnias	Confusional arousal
Disturbances in consciousness NEC	Altered state of consciousness Consciousness fluctuating
Emotional and mood disturbances NEC	Mood altered

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[redacted]

Feeling Abnormal:

HLT Name	PT Name
Partial complex seizures	Dreamy state
Thinking disturbances	Bradyphrenia Circumstantiality Confabulation Derailment Ideas of reference Illogical thinking Impaired reasoning Loose associations Magical thinking Morbid thoughts Obsessive rumination Perseveration Poverty of thought content Tachyphrenia Tangentiality Thinking abnormal Thought blocking

Hostility:

HLT Name	PT Name
Behaviour and socialisation disturbances	Antisocial behaviour Belligerence Hostility
Impulse control disorders	Intermittent explosive disorder
Personality disorders with dramatic behaviour (Cluster B)	Psychopathic personality

Agitation:

HLT Name	PT Name
Anxiety symptoms	Agitation
Increased physical activity levels	Restlessness
Mental impairment (excl dementia and memory loss)	Disturbance in attention
Dyskinesias and movement disorders NEC	Hyperkinesia

[redacted]

Aggression:

HLT Name	PT Name
Criminal activity	Homicide Incest Physical abuse Physical assault Sexual abuse Spousal abuse Verbal abuse
Behaviour and socialisation disturbances	Aggression Violence-related symptom
Personality disorders with dramatic behaviour (Cluster B)	Antisocial personality disorder
Emotional and mood disturbances NEC	Anger Dysphoria

Delusions:

HLT Name	PT Name
Delusional symptoms	Cotard's syndrome Delusion Delusion of grandeur Delusion of reference Delusion of replacement Delusions, mixed Depressive delusion Erotomanic delusion Jealous delusion Persecutory delusion Somatic delusion Thought broadcasting Thought insertion Thought withdrawal
Delusional disorders	Alice in wonderland syndrome Delusional disorder, erotomanic type Delusional disorder, grandiose type Delusional disorder, jealous type Delusional disorder, mixed type Delusional disorder, persecutory type Delusional disorder, somatic type Delusional disorder, unspecified type
Perception disturbances	Deja vu Delusional perception Jamais vu
Behaviour and socialisation disturbances	Grandiosity

[redacted]

Hallucination:

HLT Name	PT Name
Perception disturbances	Hallucination Hallucination, auditory Hallucination, gustatory Hallucination, olfactory Hallucination, synaesthetic Hallucination, tactile Hallucination, visual Hallucinations, mixed Illusion Somatic hallucination
Narcolepsy and associated conditions	Hypnagogic hallucination Hypnopompic hallucination

Mania:

HLT Name	PT Name
Thinking disturbances	Flight of ideas
Mood alterations with manic symptoms	Hypomania Mania
Emotional and mood disturbances NEC	Elevated mood Euphoric mood
Personality disorders NEC	Self esteem inflated
Bipolar disorders	Bipolar disorder Bipolar I disorder Bipolar II disorder Cyclothymic disorder
Affect alterations NEC	Affect lability
Behaviour and socialisation disturbances	Disinhibition
Fluctuating mood symptoms	Mood swings

Panic:

HLT Name	PT Name
Panic attacks and disorders	Panic attack Panic disorder Panic disorder with agoraphobia Panic disorder without agoraphobia Panic reaction
Abnormal behaviour NEC	Breath holding

[redacted]

Paranoia:

HLT Name	PT Name
Behaviour and socialisation disturbances	Paranoia
	Suspiciousness
Personality disorders with eccentric behaviour (Cluster A)	Paranoid personality disorder
Psychiatric symptoms NEC	Hypervigilance

Psychosis:

HLT Name	PT Name
Affect alterations NEC	Flat affect Inappropriate affect
Brief psychotic disorder	Brief psychotic disorder with marked stressors Brief psychotic disorder without marked stressors Transient psychosis
Psychotic disorder NEC	Acute psychosis Hysterical psychosis Psychotic behaviour Psychotic disorder Psychotic disorder due to a general medical condition Reactive psychosis Shared psychotic disorder
Schizoaffective and schizophreniform disorders	Schizoaffective disorder Schizoaffective disorder bipolar type Schizoaffective disorder depressive type Schizophreniform disorder
Schizophrenia NEC	Schizophrenia Schizophrenia simple Schizophrenia, catatonic type Schizophrenia, disorganised type Schizophrenia, paranoid type Schizophrenia, residual type Schizophrenia, undifferentiated type
Personality disorders with eccentric behaviour (Cluster A)	Schizotypal personality disorder
Behaviour and socialisation disturbances	Negativism

[redacted]

Homicidal Ideation:

HLT Name	PT Name
Behaviour and socialisation disturbances	Homicidal ideation

Suicidal Behavior:

HLT Name	PT Name
Suicidal and self-injurious behaviour	Intentional self-injury Self injurious behaviour Suicidal behaviour Suicide attempt

Suicidal Ideation:

HLT Name	PT Name
Suicidal and self-injurious behaviour	Self-injurious ideation Suicidal ideation

Suicide:

HLT Name	PT Name
Suicidal and self-injurious behaviour	Completed suicide
Depressive disorders	Depression suicidal

[redacted]

Appendix 2. Serious Skin Adverse Events

Serious skin adverse events will be the MedDRA preferred terms included below.

Acute generalised exanthematous pustulosis
Cutaneous vasculitis
Dermatitis bullous
Dermatitis exfoliative
Dermatitis exfoliative generalised
Drug reaction with eosinophilia and systemic symptoms
Epidermal necrosis
Erythema multiforme
Exfoliative rash
Oculomucocutaneous syndrome
Skin necrosis
Stevens-Johnson syndrome
Toxic epidermal necrolysis
Toxic skin eruption

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