Protocol ACH-CYT-04 (ORCA-3 Trial)

A Second Multicenter, Double-blind, Randomized, Placebo-controlled Phase 3 Trial Evaluating the Efficacy and Safety of Cytisinicline in Adult Smokers

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CONFIDENTIAL

SYNOPSIS

Protocol Number: ACH-CYT-04 (ORCA-3 Trial)
Sponsor: Achieve Life Sciences
Title of Study: A Second Multicenter, Double-blind, Randomized, Placebo-controlled Phase 3 Trial Evaluating the Efficacy and Safety of Cytisinicline in Adult Smokers
Clinical Phase: Phase 3
Study Population: Male or female subjects ≥18 years who are daily cigarette smokers intending to make a quit attempt during the study.
Rationale: (-)-Cytisine is a naturally occurring plant-based alkaloid that is believed to reduce the severity of nicotine withdrawal symptoms by targeting nicotinic acetylcholine receptors (nAChRs) in the brain. Cytisine administered using a 1.5 mg dose in a downward titration schedule over 25 days has been used as a smoking cessation drug since the 1980's in Central and Eastern European countries, where initial clinical studies were conducted. Previous studies dating from decades ago and more current Phase 3 studies (published in 2011, 2014, and 2021) have shown that cytisine can be more effective than placebo or nicotine replacement therapy (NRT) and as effective as varenicline in helping smokers to stop smoking. In 2018, the United States Adopted Names (USAN) Council adopted "cytisinicline" as the nonproprietary, or generic, name for cytisine. In the 2011 published Phase 3 study that evaluated cytisine versus placebo in 740 primarily moderate-to-heavy smokers treated for 25 days in Poland, the RR (relative risk) for sustained 6-month abstinence was 2.9 (10.0% cytisine arm compared to 3.5% placebo arm; P<0.001).[1] In the 2014 published Phase 3 study that evaluated cytisine for 25 days versus NRT for 8 weeks in 1,310 adult daily smokers in New Zealand, the RR for continuous six-month abstinence was 1.4 for cytisine (22% cytisine arm compared to 15% in the NRT arm; P=0.002).[2] In the 2021 published Phase 3 study that evaluated cytisine for 25 days with a low maintenance dose versus varenicline for 12 weeks in 679 adult indigenous Māori smokers in New Zealand, the RR for 6 months abstinence was 1.55 for cytisine (12.1% cytisine arm compared to 7.9% in the varenicline arm).[3] Data from the international EAGLES trial (N=8,120) were used to assess predictors for continuous smoking abstinence outcomes from Weeks 9-24.[4] These analyses provided clear evidence that US origin was associated with lower success rates of stopping, regardless of treatment (varenicline, bupropion, or NRT). The continuous abstinence rates from 9-24 weeks in the US were 16.1%, 11.4% and 10.6% for varenicline, bupropion, or NRT respectively, compared to 6.7% placebo treatment. The odds ratios (OR) for these treatments in the US were 2.66, 1.78, and 1.64 respectively. The lower success rate in US smokers supports the view that smokers in the US may have reached a point in the tobacco epidemic such that those who continue to smoke, despite strong cultural pressures not to smoke, have particular characteristics that make it more difficult for them to stop smoking. This highlights the need for more effective treatments for treating smokers in the US.

Studies have been conducted by Achieve Life Sciences evaluating cytisinicline at 1.5 mg and 3 mg dose levels in the downward 25-day titration schedule as well as in a simplified three times daily (TID) schedule. The 3 mg TID schedule for cytisinicline in the ACH-CYT-09 Phase 2b (ORCA-1) trial showed the highest level of prolonged abstinence starting from the End-of-Treatment (Week 4) through Week 8 (abstinence rate of 30% compared to 8% for placebo [p=0.005]). The 3 mg TID schedule also showed a well-tolerated safety profile and treatment compliance was high at 97.6%. Since the 3 mg TID schedule is a more simplified schedule and showed significantly higher abstinence at 30%, longer treatment could possibly increase the abstinence rate. The Phase 3 program for cytisinicline includes two separate Phase 3 trials that are evaluating 3 mg cytisinicline TID as a slightly longer treatment duration of 42 days/6 weeks (instead of 25 days) as well as repeating that duration for a total of 84 days/12 weeks treatment (similar to the duration of varenicline treatment). The first Phase 3 (ORCA-2) trial has completed enrollment but is ongoing in study evaluations. This second Phase 3 (ORCA-3) study mirrors the ORCA-2 trial in study design, safety/efficacy evaluations, and statistical criteria, while being conducted in parallel at different clinical sites.

All subjects are to receive standard behavioral support for smoking cessation during the study. Subjects are to be randomized to one of three arms A, B, or C, where the intended interventions are placebo for 12 weeks plus behavioral support (Arm A), 3 mg cytisinicline TID for 6 weeks followed by placebo for 6 weeks plus behavioral support (Arm B), and 3 mg cytisinicline TID for 12 weeks plus behavioral support (Arm C).

The primary outcome measure is abstinence during the last 4 weeks of cytisinicline treatment compared to the placebo arm (Weeks 3-6 for comparison of Arm B vs Arm A; Weeks 9-12 for comparison of Arm C vs Arm A). The secondary outcome measure is abstinence continuing to Week 24 post randomization in the cytisinicline arms compared to the placebo arm (Weeks 6-24 for comparison of Arm B vs Arm A; Weeks 12-24 for comparison of Arm C vs Arm A). If the primary outcome of abstinence is significant for both 6 and 12 weeks of cytisinicline treatment, reduction in risk of relapse for those subjects achieving abstinence within a Week 3-6 period will be compared in Arm C vs Arm B from Week 7 to Week 24.

In addition, the study will compare the safety profiles of 3 mg TID dosing for 6 weeks (Arm B) and 12 weeks (Arm C), relative to placebo (Arm A).

Objectives:

Multiple Primary Efficacy Objectives:

The multiple primary objectives are based on two comparisons where study success can be based on success for either comparison:

1. Assess whether subjects randomized to Arm B (3 mg cytisinicline TID for 6 weeks followed by placebo TID for 6 weeks plus behavioral support) have a higher probability of abstinence from Week 3 to Week 6 post-randomization as compared to subjects randomized to Arm A (placebo TID plus behavioral support).
2. Assess whether subjects randomized to Arm C (3 mg cytisinicline TID for 12 weeks plus behavioral support) have a higher probability of abstinence from Week 9 to

Week 12 post-randomization as compared to subjects randomized to Arm A (placebo TID plus behavioral support).

Secondary Efficacy Objectives:

The analysis for secondary objectives 1 and 2 will be done only if the corresponding primary comparison passes statistical criterion.

1. Assess whether subjects randomized to Arm B (3 mg cytisinicline TID for 6 weeks followed by placebo TID for 6 weeks plus behavioral support) have a higher probability of continuous abstinence from Week 6 to Week 24 post-randomization as compared to subjects randomized to Arm A (placebo TID plus behavioral support).
2. Assess whether subjects randomized to Arm C (3 mg cytisinicline TID for 12 weeks plus behavioral support) have a higher probability of continuous abstinence from Week 12 to Week 24 post-randomization as compared to subjects randomized to Arm A (placebo TID plus behavioral support).

The analysis for secondary objective 3 will be conditional and performed only if both primary comparisons 1 and 2 pass statistical criterion.

3. Assess for a reduction in risk of relapse from Week 6 to Week 24 in subjects receiving 3 mg cytisinicline for 6 weeks and then either continue 3 mg cytisinicline from Week 6 to Week 12 (Arm C) or were switched to placebo from Week 6 to Week 12 (Arm B). Subjects not abstinent at Week 6 will be regarded as having relapsed.

Other Objectives:

1. To compare arms (Arm B vs Arm A; Arm C vs Arm A) on 7-day point prevalence abstinence weekly at Week 2 to Week 12, then for Weeks 16, 20, and 24.
2. To compare arms (Arm B vs Arm A; Arm C vs Arm A) on serum cotinine levels every other week at Week 2 to Week 12, then at Weeks 16, 20, and 24.
3. To compare arms (Arm B vs Arm A; Arm C vs Arm A) on expired CO levels every week at Week 2 through Week 12, then at Weeks 16, 20, and 24.
4. To compare arms (Arm B vs Arm A; Arm C vs Arm A) on use of any non-cigarette nicotine products, including vaping, during study treatment (Week 2 through Week 12) and study follow-up (Week 16 through Week 24).
5. Assess whether subjects randomized to Arm B have a higher probability of abstinence from Week 9 to Week 12 as compared to subjects randomized to Arm A (placebo).
6. Assess among the subset of subjects who achieve abstinence from Week 3 to Week 6, whether subjects randomized to Arm B have a higher probability of continuous abstinence from Week 3 to Week 24 post-randomization as compared to subjects randomized to Arm A.

7. Assess among the subset of subjects who achieve abstinence from Week 3 to Week 6, whether subjects randomized to Arm C have a higher probability of continuous abstinence at Week 24 post-randomization as compared to subjects randomized to Arm B.
8. Assess among the subset of subjects who achieve abstinence from Week 9 to Week 12, whether subjects randomized to Arm C have a higher probability of continuous abstinence from Week 9 to Week 24 post-randomization as compared to subjects randomized to Arm A.
9. Among subjects who achieve abstinence from Week 3 to Week 6, compare time to failure to maintain abstinence between arms (Arm B vs Arm A; Arm C vs Arm A) to Week 24.
10. To explore the magnitude of treatment effect between arms across various subgroups defined by demographic and baseline characteristics for the primary and secondary outcomes.
11. To explore potential relationships between subject-reported outcomes (eg, anxiety, depression, withdrawal symptoms, tobacco craving) and the primary and secondary outcomes.
12. To assess possible withdrawal symptoms at Week 7 in Arm B subjects who will have discontinued cytisinicline at Week 6, analyzing separately for nicotine status (eg, either smoking, abstinent, or if using other nicotine products including vaping or nicotine replacement therapy [NRT]) compared to Arms A and C.

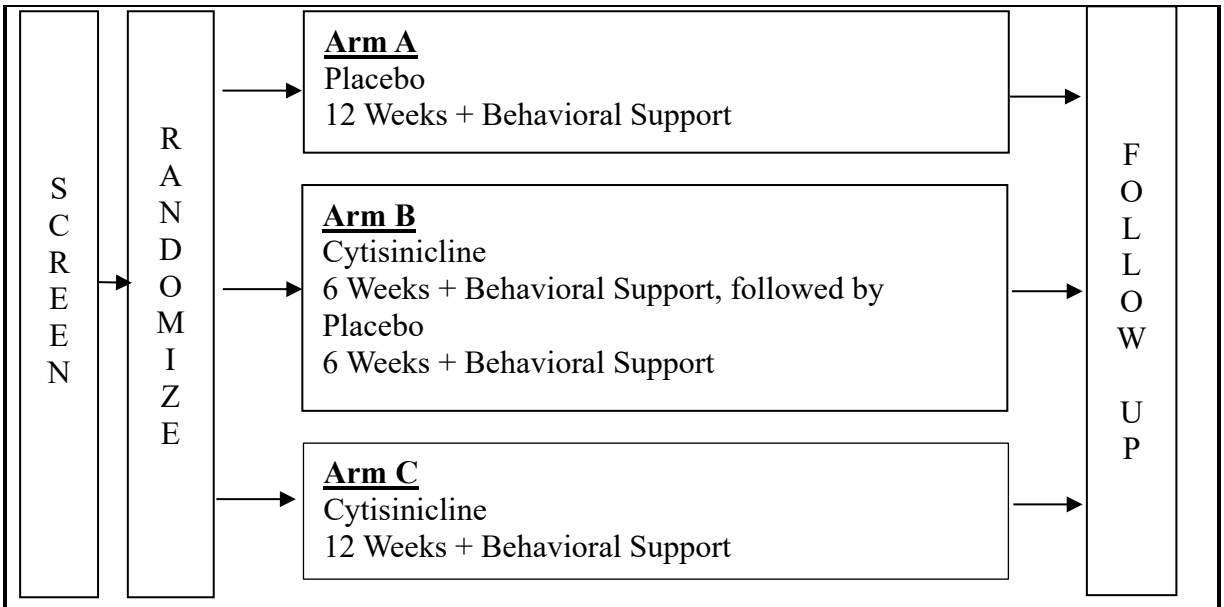
Safety Objectives:

1. To evaluate the safety profile of 3 mg TID cytisinicline compared to placebo (Arm B vs Arm A; Arm C vs Arm A).
2. To compare the safety profiles of Arm B subjects versus Arm C subjects with respect to adverse events occurring after Week 6 on the study.

Study Design:

This trial mirrors the Phase 3 ACH-CYT-03 (ORCA-2) study by enrolling a similar target population, and using the same objectives, procedures and analyses in order to demonstrate additional efficacy and safety results for cytisinicline. This will be a multi-center, double-blind, randomized, placebo-controlled, Phase 3 study conducted in male or female adults who are daily cigarette smokers, intending to quit smoking, and are willing to set a quit date that is within 5-7 days of the start of treatment. Study treatment must start the day after randomization.

Subjects must meet all requirements outlined in the inclusion and exclusion criteria. Approximately 750 subjects will be randomly assigned with equal probability to one of three Arms: (Arm A, 12 weeks placebo: N=250; Arm B, 6 weeks cytisinicline followed by 6 weeks placebo: N=250; Arm C, 12 weeks of cytisinicline: N=250) as shown in the study design figure below.



Each randomized subject will receive 12 weeks of treatment using a TID dosing schedule. Smoking cessation assessments will begin on Week 2 (Day 14±1 post-randomization) and will continue weekly during the Treatment Period through the Weeks 16, 20 and 24 Follow-up Period visits by the subject's self-report of abstinence with carbon monoxide (CO) biochemical verification.

All subjects will receive concurrent smoking cessation behavioral support during the study Treatment Period (Weeks 1-12). Additional behavioral support will be provided during the Follow-up Period based on issues/concerns/questions raised by the subject.

Safety assessments at clinic visits will occur on Day 7 (Week 1) and then weekly throughout the Treatment Period. Laboratory hematology and chemistry assessments will be made on Day 7, Week 6, and Week 12 during the Treatment Period. Any ongoing adverse events at Week 12 will be followed until resolved or determined to be chronic. The end of study is defined as the last follow-up visit (up to the Week 24 visit) for the last subject.

Selection Criteria

Inclusion Criteria:

1. Male or female subjects, age ≥18 years.
2. Current daily cigarette smokers (averaging at least 10 cigarettes per day upon completing a 7-day screening smoking diary) and who intend to quit smoking.
3. Expired air carbon monoxide (CO) ≥10 ppm.
4. Failed at least one previous attempt to stop smoking with or without therapeutic support.
5. Willing to initiate study treatment on the day after randomization and set a quit date within 5-7 days of starting treatment.
6. Willing to actively participate in the study's smoking cessation behavioral support provided throughout the study.

7. Able to fully understand study requirements, willing to participate, and comply with dosing schedule.
8. Sign the Informed Consent Form.

Exclusion criteria:

1. More than 1 study participant in same household during the 12-week treatment period.
2. Previous cytisinicline treatment in a prior clinical study or any other cytisine usage.
3. Known hypersensitivity to cytisinicline or any of the excipients.
4. Positive urinary drugs of abuse screen, determined within 28 days before the first dose of cytisinicline.
5. Clinically significant abnormal serum chemistry or hematology values within 28 days of randomization (ie, requiring treatment or monitoring).
6. Clinically significant abnormalities in 12-lead ECG determined after minimum of 5 minutes in supine position within 28 days of randomization (ie, requiring treatment or further assessment).
7. Recent history (within 3 months) of acute myocardial infarction, unstable angina, stroke, cerebrovascular incident or hospitalization for congestive heart failure.
8. Current uncontrolled hypertension (blood pressure ≥160/100 mmHg).
9. Currently psychotic or having had a psychotic event within 3 months. If any subject becomes psychotic during the study, they must be removed from treatment and/or additional study visits.
10. Currently having suicidal ideation or risk for suicide ("Yes" to question 4 or question 5 OR "Yes" to any suicidal behavior question on the C-SSRS with clear suicidal intent or previous attempt).
11. Current symptoms of moderate to severe depression (depression score ≥11on the HADS).
12. Renal impairment defined as a creatinine clearance (CrCl) <60 mL/min (estimated with the Cockroft-Gault equation).
13. Hepatic impairment defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.0 x the upper limit of normal (ULN).
14. Women who are pregnant or breast-feeding.
15. Male or female subjects of childbearing potential who do not agree to use acceptable methods of birth control during the study treatment period.
16. Participation in a clinical study with an investigational drug in the 4 weeks prior to randomization.
17. Treatment with other smoking cessation medications (bupropion, varenicline, nortriptyline, or any nicotine replacement therapy [NRT]) in the 4 weeks prior to randomization or planned use of these other smoking cessation medications during the study.

18. Use within the 2 weeks prior to randomization or planned use during the study of non-cigarette and/or noncombustible nicotine products (pipe tobacco, cigars, snuff, smokeless tobacco, hookah, e-cigarettes/vaping) or marijuana smoking or vaping.
19. Any other reason that the investigator views the subject should not participate or would be unable to fulfill the requirements for the study.

Number of Subjects, Randomization, and Stratification:

Approximately 750 subjects will be randomized at 15-19 sites in the United States, with 250 subjects per arm. Subjects will be randomized within site.

Study Treatments:

Identical appearing tablets containing 3 mg cytisinicline or matched placebo will be administered orally. During the 12-Week Treatment Period, subjects will take one tablet three times daily. Tablets will be blister sealed and configured into medication packs for one week of dosing. Each pack will contain 21 tablets for TID dosing for 7 days. Six weeks of dosing packs will be contained in a carton such that 2 cartons will be assigned to a subject during the study treatment (ie, 12 total packs for 12 weeks of study treatment).

Clinic staff will distribute and collect packs as the subject progresses through the clinic visits and will conduct ongoing accountability during each weekly clinic visit by reviewing a subject's treatment diary and associated blister packs. Used packs will be retained so that the Sponsor's monitoring staff can verify accountability records.

Duration of Study:

All randomized subjects will initiate study treatment the day after randomization, receive 12 weeks of treatment, and will then be followed for up to 24 weeks post-randomization. Therefore, the duration of the study will be approximately 24 weeks post-randomization for a subject.

Study Procedures:

Prior to taking part in the trial, subjects will be provided with an informed consent document outlining study requirements and procedures. Subjects will be given adequate time to review, discuss, and decide whether they wish to participate.

Subjects providing signed informed consent will be assessed during the Screening Period to determine their eligibility for the trial. If eligible, subjects will be required to attend a clinic visit prior to randomization in order to establish a quit date that will in turn determine the date of randomization. The quit date must be within 5-7 days of starting treatment and treatment must begin on the day after randomization. Subjects will be randomized in a blinded manner to receive Arm A, Arm B, or Arm C study drug for the 12-Week Treatment Period. Subjects will be provided with smoking cessation counseling beginning on the clinic visit during screening prior to randomization (setting quit date and plan), again on day of randomization, and continuing through the Week 12 visit. Additional counseling will also be provided during the Follow-up Period.

Compliance will be assessed during treatment by reviewing subject's treatment diary (date and time of dosing) as well as ongoing drug accountability at each weekly clinic visit.

Subjects will be assessed for smoking cessation by self-report of abstinence with biochemical verification documented weekly starting at Week 2 through Week 12. Additional follow-up assessments will occur at Week 16, 20 and 24 to evaluate long-term continuous abstinence.

Subjects will be assessed for safety (vital signs, adverse event reporting and concomitant medications) on Day 7 (Week 1) of treatment (Note: clinic will also contact subject via telephone on Day 1 of treatment to assess for any initial reported adverse events) and then safety assessments will occur weekly at each clinic visit during the Treatment Period. In addition to the above safety assessments, hematology and chemistry assessments will be made on Day 7, Week 6 and Week 12 during the Treatment Period. At Week 12, any adverse event or abnormalities considered to be clinically significant by the investigating physician will be followed with appropriate medical management until values are considered to be clinically acceptable or deemed chronic.

Follow-up visits will occur at Week 16, Week 20 and Week 24.

Statistical Considerations:

Analysis Sets

Screening Analysis Set: The Screening Analysis Set is defined as all subjects who give written informed consent and have entered screening but are not randomized. Analyses in this population will be restricted to presentation of baseline data and reasons for non-participation only.

Safety Analysis Set: The Safety Analysis Set (SAS) is defined as all randomized subjects who take at least one dose of study drug.

Efficacy Analysis Set: The All Randomized Analysis Set (ARS) is based on the 'intention-to-treat' principle and will include data from all randomized subjects.

Efficacy Outcomes

Primary efficacy outcomes: The primary efficacy outcome is binary and for each subject success is abstinence determined at Weeks 3, 4, 5, and 6 (Arm B) and Weeks 9, 10, 11, and 12 (Arm C) post-randomization compared to the corresponding weekly assessments in the placebo arm (Arm A), with success defined as having reported abstinence in smoking by subject's self-report with CO biochemical verification. Absence of success (non-success) is having been assessed but not meeting the criterion for success or not available for assessment per criteria.

Secondary efficacy outcomes: The secondary outcome measure for the two comparison analyses associated with the secondary efficacy objectives 1 and 2 (Arm A versus Arm B and Arm A versus Arm C, respectively) is success with respect to continuous abstinence through Week 24. The secondary outcome measure for the comparison analysis associated with the secondary efficacy objective 3 (comparing Arm B to Arm C) is success with respect to being without relapse at Week 24. The considerations relative to the definition of these endpoints are similar. The analyses associated with these three objectives will be done as Intent-to-Treat (ITT) analyses.

Subjects not observed to meet all success criteria will be regarded as non-success relative to secondary efficacy outcomes. Non-success will have two types: (1) subjects with adequate

data that fail to meet the criteria, and (2) subjects having insufficient data to be assessed as a success.

The statistical model used for the secondary efficacy objectives 1 and 2 will be the same statistical model used for the analysis of the corresponding multiple primary objectives.

Other outcomes: All other outcomes, including point prevalence abstinence, time to abstinence failure, magnitude of treatment effect across subsets defined by demographic and baseline characteristics, etc., will be considered exploratory outcomes.

Statistical Methods

Primary Analysis

The primary analysis will include all randomized subjects by randomized arm (intent-to-treat analysis). The multiple primary comparisons will be for 6 weeks cytisinicline (Arm B) vs placebo (Arm A) and for 12 weeks cytisinicline (Arm C) vs placebo (Arm A). If the primary efficacy comparison meets statistical criterion, then the corresponding secondary efficacy outcome analyses will have formal meaning. The primary comparisons will be comparing the arms based on the ratio of the odds of success in the experimental arm divided by the odds of success in the control arm (odds ratio) using exact computations for stratified 2x2 frequency tables. The estimated odds ratio and exact confidence interval for the marginal 2x2 table across sites (unadjusted odds ratio), and the estimated difference in proportions and the associated derived exact confidence interval using the exact confidence interval on the odds ratio will also be reported.

Trial Size

The target accrual for each arm is planned for 250 (Approximately 750 for the study). The significance level to be used for the multiple primary comparisons is adjusted from the overall type I error probability of one-sided 0.025 to one-sided 0.0125 using the Bonferroni method to control for multiplicity. The assumed control arm probability of success (Weeks 9-24 abstinence) is 0.07 (7%). The hypothesized experimental arm minus control arm probability difference is specified as 0.12 (12%), corresponding to a hypothesized odds ratio of 3.12 (7% for placebo vs 19% for cytisinicline treatment). The statistical operating characteristics for each comparison are illustrated using simulation with 10,000 replicates. These specifications are consistent with 95.7% power for each comparison with, conditional on 0.07 control arm probability outcome, an odds ratio critical region of $\geq$1.83, corresponding to a critical difference of $\geq$0.051 (7% for placebo vs 12% for cytisinicline treatment).

Safety

The profiles of adverse events for the arms with regard to incidences of treatment emergent adverse events will be assessed. Treatment emergent adverse events are defined as those events that appear during treatment or are present before treatment and subsequently worsen. Laboratory, vital signs and ECG data will primarily be assessed for clinical safety. Data will be listed and summarized for each treatment according to measurement time.

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ABBREVIATION/TERM	DEFINITION
ACh	Acetylcholine
ADR	Adverse Drug Reaction
AE	Adverse Event
AUC	Area Under the Curve
ALT	Alanine Aminotransferase
ARS	All Randomized Analysis Set
AST	Aspartate Aminotransferase
BMI	Body Mass Index
CI	Confidence Interval
C_{max}	Maximum Observed Plasma Concentration
CO	Carbon Monoxide
CrCl	Creatinine Clearance
CRF	Case Report Form
CRO	Contract Research Organization
C-SSRS	Columbia - Suicide Severity Rating Scale
DDI	Drug-to-Drug Interaction
DPF	Dose-Proportionality Factor
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
FTND	Fagerstrom Test of Nicotine Dependence
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Good Laboratory Practice
HADS	Hospital Anxiety and Depression Scale
HED	Human Equivalent Dose
ICH	International Conference on Harmonization
I.D.	Identification
IMP	Investigational Medicinal Product (for this protocol indicates cytisinicline 3 mg film coated tablet)
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
nAChRs	Nicotinic Acetylcholine Receptors
NMR	Nicotine Metabolite Ratio
NRT	Nicotine Replacement Therapy
NOAEL	No-Observed-Adverse-Effect-Level
MedDRA	Medical Dictionary for Regulatory Activities
MNWS	Minnesota Nicotine Withdrawal Scale
OR	Odds Ratio
PSUR	Periodic Safety Update Reports
QSU-Brief	Brief Questionnaire of Smoking Urges
RR	Relative Risk
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SAS	Safety Analysis Set
SD	Standard Deviation
SEQ	Self-Efficacy Questionnaire
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SmPC	Summary of Product Characteristics
SOC	MedDRA System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction

ABBREVIATION/TERM	DEFINITION
TEAE	Treatment Emergent Adverse Event
TID	Three Times a Day
T_{max}	Time to Maximum Observed Concentration
UADR	Unexpected Adverse Drug Reaction
UAE	Unexpected Adverse Event
ULN	Upper Limit of Normal
USAN	United States Adopted Names

1. INTRODUCTION AND BACKGROUND

1.1. History of the Investigational Product

Cytisine is a plant-based alkaloid used as a smoking cessation drug since the 1980's in Eastern and Central Europe, marketed by Sopharma, Sofia, Bulgaria.[5] The molecular structure of cytisine has similarities to nicotine and acetylcholine (ACh). Nicotine addiction results, at least in part, from its interaction with neuronal nicotinic acetylcholine receptors (nAChRs). Both cytisine and nicotine compete for these receptors.[6-8] Cytisine has high affinity and specificity for neuronal nicotinic ($\alpha_4\beta_2$) receptors.

Despite its widespread use, cytisine has not been market-approved for use outside Eastern and Central Europe. [redacted]. In 2018, the United States Adopted Names (USAN) Council adopted "cytisinicline" as the nonproprietary, or generic, name for cytisine. This protocol uses the USAN cytisinicline nomenclature except when referring to previous published data using cytisine nomenclature. [redacted]

1.2. Nicotine Addiction and Impact on Health

Nicotine is an addictive substance that is rapidly absorbed during cigarette smoking. The drug distributes quickly and is thought to interact with nAChRs in the central nervous system (CNS). Although many smokers attempt to quit smoking, few succeed without pharmacological supportive treatment.

Tobacco smoking contributes to some 8 million premature deaths each year worldwide.[9] It is highly addictive, with more than 95% of unaided attempts at cessation failing by 6 months.[10] Every year that a smoker delays quitting beyond the mid-30s, there is an estimated 3 months reduction in life expectancy.[11]

Although nicotine is primarily responsible for the addictive properties of cigarette smoking, tobacco smoke also contains several hundred gaseous substances and several thousand compounds. There is increasing evidence that the presence of carbon monoxide in cigarette smoke plays a role in cardiovascular disease and that tar is a major factor in respiratory disease

and cancer.[12] Nicotine, of which 1 to 3 mg is typically absorbed from each cigarette, is a peripheral vasoconstrictor and a sympathomimetic stimulant, which also leads to improvement in mood and attention.

1.3. Treatments for Smoking Cessation

The pharmacotherapies currently available in the US and Western Europe to help smokers quit include nicotine replacement therapy (NRT) and two non-nicotine containing medications: bupropion (Zyban®, Glaxo-SmithKline) and varenicline (Chantix®/Champix®, Pfizer). NRT and bupropion appear to have about equal efficacy.[13,14] Varenicline is more effective than NRT and bupropion. A brief description of each pharmacotherapy is given below.

Nicotine replacement therapy was first introduced in 1978. NRT replaces the nicotine absorbed from cigarettes and helps subjects stop smoking by reducing nicotine cravings, withdrawal symptoms, and mood changes. Available over-the-counter and prescription-only NRT products include: chewing gums, lozenges, transdermal patches, nasal sprays and inhalers. The purpose of all NRT products is to achieve a sufficient plasma concentration of nicotine (and hence concentration of nicotine at central nAChRs) and so reduce craving for nicotine derived from cigarette smoke. However, the efficacy of NRT (expressed as a pooled Relative Risk (RR) compared with placebo treatment) is limited (overall RR 1.60).[14] In general, the delivery of nicotine from NRT products is relatively slow, and the pharmacokinetic profile does not resemble that of cigarettes: the time to peak plasma concentration (T_{max}) tends to be longer for NRT, and the C_{max} is not characterized by a sharp peak, but by a lower and flatter peak. Thus, the smoker does not have the same nicotine experience with NRT products that they do from smoking. Although there do not appear to be safety concerns for NRT usage, the relatively poor response to NRT products as aids to smoking cessation limits their effectiveness as treatment. Side effects of NRT products include: nausea, dizziness, weakness, vomiting, fast or irregular heartbeat, mouth problems with the lozenge or gum, and redness or swelling of the skin around the patch.

Bupropion is one of the most frequently prescribed antidepressants in the US. Zyban is bupropion re-profiled as a smoking cessation medication in tablet form. Although it reduces nicotine withdrawal symptoms and craving and enhances tobacco cessation, the precise mechanism by which it aids smoking cessation is unknown. The efficacy of bupropion is similar to that of NRT (overall RR 1.62).[13] Although the most commonly observed adverse events consistently associated with the use of bupropion are dry mouth and insomnia, the medication guide for bupropion cites other adverse events and risks related to this product, including seizures, high blood pressure, and allergic reactions. Because bupropion contains the same active substance as the antidepressant Wellbutrin®, users and potential users are urged to talk to their health care professional about risks of treatment with antidepressant medicines.

Varenicline was synthetically developed as a new class of $\alpha_4\beta_2$ nicotine receptor partial agonists, in part, using (-)-cytisine as the structural starting point.[8] Varenicline is a partial agonist at nicotine receptors and acts as a nicotine substitute leading to a gradual decrease in the smoker's physical and psychological dependence on cigarettes. In a recent Cochrane analysis report detailing 6-month abstinence rates, varenicline was found to be more effective than placebo (overall RR=2.25) or bupropion (overall RR=1.39).[15] The most common side effects of varenicline (>5% or twice the rate seen with placebo) include nausea, abnormal (vivid, unusual,

or strange) dreams, constipation, flatulence, and vomiting. In addition, the Prescribing Information for varenicline cites other possible serious side effects and risks including new or worsening mental health problems such as changes in behavior, hostility, agitation, or depressed mood. Other warnings and precautions include new or worsening seizures, accidental injury (eg, trouble driving or operating heavy machinery), cardiovascular events (new or worsening cardiovascular symptoms), allergic hypersensitivity reactions, serious skin reactions, and nausea.

The recently published, international trial (referred as the EAGLES trial[16]) was a large randomized, double-blind, placebo-controlled and active-controlled (nicotine patch) trial comparing varenicline and bupropion at 140 centers in 16 countries between Nov 30, 2011, and Jan 13, 2015. The trial randomized 8,144 participants. The study did not show a significant increase in neuropsychiatric adverse events attributable to varenicline or bupropion relative to nicotine patch or placebo. Varenicline was more effective than placebo, nicotine patch, and bupropion in helping smokers achieve abstinence, whereas bupropion and nicotine patch were more effective than placebo. Across cohorts, the most frequent adverse events by treatment group were nausea (varenicline, 25%), insomnia (bupropion, 12%), abnormal dreams (nicotine patch, 12%), and headache (placebo, 10%).

In summary, new treatments are still needed that are less costly, more effective, have an improved safety profile, or can more successfully treat individuals who have failed to quit using the above treatments.

2. SAFETY OVERVIEW FOR CYTISINICLINE

2.1. Non-Clinical Studies

The US National Center for Complementary and Integrative Health (NCCIH) designated cytisine as "*a drug of national Public Health importance*" and, in collaboration, has sponsored a series of recent pharmacology and toxicology studies in support of the cytisinicline IND and in preparation for this Phase 3 study. In that regard, NCCIH and the National Cancer Institute (NCI) sponsored non-clinical GLP studies that have included 28-day repeat dosing for toxicology assessments in rats and dogs as well as reproductive/developmental studies in rats and rabbits. Achieve has also completed a 39-Week chronic toxicology study in dogs and a 26-Week chronic toxicology study in rats.

[redacted]

[redacted]

[redacted]

2.2. General Safety of Cytisine as a Marketed Product

Cytisine has been marketed for many years by Sopharma in Central and Eastern Europe (including four countries in the European Union). It is estimated to have treated over 21 million smokers worldwide. Periodic Safety Update Reports (PSURs) have been submitted to the relevant European and national authorities following the European and local regulations and requirements**.**

[redacted]

Thus, from marketing safety reporting for cytisine, the most frequent adverse effects include: nausea, gastrointestinal symptoms (including abdominal pain, dyspepsia, and dry mouth), sleep disorder, dizziness and headache. Most reported adverse effects appear mainly at the beginning of therapy, are short-lived, mild-to-moderate intensity, and resolved spontaneously. It is not possible to dissociate these effects due to cytisine and those related to nicotine withdrawal.

2.3. Special Populations

Safety or pharmacokinetic information for the administration of cytisinicline in subjects with coronary disease, cardiac insufficiency, arterial hypertension, cerebrovascular diseases, hyperthyroidism, peptic ulcer, diabetes, renal, or hepatic insufficiency have not yet been obtained. Exclusion criteria have therefore been developed with external clinical input to exclude subjects that may have, or are being treated for, these underlying medical conditions. [redacted]

3. PRIOR PHASE 3 EVIDENCE FOR CYTISINE AS A SMOKING CESSATION TREATMENT

Cytisine was evaluated in two previous randomized Phase 3 clinical trials according to Good Clinical Practice (GCP) in more than 2,000 participants and published in 2011 and 2014. The overall objectives in these trials were to confirm the efficacy and safety of cytisine versus placebo or NRT, according to current clinical development standards. Cytisine was recently compared to varenicline as a smoking cessation treatment and results published in 2021. All three studies used cytisine manufactured by Sopharma.

The Phase 3 trial (TASC[1] trial) was sponsored by the UK Centre for Tobacco Control Studies and evaluated cytisine versus placebo in 740 primarily moderate-to-heavy smokers treated for 25 days in a single center in Warsaw, Poland. The primary outcome measure was sustained, biochemically-verified smoking abstinence for 12 months after the End-of-Treatment. The TASC trial was conceived by Professor Robert West (Department of Epidemiology and Public Health, University College London) and was funded by a grant from the National Prevention Research Initiative, including contributions from Cancer Research UK, Medical Research Council, United Kingdom Department of Health, and others. The results of the TASC trial were published in the *New England Journal of Medicine* in September 2011.[1] The Relative Risk (RR) for sustained 12-month abstinence was 3.4 for cytisine compared to placebo (8.4% cytisine arm compared to 2.4% placebo arm; P<0.001). The RR for sustained 6-month abstinence was 2.9 (10.0% cytisine arm compared to 3.5% placebo arm; P<0.001). Cytisine was well tolerated with an increase in all-combined gastrointestinal (GI) adverse events (although there was no significant difference in individual GI events between the arms). The safety profile of cytisine was similar to that of a placebo, with no overall difference in the rate of side effects in the two arms.

The second Phase 3 trial (CASCAID[2] trial) was conducted by the Health Research Council of New Zealand and was an open-label trial that randomized 1,310 adult daily smokers. Subjects were randomized to receive either cytisine for 25 days or NRT for 8 weeks. Both treatment groups were offered low-intensity telephone behavioral support during trial treatment. The primary outcome measure was continuous self-reported abstinence from smoking one month after a quit date. The RR for continuous one-month abstinence was 1.3 for cytisine (40% cytisine arm compared to 31% in the NRT arm; P<0.001). A secondary outcome included the RR for continuous six-month abstinence which was 1.4 for cytisine (22% cytisine arm compared to 15% in the NRT arm; P=0.002). Cytisine was generally well tolerated, although self-reported adverse events were higher in the cytisine arm compared with the NRT arm. The most frequent adverse events were nausea and vomiting and sleep disorders. The results of the CASCAID trial, which were published in the *New England Journal of Medicine* in December 2014, showed that cytisine was superior to NRT for smoking cessation and, specifically, that cytisine was 1.43 times more likely than nicotine gums or patches to help participants stop smoking and remain non-smokers for six months.[2]

The recent third Phase 3 trial (RAUORA[3] trial) was conducted by Natalie Walker in New Zealand to determine whether cytisine was at least as effective as varenicline in supporting smoking abstinence for ≥6 months in the New Zealand indigenous Māori or *whānau* (extended-family) of Māori, given the high smoking prevalence in this population. The study design was a pragmatic, open-label, randomized, community-based non-inferiority trial. Adult daily smokers who identified as Māori or *whānau* of Māori, motivated to quit in within 2 weeks, aged ≥18 years, and eligible for subsidized varenicline were enrolled and 679 people were randomly assigned (1:1) to receive a prescription for 12-weeks of cytisine or varenicline, plus low-intensity cessation behavioral support. Cytisine was administered first via the 25-day downward titration regimen followed by a daily maintenance of 1.5mg cytisine twice a day for the remaining 12 weeks and varenicline was administered for 12 weeks per market approved prescription. The primary outcome was carbon-monoxide verified continuous abstinence at 6 months, analyzed as intention to treat (with multiple imputation for missing data). Secondary outcomes included adverse event analyses. Verified continuous abstinence rates at 6 months post-quit date were 12.1% (41 of 337) for cytisine vs 7.9% (27 of 342) for varenicline (risk difference 4.29%, 95% confidence interval [CI] -0.22 to 8.79; relative risk 1.55; 95% CI 0.97 to 2.46). Sensitivity analyses confirmed the findings were robust. Self-reported adverse events over 6 months occurred significantly more frequently in the varenicline group (cytisine: 313 events in 111 participants; varenicline: 509 events in 138 participants, incidence rate ratio 0.56, 95% CI 0.49 to 0.65, p<0.001) compared with the cytisine group. Common adverse events were headache, nausea, and difficulty sleeping. The results of the RAUORA trial, which were published in *Addiction* in March 2021, showed that cytisine was at least as effective as varenicline at supporting smoking abstinence in New Zealand indigenous Māori or *whānau* (extended-family) of Māori, with significantly fewer adverse events.

4. RECENT STUDIES COMPLETED BY SPONSOR

Achieve has sponsored and completed the following clinical studies:

ACH-CYT-01 “A Phase 1 Open Label, Randomized, Two-Way Crossover Study in Healthy Volunteers to Investigate the Effect of Food on the Bioavailability of Cytisine”

ACH-CYT-02 “Repeat-Dose Pharmacokinetic and Pharmacodynamic Evaluation of Cytisine in Healthy Smokers”

ACH-CYT-07 “A Phase 1 Open Label, Randomized, Two-Way Crossover Study in Healthy Smokers to Investigate the Effect of Food on the Bioavailability of Cytisine in a New Formulation”

ACH-CYT-08 “A Phase I, Double-blind, Randomized, Placebo-controlled, Single Dose-escalation Study to Evaluate the Tolerability and Safety of Cytisine in Adult Smokers”

ACH-CYT-09 (ORCA-1) “A Multicenter, Double-blind, Randomized, Placebo-controlled Phase 2b Trial of Cytisine in Adult Smokers”

[redacted] 4.1 [redacted]

[redacted] Table 2, [redacted]

Table 2: [redacted]

[redacted]

[redacted]

4.3. Summary of the Multicenter, Double-blind, Randomized, Placebo-controlled ORCA-1 (ACH-CYT-09) Trial of Cytisinicline in Adult Smokers

ORCA-1 "A Multicenter, Double-blind, Randomized, Placebo-controlled Phase 2b Trial of Cytisine in Adult Smokers" was a Phase 2b study evaluating cytisinicline doses using different administration schedules within a 25-day treatment period and was conducted at clinical sites within the US.

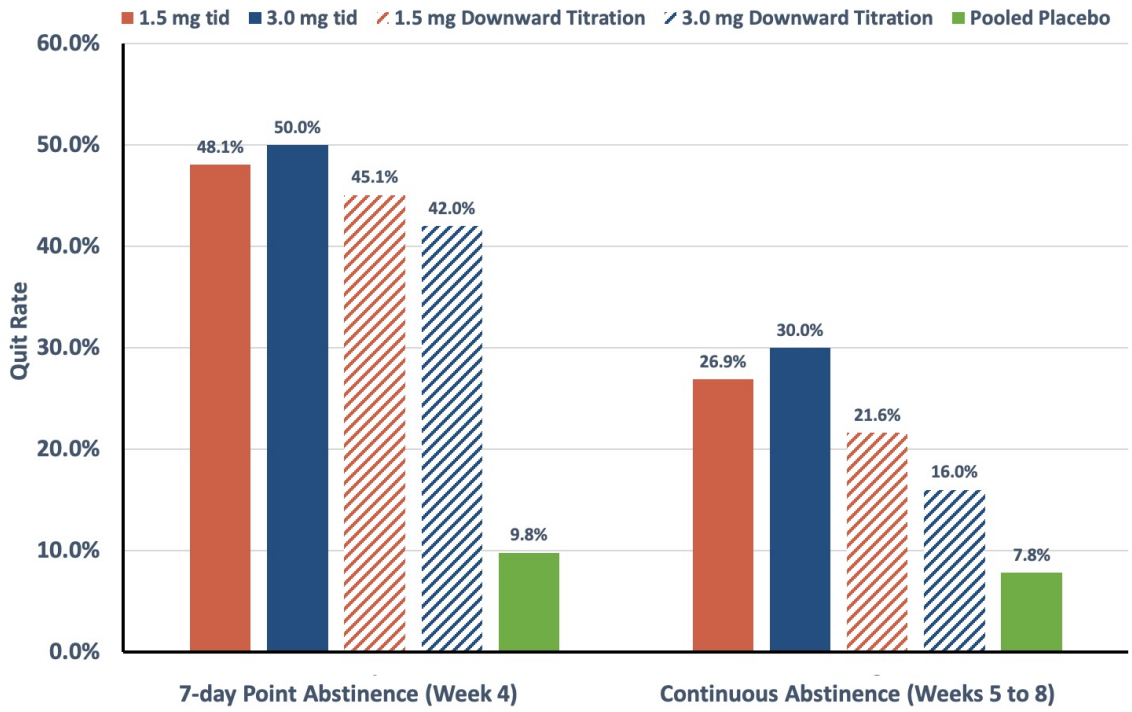
The study was a Phase 2b, six-arm, multi-center, double-blind, randomized, placebo-controlled trial conducted in male or female adults who were daily cigarette smokers, intending to quit smoking, and were willing to set a quit date that was 5-7 days after the start of treatment. The study arms consisted of the 1.5 mg dose/downward titration schedule that is currently marketed in European countries, a higher dose of 3 mg using the same downward titration schedule, as well as a 1.5 mg and 3 mg dose using a simplified three times a day (TID) schedule, and respective placebo arms. The study was double-blinded to dose but not to the administration schedule. Study treatment started the day after randomization and was completed in 25 days. Follow-up assessments for smoking status and abstinence started at the End-of-Treatment visit (EOT: also defined as Week 4) and continued weekly to Week 8.

Of the 254 subjects enrolled in the study, 121 (47.6%) were men and 133 (52.4%) were women. The mean (SD) age was 48.4 (13.0) years. For all subjects, the mean (SD) number of years as a smoker was 32.1 (13.7), with an average of 18.2 (6.0) cigarettes smoked per day. All subjects in the study attempted to quit smoking in the past, with an average (SD) of 4.5 (4.8) previous quit attempts.

Below are the most relevant efficacy results for initial quit rates at Week 4 and continuous abstinence rates through Weeks 5-8. Initial quit rate at Week 4 was defined for a subject as having reported smoking no cigarettes from Day 21 to the Day 27 EOT visit, with an expired air carbon monoxide (CO) reading <10 ppm at the EOT visit. Continuous abstinence, defined as no cigarettes smoked from Week 5 to Week 8, was measured for a subject as having reported smoking abstinence (no cigarettes since the last clinic visit and over the past 7 days) at each clinic assessment from Weeks 5, 6, 7, to Week 8 with biochemical CO verification at each weekly assessment.

The respective titration placebo and TID placebo arms were pooled based on demonstrating the same efficacy outcome measures. Treatment compliance was high for all arms with >94% mean compliance for study drug administration.

Figure 1: ORCA-1 Study: CO-Verified Abstinence Results



CO-verified 7-day point abstinence rates at EOT (Week 4) were statistically higher in all cytisinicline treatment arms compared to placebo: 45% and 42% for the 1.5 mg and 3 mg downward titration arms and 48% and 50% for the 1.5 mg and 3 mg TID arms, respectively, compared to 10% for the placebo arms (Figure 1).

Continuous abstinence as of the Week 5 assessment through to the Week 8 assessment (total of 4 weeks of continual abstinence after the end of treatment) is also shown in Figure 1. The TID schedule for cytisinicline had statistically higher continuous abstinence rates compared to placebo, with subjects in the 3 mg cytisinicline TID arm having the highest continuous abstinence rate at 30% compared to 8% for placebo. Subjects in the 3 mg TID arm also had higher odds for continuous abstinence from cigarettes from Week 5 to Week 8 compared with placebo (OR: 5.04, 95% CI: 1.42, 22.32). The OR for the 1.5 mg TID arm was 4.33 (95% CI:

1.21, 19.30). On the downward titration schedule, the ORs for the 1.5 mg and 3 mg arms were 3.23 (95% CI: 0.86, 14.85) and 2.24 (95% CI: 0.55, 10.82), respectively.

No subject experienced a serious adverse event. No new or unexpected adverse events were identified during the study. Most adverse events were mild or moderate in intensity; only 2 (0.8%) were severe in intensity, and both were unrelated to study drug. About half of the adverse events (52.9%) were not related or unlikely to be related to the study drug. Most (95.3%) adverse events did not result in a change in dosing, and the subject was considered recovered (88.2%) during the study. A total of 3 subjects who received cytisinicline and 2 subjects who received placebo discontinued study treatment early due to an adverse event. Adverse events experienced by ≥2% of subjects in the trial are summarized in Table 3.

Table 3: ORCA-1 Study: Most Common Treatment-emergent Adverse Events Experienced by ≥2% of Subjects

	Cytisinicline Downward Titration Schedule		Cytisinicline TID Schedule		Pooled Placebo (N=51) n (%)	All Subjects (N=254) n (%)
	1.5 mg (N=51) n (%)	3 mg (N=50) n (%)	1.5 mg (N=52) n (%)	3 mg (N=50) n (%)		
Upper respiratory tract infection	3 (5.9)	2 (4.0)	5 (9.6)	3 (6.0)	7 (13.7)	20 (7.9)
Abnormal dreams	4 (7.8)	7 (14.0)	4 (7.7)	3 (6.0)	1 (2.0)	19 (7.5)
Nausea	5 (9.8)	3 (6.0)	1 (1.9)	3 (6.0)	5 (9.8)	17 (6.7)
Insomnia	3 (5.9)	4 (8.0)	4 (7.7)	3 (6.0)	1 (2.0)	15 (5.9)
Headache	1 (2.0)	1 (2.0)	6 (11.5)	2 (4.0)	2 (3.9)	12 (4.7)
Fatigue	1 (2.0)	2 (4.0)	3 (5.8)	1 (2.0)	2 (3.9)	9 (3.5)
Nasopharyngitis	2 (3.9)	2 (4.0)	0	2 (4.0)	1 (2.0)	7 (2.8)
Gastroenteritis	1 (2.0)	0	2 (3.8)	1 (2.0)	2 (3.9)	6 (2.4)
Anxiety	1 (2.0)	1 (2.0)	0	1 (2.0)	3 (5.9)	6 (2.4)
Vomiting	2 (3.9)	2 (4.0)	0	1 (2.0)	0	5 (2.0)
Constipation	0	0	1 (1.9)	3 (6.0)	1 (2.0)	5 (2.0)
Diarrhoea	2 (3.9)	1 (2.0)	0	0	2 (3.9)	5 (2.0)
Hypertension	2 (3.9)	0	2 (3.8)	0	1 (2.0)	5 (2.0)

TID = 3 times daily
N: Number of safety subjects in the specified treatment arm.
n: Number of subjects with data available in the specified treatment arm.
Treatment-emergent AE was defined as any AE that was new in onset or was aggravated in severity or frequency after the first dose of study drug up to and including the last visit of the study.
Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 21.0.
If a subject experienced more than 1 finding within a given system organ class, that subject was counted only once for that system organ class. If a subject experienced more than 1 finding with a given preferred term, that subject was counted only once for that preferred term.

5. RATIONALE FOR THE STUDY

Previous Phase 3 studies have shown that cytisine can be effective in helping smokers to stop smoking.[1-3] These Phase 3 studies showed that cytisine was more effective than placebo and NRT, and as effective as varenicline for smoking cessation with an excellent safety profile. These trials used cytisine manufactured by Sopharma and safety results were consistent with the safety profile reported by Sopharma. Since tobacco smoking contributes to some 9 million premature deaths each year worldwide,[9] using cytisinicline as a smoking cessation aid could offer far more benefit with minor risks of treatment when compared to that of continued smoking.

Data from the international EAGLES trial (N= 8120) were used to assess predictors for continuous smoking abstinence outcomes from weeks 9-24.[4] These analyses provided clear evidence that US origin was associated with lower success rates of stopping, regardless of treatment (varenicline, bupropion, or NRT). The continuous abstinence rates from 9-24 weeks in the US were 16.1%, 11.4% and 10.6% for varenicline, bupropion, or NRT, respectively, compared to 6.7% placebo treatment. The odds ratios (OR) for these treatments in the US were 2.66, 1.78, and 1.64, respectively. The lower success rate in US smokers support the view that smokers in the US may have reached a point in the tobacco epidemic such that those who continue to smoke, despite strong cultural pressures not to smoke, have particular characteristics that make it more difficult for them to stop smoking. This highlights the need for more effective treatments for treating smokers in the US.

In the ORCA-1 Trial, conducted only in the US, the study population represented highly addicted smokers who on average were 48.4 years old and had been smoking for 32 years, meaning that most of them had started smoking in their adolescent years. In addition, they had an average of 4.5 prior quit attempts with the last quit attempt approximately 3.7 years prior to entering the study and were currently smoking an average of 1 pack of 20 cigarettes a day. Although the 3 mg TID schedule for cytisinicline showed significant abstinence rates starting from the End-of-Treatment (Week 4) through Week 8 (continuous abstinence rate of 30% compared to 8% for placebo), comments from study investigators and smokers participating in the study stated that a longer treatment would have been preferred. Since the 3 mg TID schedule is a more simplified schedule with high treatment compliance and a well-tolerated safety profile, a slightly longer 6-Week 3 mg cytisinicline treatment will be evaluated as well as another 6 weeks of treatment for a total of 12 weeks.

This Phase 3 study will be the second Phase 3 to be conducted at separate sites within the US and will also evaluate the 3 mg cytisinicline TID schedule for a longer treatment duration of 6 weeks as well as repeating that duration for a total of 12 weeks treatment. All subjects will receive standard behavioral support for smoking cessation during the study. Study treatment will be blinded and the 3 study treatment arms are defined below:

- Arm A (placebo TID for 12 weeks plus behavioral support).
- Arm B (3 mg cytisinicline TID for 6 weeks followed by placebo TID for 6 weeks plus behavioral support).
- Arm C (3 mg cytisinicline TID for 12 weeks plus behavioral support).

6. STUDY OBJECTIVES

6.1. Multiple Primary Efficacy Objectives

The multiple primary objectives are based on two comparisons where study success can be based on success for either comparison:

1. Assess whether subjects randomized to Arm B (3 mg cytisinicline TID for 6 weeks followed by placebo TID for 6 weeks plus behavioral support) have a higher probability of abstinence from Week 3 to Week 6 post-randomization as compared to subjects randomized to Arm A (placebo TID plus behavioral support).
2. Assess whether subjects randomized to Arm C (3 mg cytisinicline TID for 12 weeks plus behavioral support) have a higher probability of abstinence from Week 9 to Week 12 post-randomization as compared to subjects randomized to Arm A (placebo TID plus behavioral support).

6.2. Secondary Efficacy Objectives

The analysis for secondary objectives 1 and 2 will be done only if the corresponding primary comparison passes statistical criterion.

1. Assess whether subjects randomized to Arm B (3 mg cytisinicline TID for 6 weeks followed by placebo TID for 6 weeks plus behavioral support) have a higher probability of continuous abstinence from Week 6 to Week 24 post-randomization as compared to subjects randomized to Arm A (placebo TID plus behavioral support).
2. Assess whether subjects randomized to Arm C (3 mg cytisinicline TID for 12 weeks plus behavioral support) have a higher probability of continuous abstinence from Week 12 to Week 24 post-randomization as compared to subjects randomized to Arm A (placebo TID plus behavioral support).

The analysis for secondary objective 3 will be conditional and performed only if both primary comparisons 1 and 2 pass statistical criterion.

3. Assess for a reduction in risk of relapse from Week 6 to Week 24 in subjects receiving 3 mg cytisinicline for 6 weeks and then either continue 3 mg cytisinicline from Week 6 to Week 12 (Arm C) or were switched to placebo from Week 6 to Week 12 (Arm B). Subjects not abstinent at Week 6 will be regarded as having relapsed.

6.3. Other Objectives

1. To compare arms (Arm B vs Arm A; Arm C vs Arm A) on 7-day point prevalence abstinence weekly at Week 2 to Week 12, then for Weeks 16, 20, and 24.
2. To compare arms (Arm B vs Arm A; Arm C vs Arm A) on serum cotinine levels every other week at Week 2 to Week 12, then at Weeks 16, 20, and 24.
3. To compare arms (Arm B vs Arm A; Arm C vs Arm A) on expired CO levels every week at Week 2 through Week 12, then at Weeks 16, 20, and 24.

4. To compare arms (Arm B vs Arm A; Arm C vs Arm A) on use of any non-cigarette nicotine products, including vaping during study treatment (Week 2 through Week 12) and study follow-up (Week 16 through Week 24).
5. Assess whether subjects randomized to Arm B have a higher probability of abstinence from Week 9 to Week 12 as compared to subjects randomized to Arm A (placebo).
6. Assess among the subset of subjects who achieve abstinence from Week 3 to Week 6, whether subjects randomized to Arm B have a higher probability of continuous abstinence from Week 3 to Week 24 post-randomization as compared to homologous subjects randomized to Arm A.
7. Assess among the subset of subjects who achieve abstinence from Week 3 to Week 6, whether subjects randomized to Arm C have a higher probability of continuous abstinence at Week 24 post-randomization as compared to subjects randomized to Arm B.
8. Assess among the subset of subjects who achieve abstinence from Week 9 to Week 12, whether subjects randomized to Arm C have a higher probability of continuous abstinence from Week 9 to Week 24 post-randomization as compared to homologous subjects randomized to Arm A.
9. Among subjects who achieve abstinence from Week 3 to Week 6, compare time to failure to maintain abstinence between arms (Arm B vs Arm A; Arm C vs Arm A) to Week 24.
10. To explore the magnitude of treatment effect between arms across various subgroups defined by demographic and baseline characteristics for the primary and secondary outcomes.
11. To explore potential relationships between subject-reported outcomes (eg, anxiety, depression, withdrawal symptoms, tobacco craving) and the primary and secondary outcomes.
12. To assess possible withdrawal symptoms at Week 7 in Arm B subjects who will have discontinued cytisinicline at Week 6, analyzing separately for nicotine status (eg, either smoking, abstinent, or if using other nicotine products including vaping or nicotine replacement therapy [NRT]) compared to Arms A and Arm C.

6.4. Safety Objectives

1. To evaluate the safety profile of 3 mg TID cytisinicline compared to placebo (Arm B vs Arm A; Arm C vs Arm A).
2. To compare the safety profiles of Arm B subjects versus Arm C subjects with respect to adverse events occurring after Week 6 on the study.

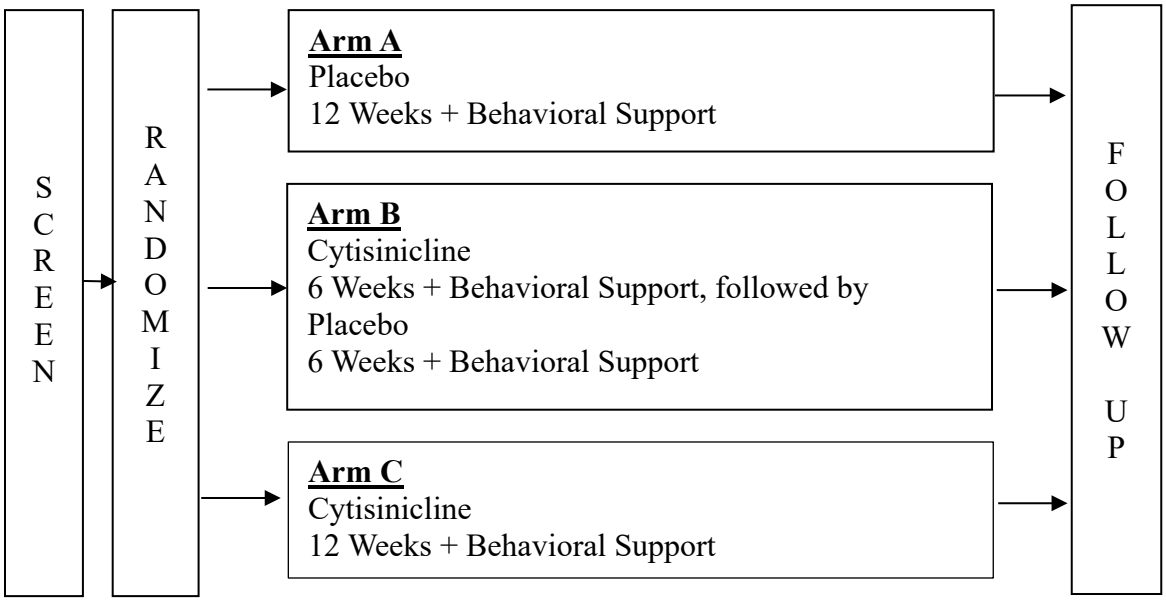
7. STUDY DESIGN OVERVIEW

7.1. Study Design

This will be a multi-center, double-blind, randomized, placebo-controlled, Phase 3 study conducted in male or female adults who are ≥18 years age, current daily cigarette smokers, intending to quit smoking, and are willing to set a quit date within 5-7 days of being randomized on the study. Study treatment must start the day after randomization such that study treatment is initiated prior to the quit date.

Subjects must meet all requirements outlined in the inclusion and exclusion criteria. Approximately 750 subjects will be randomly assigned with equal probability (1:1:1) to three arms: (Arm A, 12 weeks placebo: N=250; Arm B, 6 weeks cytisinicline followed by 6 weeks placebo: N=250; Arm C, 12 weeks of cytisinicline) as shown in the study design figure below.

Figure 2: ACH-CYT-04 (ORCA-3) Study Design Overview



This study will be conducted at approximately 15-19 clinical sites across the US. Subjects will be randomized within site, with the goal of balancing between arm allocation within clinical sites in order to minimize imbalance for the assessment of evidence of heterogeneity of effect estimates across sites. Clinical sites will be used as a stratification factor in primary analyses.

The study will be comprised of a pre-study screen, followed by 12 weeks of treatment, and post-treatment follow up visits to 24 weeks post-randomization.

Each randomized subject will receive 12 weeks of treatment using a TID dosing schedule. Determination of smoking cessation will be made from the subject's self-report of abstinence accompanied by expired carbon monoxide (CO) biochemical verification. Assessments of smoking abstinence will begin on Week 2 (Day 14±1 post-randomization) and will continue weekly during the Treatment Period, then at the Weeks 16, 20 and 24 Follow-up Period visits.

All subjects will receive concurrent smoking cessation behavioral support during the study Treatment Period (Weeks 1-12). Additional behavioral support will be provided during the Follow-up period based on issues/concerns/questions raised by the subject.

Safety assessments at clinic visits will occur on Day 7 during Week 1 and then weekly throughout the Treatment Period. Laboratory hematology and chemistry assessments will be made on Day 7, Week 6 and Week 12 during the Treatment Period. Adverse events will be monitored though the Follow-up Period. Any ongoing adverse events at Week 24 will be followed until resolved or determined to be chronic. The end of study is defined as the last follow-up visit (up to the Week 24 visit) for the last subject.

Treatment assignment unblinding for subjects will not occur until the end of the study has been reached, the database has been locked, and final study analyses have been performed, unless defined as an unblinding exception in Section 7.3.4.

7.2. Treatment Period (12 Weeks)

Treatment Period must begin on the day after randomization. Study treatment will be blinded, and subjects will take one study tablet three times during the day, approximately 5 hours apart. Subjects randomly assigned to Arm A will take one placebo tablet at each dosing per day for 12 weeks. Arm B subjects will take one cytisinicline tablet at each dosing per day for the first 6 weeks followed by one placebo tablet at each dosing per day for the last 6 weeks. Arm C subjects will take one cytisinicline tablet at each dosing per day for 12 weeks.

7.3. Discussion of Study Design

7.3.1. Placebo Control

A placebo control in this study design is necessary to control for response bias in evaluating cessation and safety. Behavioral support alone has been shown to be effective in helping smokers to quit and all subjects, including placebo control subjects, will receive behavioral support to aid their smoking cessation attempt. In addition, this study evaluates the effectiveness of cytisinicline when administered for either 6 weeks or 12 weeks compared to one placebo group, and the 1:1:1 randomization schedule means that subjects have a 2 in 3 chance of receiving active study drug. The use of a placebo group is therefore considered justified.

7.3.2. Primary Endpoint

Smoking abstinence during the last 4 weeks of treatment as the primary endpoint mirrors the prior varenicline Phase 3 trials and other smoking cessation trials for regulatory approval. Most of these prior Phase 3 trials had a “grace” period with success determined as having 4 weeks abstinence during the last 4 weeks of treatment. For varenicline, treatment was for 12 weeks with the first 8 weeks as a “grace” period and weekly assessments at Weeks 9-12 while on treatment was the primary endpoint assessment. Arm B in this study will assess the benefit of a shorter, 6-Week cytisinicline treatment having the first 2 weeks as a “grace period” and weekly assessments at Weeks 3-6 while on treatment as the primary endpoint assessment. Arm C in this study will mirror that same treatment duration as varenicline with weekly assessments at Weeks 9-12 while on treatment as the primary endpoint assessment.

Cytisinicline treatment was developed as a shorter treatment for smoking cessation, especially for smokers who do not want to commit to 12 weeks of treatment. However, the commercial 25-day treatment period may be too short on treatment, since smoking relapse appeared high in ORCA-1 from the end of treatment abstinence (Week 4) during the Weeks 5-8 assessment period. Therefore, this study will evaluate the benefit of a slightly longer 6-Week treatment period as well as repeating the treatment period for a 12-Week treatment duration. The 6-Week treatment period which is half in duration may still be beneficial and have a better safety profile due to less time on treatment.

For the primary endpoint, success is defined as complete abstinence during the last 4 weeks of treatment with weekly expired CO measurements ≤10 ppm for both 6- and 12-Week cytisinicline treatment durations plus behavioral support (Arm B and Arm C, respectively) compared to placebo plus behavioral support (Arm A).

7.3.3. Blinding

This double-blind study design protects against subjective bias in reporting both efficacy and safety. Blinding will occur by coding the individual study drug cartons and packs by an independent vendor assigned to the trial. The Sponsor and site personnel will not have access to the treatment assignment for individual subjects (except as an emergency; refer to Section 7.3.4) until the database is locked and final study analysis at 24 weeks post-randomization has been performed.

7.3.4. Unblinding

There is no intention to routinely unblind individual subjects at any time. During the study, emergency unblinding for treatment or regulatory reporting of adverse events might need to be performed as described below.

Unblinding may be done if the subject's well-being or treatment of adverse events requires knowledge of study drug assignment. The investigator must first contact the Study Medical Monitor, or representative, who will coordinate access to the study drug treatment assignment code via the independent vendor.

Examples of unblinding for treatment emergencies include:

- A life-threatening, unexpected adverse event that is thought to be related to study drug and for which unblinding would change or influence treatment decisions.
- Medication error, such as an accidental overdose, that would warrant unblinding in order to more effectively manage toxicity.

Unblinding by the Sponsor may also be necessary to determine whether a serious and unexpected suspected adverse reaction (SUSAR) requires expedited reporting to FDA or warrants an independent Data Safety Monitoring Committee (DSMC) assessment in the context of the study population. Per FDA guidance, the sponsor must report an adverse event as a SUSAR only if there is evidence to suggest a causal relationship between the investigational drug and the adverse event such as:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure;

- One or more occurrences of an event that is not commonly associated with the investigational drug exposure, but is otherwise uncommon in the population exposed to the drug;
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the investigational drug treatment group than in the concurrent control group.

Any unblinding of specific subjects by the Sponsor or required at the site level must be documented by the Sponsor.

7.4. Number of Subjects

Approximately 750 subjects will be randomized to the study, with approximately 250 subjects per arm. Efforts will be taken to coordinate weekly limits to enrollment rates among the participating sites in order to ensure adequate subject management and timely study data entry. The maximum number of subjects that a single site may be allowed to enroll, is 10% of the study total.

7.5. Randomization

Sites will utilize an Interactive Response Technology (IRT) system for treatment arm assignment at randomization (Day 0). The IRT will randomize within site. Detailed instructions are provided in the Study Reference Manual.

7.6. Number of Clinical Sites

This will be a multicenter clinical trial within the US. Approximately 15-19 clinical sites will participate.

7.7. Estimated Duration/Completion of Study

Duration of this study is estimated to be approximately 24 weeks for an individual subject (from randomization to Week 24 follow-up visit). Completion of the entire study is estimated at 12 months [redacted]

8. SELECTION OF STUDY POPULATION

Each potential subject will be provided with an informed consent form that has been reviewed and approved by the site's governing institutional review board (IRB). In accordance with the International Conference on Harmonization (ICH) guidelines on informed consent, the Principal Investigator (or designee) will provide potential subjects with a verbal description of the study including, but not limited to, study purpose, study procedures, risks and duration. Potential subjects will be asked to read the consent form and to sign and date it once all of their questions have been answered and they voluntarily agree to participate in the study. A copy of the signed informed consent form will be provided to the subject.

Upon obtaining signed informed consent, each subject will undergo the screening procedures outlined in Section 12.2.1. A screening log will be maintained by the site and will include documentation for screening failures. Subjects meeting all inclusion/exclusion criteria will then be randomized to treatment and begin the study procedures. All subjects are considered enrolled once randomized.

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

8.1. Inclusion Criteria

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

1. Male or female subjects, age ≥18 years.
2. Current daily cigarette smokers (averaging at least 10 cigarettes per day upon completing a 7-day screening smoking diary) and who intend to quit smoking.
3. Expired air carbon monoxide (CO) ≥10 ppm.
4. Failed at least one previous attempt to stop smoking with or without therapeutic support.
5. Willing to initiate study treatment on the day after randomization and set a quit date within 5-7 days of starting treatment.
6. Willing to actively participate in the study's smoking cessation behavioral support provided throughout the study.
7. Able to fully understand all study requirements, willing to participate, and comply with dosing schedule.
8. Sign the Informed Consent Form.

8.2. Exclusion Criteria

Subjects meeting ANY of the following exclusion criteria will NOT be eligible for inclusion into the study.

1. More than 1 study participant in same household during the 12-week treatment period.
2. Previous cytisinicline treatment in a prior clinical study or any other cytisine usage.
3. Known hypersensitivity to cytisinicline or any of the excipients.
4. Positive urinary drugs of abuse screen, determined within 28 days before the first dose of cytisinicline.
5. Clinically significant abnormal serum chemistry or hematology values within 28 days of randomization (ie, requiring treatment or monitoring).
6. Clinically significant abnormalities in 12-lead ECG determined after minimum of 5 minutes in supine position within 28 days of randomization (ie, requiring treatment or further assessment).

7. Recent history (within 3 months) of acute myocardial infarction, unstable angina, stroke, cerebrovascular incident, or hospitalization for congestive heart failure.
8. Current uncontrolled hypertension (blood pressure ≥160/100 mmHg).
9. Currently psychotic or having had a psychotic event within 3 months. If any subject becomes psychotic during the study, they must be removed from treatment and/or additional study visits.
10. Currently having suicidal ideation or risk for suicide ("Yes" to either question 4 or question 5 OR "Yes" to any suicidal behavior question on the C-SSRS with clear suicidal intent or previous attempt).
11. Current symptoms of moderate to severe depression (depression score ≥11on the HADS).
12. Renal impairment defined as a creatinine clearance (CrCl) <60 mL/min (estimated with the Cockroft-Gault equation).
13. Hepatic impairment defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.0 x the upper limit of normal (ULN).
14. Women who are pregnant or breast-feeding.
15. Male or female subjects of childbearing potential who do not agree to use acceptable methods of birth control during the study treatment period.
16. Participation in a clinical study with an investigational drug in the 4 weeks prior to randomization.
17. Treatment with other smoking cessation medications (bupropion, varenicline, nortriptyline, or any nicotine replacement therapy [NRT]) in the 4 weeks prior to randomization or planned use of these other smoking cessation medications during the study.
18. Use within the 2 weeks prior to randomization or planned use during the study of non-cigarette and/or noncombustible nicotine products (pipe tobacco, cigars, snuff, smokeless tobacco, hookah, e-cigarettes/vaping) or marijuana smoking or vaping.
19. Any other reason that the investigator views the subject should not participate or would be unable to fulfill the requirements for the study.

8.3. Modifying or Discontinuing Study Treatment and/or Study

8.3.1. Study Treatment Modifications during the 12-Week Treatment Period

Dose modifications in general are not allowed. On a case by case exception, the study treatment may be reduced to a twice a day (BID) schedule. These exceptions are only allowed for subjects who experience moderate or severe AEs (eg, nausea, insomnia, nightmares, anxiety) that might be attributed to study drug and would otherwise discontinue study treatment due to the AE. The reduction of one dose from a TID to a BID schedule should be related to the timing of the moderate or severe AE. For example, removing the evening dose for AEs related to insomnia or nightmares OR removing the morning dose for nausea or other gastrointestinal symptoms related to possible fasting conditions. Any dose reductions need to be discussed and coordinated with

the Study Medical Monitor, or representative, prior to any dose reduction. Once a dose reduction to a BID schedule occurs, no re-escalation back to a TID schedule is allowed. If the dose reduction to a BID schedule does not improve the AE symptoms to a tolerable level then further dose reductions should not occur and the subject should discontinue study treatment.

8.3.2. Discontinuation of Study during the 12-Week Treatment Period

Subjects can be discontinued from study during the Treatment Period for the reasons below**:**

1. If a subject experiences a serious or intolerable adverse event that prevents the subject from continuing study drug.
2. If a subject becomes psychotic.
3. At the Investigator's request (eg, if the Investigator considers that the subject's health might be compromised by continuing study drug). Non-compliance should not be a reason for discontinuing treatment.
4. If a subject becomes pregnant during the study treatment period, study drug should be discontinued; however, the subject should remain on the study for continued safety assessments and other study evaluations.
5. At the request of the subject who does not want to continue study drug treatment.

The reason for discontinuation of study will be recorded in the CRF.

If discontinuing study during the 12-Week Treatment Period, subjects are to complete the planned 12-week assessments at the time of discontinuing, and record on the Early Discontinuation CRF.

If a subject discontinues study due to any adverse event or any abnormalities considered to be clinically significant by the investigating physician, the subject will be followed until values are considered to be clinically acceptable or deemed chronic.

8.3.3. Discontinuation of Study during the Follow-up Period

All subjects should remain in the study and provide the required follow-up visits until the Week 24 follow-up assessment is completed except if a subject becomes psychotic or is lost to follow-up (eg, moved to an untraceable address) or withdraws consent for the follow-up visits. If a subject discontinues from the study during the follow-up period, the date of discontinuation and reason will be recorded in the CRF.

9. INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

9.1. Cytisinicline Film-Coated Tablets

Cytisinicline will be supplied by the Sponsor. The cytisinicline drug product is formulated as a compressed film-coated tablet containing 3 mg cytisinicline in a single tablet. Each tablet is composed of cytisinicline active substance (as the base) and well-established tablet-forming excipients. [redacted]

9.2. Placebo Tablets

Placebo tablets will contain the same excipients as in the cytisinicline tablet formulation plus additional cellulose powder in order to match final weight of the cytisinicline tablet. Placebo tablets will be identical in size, shape, color, and packaging in order to preserve the double-blind design of the study.

9.3. Receipt and Storage

The Study Drug will be supplied in 1-week treatment blister packs with 6 individual weekly blister packs in a carton (6 weeks of treatment). Each subject will be assigned 2 cartons for completing the 84 days (12 weeks) of study treatment. The first carton will be assigned on Day 0 and the second carton will be assigned on Day 35 (Week 5) so that treatment can follow assigned treatment arm (Figure 2). A clinical supplies management vendor will label, package, and distribute study drug to the sites.

Drug supply will be managed via an IRT program to maintain predetermined stock levels at the sites and/or handle resupply using site initiated requests. Upon receipt, details of study drug supplied shall be documented using the IRT and/or internal site login procedures.

The study drug shall be stored in a secure, temperature controlled location and only dispensed by suitably trained staff.

9.4. Administration

Study drug will be supplied as compressed tablets in blister packs. Tablets should be swallowed whole with water. Food does not influence the overall absorption of cytisinicline, so there are no restrictions on dosing with respect to the timing of meals.

9.5. Return/Destruction

At the end of the study, all unused study drug should be destroyed by the sites as directed by the Sponsor, unless a prearranged return to depot or to the Sponsor has been requested.

9.6. Method of Assigning Subjects to Arms

Subjects will be allocated to arms according to a predetermined randomization schedule and randomly assigned with equal probability (1:1:1) once all screening procedures are completed and verified. Randomization will be stratified by site.

[redacted]

The clinical research staff will record study drug (tablet) administration and all related information on the applicable source documents, to allow investigational product accountability and evaluation of subject compliance.

9.7. Study Drug Dosing Schedule

All subjects will receive 1 tablet for each of three dosing times, approximately every 5 hours per day. This 3 times a day (TID) schedule will be maintained for the 12-Week Treatment Period.

Initial treatment Day 1 for the 12-Week Treatment Period must start on the day after randomization.

9.8. Accountability

The pharmacist or pharmacist designee will maintain records of study drug receipt at the trial site, inventory at the site, dispensing for each subject, and any destruction or possible return of unused doses to the site for investigational product accountability.

Study drug for each subject will be configured into 2 coded study drug cartons, one of which will be assigned at randomization and the other will be assigned just prior to the Day 42 (Week 6) visit. Each carton will in turn contain 6 study drug packs and each pack will contain 21 tablets to cover 7 days (1 week) dosing. Clinic staff will distribute and collect the 7-day packs as the subject progresses through the clinic visits and will conduct ongoing accountability during each clinic visit by reviewing each subject's dosing timing in the treatment diary and associated blister packs. Used packs will be retained so that the Sponsor's monitoring staff can verify accountability records.

Upon completion of the study, all the investigational study drug product that has not been used and all the empty containers of the used investigational product at the sites will be destroyed or returned to the depot or Sponsor.

10. PREVIOUS AND CONCOMITANT MEDICATIONS

All subjects will continue to receive any existing prescription medication. Every effort should be made to ensure that the regimen of existing medications remain stable during the study.

At the discretion of the Investigator, the use of non-study drug medications (either prescription or over-the-counter) may be given if clinically-indicated during the study. Full details of any new medications must be recorded in the subject's Case Report Form (CRF).

All concomitant medication(s) taken during the trial, and any changes (additions, deletions, dose changes) must be recorded in the CRF.

11. TREATMENT COMPLIANCE

Treatment compliance will be monitored during the 84-day (12 week) Treatment Period via review of dose timing and drug accountability. Subjects will have a daily treatment diary that will record the number of tablets taken and time taken. Subjects will be instructed to bring their medication packs (blister packs) to each clinic visit so that clinic staff can reconcile against the treatment diary, recording the number of tablets taken and the number of missed tablets. In addition, an optional text messaging system will be implemented that will provide each subject with reminder texts corresponding to the approximate time of dosing.

12. STUDY PROCEDURES

After providing signed informed consent, all subjects will be evaluated for inclusion in the study within a 28-day Screening Period. Subjects who meet inclusion criteria will be required to provide a quit date that must be within 5-7 days after the start of treatment and agree to initiating study treatment the day after randomization. Both planned quit and treatment start dates must be documented to confirm inclusion. Once all eligibility criteria are confirmed, randomization can occur. Study Day 1 will be defined as the first day of treatment. Subjects will complete a clinic visit on Day 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77 and 86. Follow-up visits will be scheduled at Weeks 16, 20 and 24.

12.1. Procedure Schedule

Table 4 provides a summary of required study evaluations. Refer to Section 12.2 for a detailed description of each study visit. Screening evaluations are to occur within a 28 day interval from initiation of screening evaluations to randomization. Subjects must initiate study treatment the day after randomization, such that study treatment is initiated on Day 1 prior to the quit date, within 5-7 days of Day 1.

Table 4: Schedule of Study Procedures During Treatment Period

Study Assessment	Screening Period (Day-28 to Rand)		Randomization	Treatment Period Week 1 – Week 12 (Day 84) (Days 7-86 are ±1 Day)												
	SV 1	SV 2[1]	Day 0	D1[2]	W1 (D7)	W2 (D14)	W3 (D21)	W4 (D28)	W5 (D35)	W6 (D42)	W7 (D49)	W8 (D56)	W9 (D63)	W10 (D70)	W11 (D77)	W12[3] (D86)
Informed Consent	•															
Inclusion/Exclusion	•															
Demographics	•															
Medical and Psychiatric History	•															
C-SSRS Questionnaire[4]	•									•						•
Physical Exam	•[5]															
Smoking History	•															
Urine Pregnancy Test for all Females[6]	•		•					•				•				•
Drugs of Abuse Screen[7]	•															
Vital Signs including weight	•[8]		•		•	•	•	•	•	•	•	•	•	•	•	•
Hematology and Chemistry	•				•					•						•
12-lead ECG	•									•						•
Concomitant Medications	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Quit Date Set and Treatment Day 1 Scheduled		•														
Review Smoking & Treatment Diary Completion Instructions[9]	•		•	•												
Review Smoking Diary[10]	•	•														
Review Treatment Diary Entries for Completeness and Compliance[11]					•	•	•	•	•	•	•	•	•	•	•	•
Adverse Event Reporting	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Study Drug Distribution,			•		•	•	•	•	•	•	•	•	•	•	•	•

Study Assessment	**Screening Period (Day-28 to Rand)**		**Randomization**	**Treatment Period Week 1 – Week 12 (Day 84) (Days 7-86 are ±1 Day)**												
	SV 1	SV 2[1]	Day 0	D1[2]	W1 (D7)	W2 (D14)	W3 (D21)	W4 (D28)	W5 (D35)	W6 (D42)	W7 (D49)	W8 (D56)	W9 (D63)	W10 (D70)	W11 (D77)	W12[3] (D86)
Accountability and Collection																
Behavioral Support		•[12]	•		•	•	•	•	•	•	•	•	•	•	•	•
Fagerström Test of Nicotine Dependence			•													
Self-Efficacy Questionnaire			•													
QSU-Brief Questionnaire			•		•	•	•	•	•	•						
MNWS Questionnaire[13]			•		•	•	•	•	•	•	•					
HADS Questionnaire	•									•						•
Smoking Cessation Status						•	•	•	•	•	•	•	•	•	•	•
Expired CO	•		•			•	•	•	•	•	•	•	•	•	•	•
Use of any non-cigarette nicotine products[14]						•	•	•	•	•	•	•	•	•	•	•
Serum Cotinine	•[15]					•		•		•		•		•		•

[1]Randomization *may* occur at the SV2 visit IF subject can commit to a quit date that allows start of treatment the following day. In such cases all Day 0 (Randomization) procedures must be completed at the SV2 clinic visit.

[2]Clinic will telephone each subject towards the end of Day 1 (first day of treatment) to make sure subject has taken medication according to dosing schedule, answer any questions, assess for adverse events and any concomitant medications.

[3]The final day of treatment should be on Day 84. In order to ensure subject completes all treatment prior to assessments, the W12 visit is to be scheduled on Day 86±1 Day. If subject discontinues the study prior to Week 12, complete the planned 12-week assessments at the time of discontinuing, and record on the Early Discontinuation CRF.

[4] The Screening assessment for suicidal ideation (questions 1-5) will be asked in the temporal context of "within the past 3 months" and the Suicidal Behavior questions will be asked within the temporal context of "within lifetime" in order to fully evaluate current ideation or risk of suicide. Assessments conducted at Week 6 and Week 12 will ask all questions in the temporal context of "since last assessment" for suicidal ideation/risk.

[5]Physical exam may be conducted at either the SV1 or the SV2.

[6] Urine pregnancy test kits supplied to site by central laboratory. All other testing performed by a central laboratory. Test results must be negative at the SV1 and D0 visit for inclusion into the study, excluding females who are surgically sterile (hysterectomy or tubal ligation) or are >2 years post-menopausal.

[7] Drugs of abuse to include at a minimum amphetamines, methamphetamines, barbiturates, benzodiazepines, cocaine, ecstasy, opiates, and phencyclidine.

[8] To include height at screening for BMI calculation.

[9] There are two distinct diaries to be used: The screening smoking diary will capture daily cigarette consumption for 7 consecutive days so that an average can be obtained to assess Inclusion Criteria #2. The on-study treatment diary is to assess treatment compliance and will capture each study drug dose date and time.

[10]Number of cigarettes smoked daily will be recorded in a 7-day smoking diary to be completed by the subject between SV1 and SV2. Adequate completion of the 7-day screening diary with an average of at least 10 cigarettes smoked per day is required for inclusion into the study.
[11]Study subjects are to make daily diary entries noting date and time of each dose. Sites are to review these prior (via on-line access) and during clinic visits to ensure subject is completing entries in real-time and accurately.
[12]Setting the quit date and plan is to be considered the first behavioral support counseling session.
[13]The MNWS questionnaire to assess withdrawal will be administered to all subjects on Day 0 and then weekly at Week 1 through Week 7 clinic visits.
[14] Although planned use during the study is an exclusion criteria, record any actual use of non-cigarette nicotine products, including vaping.
[15]Serum will be collected with other laboratory testing at SV1 for cotinine testing and another sample will be frozen/stored for possible Nicotine Metabolite Ratio (NMR) testing at baseline only. Serum collected on subjects that are screen-failed will be destroyed.

Table 5: Schedule of Procedure During Follow-up Period

Study Assessment	Follow-up Period Week 16–Week 24[1] (Week Visits ±1 Week)		
	Week 16	Week 20	Week 24
Behavioral Support[2]	•	•	•
Adverse Event Reporting	•	•	•
Smoking Cessation Status	•	•	•
Expired CO	•	•	•
Use of any non-cigarette nicotine products[3]	•	•	•
Serum Cotinine	•	•	•

[1]All subjects regardless of smoking status at Week 12 will continue for follow-up at the Week 16, Week 20 and Week 24 clinic visits.
[2]Behavioral support sessions during the Follow-up Period are abbreviated and based only on issues/concerns/questions raised by subject for Weeks 16, 20 and 24.
[3]Record any actual use of non-cigarette nicotine products, including vaping.

12.2. Detailed Description of Study Visits

12.2.1. Screening Phase (SV1 – SV2)

Screening assessments used to evaluate inclusion and exclusion criteria (SV1) can occur during 1 or more clinical visits over a 28-day period prior to randomization.

Screening (Day -28 to Randomization Day 0)

Study procedures include:

1. Written informed consent obtained.
2. Demographic data.
3. Document medical and psychiatric history (including, but not limited to, any diagnosis of schizophrenia or bipolar psychiatric illness, and any occurrences of panic attacks or post-traumatic stress disorder).
4. Document suicidal ideation, risk, intent, or attempt as determined via administration and assessment of the Screening C-SSRS questionnaire (Appendix 1).
5. Depression is to be assessed via subject's completion of the HADS questionnaire, using total score derived from the depression-related questions **only** (Appendix 6).
6. Physical examination.
7. Document any existing adverse events.
8. Concomitant medications.
9. Review of smoking history, to include year started smoking, information about previous quit attempts (and methods/treatments used), average number of cigarettes smoked per day over the past 30 days, and type of cigarettes typically smoked (regular vs menthol).
10. Provide smoking diary instructions to capture number of cigarettes smoked for 7 consecutive days. This diary will be reviewed at Screening Visit 2 to verify that Inclusion #2 is met (averaging at least 10 cigarettes per day over a 7 day period).
11. Expired CO.
12. Vital signs, including weight and height for BMI calculation.
13. Urine pregnancy for all female subjects, excluding those who are surgically sterile (hysterectomy or tubal ligation) or are > 2 years post-menopausal.
14. Drugs of abuse screen.
15. Hematology and Chemistry testing.
16. Serum collected and frozen for cotinine testing. Actual baseline cotinine testing will be completed only for subjects that are randomized (batch tested). NOTE: An additional minimum 1.0 mL serum will be frozen and stored by the central laboratory for possible Nicotine Metabolite Ratio (NMR) testing at baseline only. These serum samples will be destroyed for all subjects that are screen-fails.

17. 12-lead ECG.
18. Review all inclusion and exclusion criteria and if satisfied, schedule Screening Visit #2.

Screening Visit prior to randomization (SV2)

1. During the Screening Visit document any existing adverse events and concomitant medications. **Note**: Subjects must have adequately completed the 7-day daily smoking diary and have reported smoking an average of at least 10 cigarettes on 7 consecutive days to be eligible for inclusion into the study.
2. Each subject to provide their quit date, which must be 5-7 days after randomization (Treatment Day 5, 6 or 7) and the quit date must be documented. Setting a quit date and plan will be considered as the initial behavioral support session with the subject. The quit date will then determine the date for randomization. If a subject can commit to a quit date that allows for treatment to start the following day, the Screening Visit may be treated as Day 0 and the subject can be randomized. In such cases, all procedures outlined in (Section 12.2.2) must be completed.

12.2.2. Randomization

Randomization (Day 0)

Randomization must be performed within 5-7 days prior to the agreed upon quit date. All other screening evaluations must be completed with 28 days prior to the Randomization Day. Study treatment must start on the day after randomization.

Study procedures include:

1. Update concomitant medication(s).
2. Document any existing adverse events.
3. Vital signs, including weight.
4. Urine pregnancy for all female subjects, excluding those who are surgically sterile (hysterectomy or tubal ligation) or are > 2 years post-menopausal.
5. Expired CO.

Upon completion of procedures 1-5 above, assess for final confirmation/verification of eligibility (NOTE: The expired CO value on Day 0 does not need to meet screening criteria [≥10 ppm] unless this is the only pre-treatment CO value available). If confirmation supports inclusion, complete the following:

1. Subject to complete the following questionnaires:
    a. Fagerström Test for Nicotine Dependence (Appendix 2).
    b. Smoking Self-Efficacy questionnaire (SEQ-12) (Appendix 3).
    c. Brief Questionnaire of Smoking Urges (QSU-Brief) questionnaire (Appendix 4).
    d. Minnesota Nicotine Withdrawal Scale (MNWS) questionnaire (Appendix 5).
2. Provide subject with behavioral support information that includes counseling (Appendix 7). NOTE: it should be stressed to subjects that they must maintain their dosing schedule throughout the Treatment Period.

3. Randomize according to a pre-determined, blinded, randomization schedule (see Section 7.5) and obtain the first study treatment carton (Carton #1) which will contain treatment packs for Weeks 1-6.
4. Provide study treatment Week 1 and Week 2 packs and review dosing requirements. Review the layout and dosing instructions printed on the study treatment packs. Although packs will be marked with the week designation and dates, there will be times during the Treatment Period where a subject has multiple packs on hand. Review this with the subject and make sure it is understood that each pack must be completed for the designated time period before moving on to the next. Instruct subject that any/all packs in their possession must be brought back to the clinic at each visit and should never be thrown away. Used packs will be collected and all cartons and packs must be maintained by the site for drug accountability by the assigned study monitor.
5. Develop an appointment schedule that includes dates and times for each required clinic visit during the trial, providing a copy to the subject.
6. Provide study treatment diary instructions that require daily entries for both date and time of each dose taken.
7. Schedule a time on the following day (Day 1 of treatment, late in the day) when clinic will contact subject to assess compliance, any possible adverse events and any changes/additions in concomitant medications.

12.2.3. Treatment Period

Treatment Day 1

All subjects must begin treatment on the morning of Day 1 and record all dosing in the diary.

Clinic to contact subject via telephone call in afternoon or evening of Treatment Day 1 to:

1. Verify subject is taking treatment (one tablet three times a day), review diary completion requirements and answer any questions.
2. Ask subject if any adverse events have occurred and/or any changes in concomitant medications.
3. Reconfirm planned quit attempt on Treatment Day 5, 6, or 7.
4. Remind subject of their appointment time for Day 7 (Week1) visit and that they must bring with them their study treatment pack.

Treatment Day 7/Week 1 (±1 day)

1. Confirm the quit attempt on Treatment Day 5, 6, or 7.
2. Subject to complete the following questionnaires:
   a. QSU-Brief questionnaire (Appendix 4).
   b. MNWS questionnaire (Appendix 5).
3. Review study treatment diary to verify dosing up to time of visit.
4. Assess for AEs and any changes to concomitant medications.
5. Vital signs, including weight.
6. Review study treatment Week 1 pack for compliance. Ensure that subject has study treatment Week 2 pack covering the next 7 days and provide a study treatment Week 3 pack.
7. Provide subject with behavioral support information that includes counseling. (NOTE: it should again be stressed to subjects that even if they are smoking less or have quit smoking, they must maintain their dosing schedule throughout the Treatment Period.
8. Blood for hematology and serum chemistry testing.
9. Remind subject of their Day 14 (Week 2) appointment date and time and that they must bring with them all study treatment packs.

Treatment Day 14/Week 2 (±1 day)

1. Subject to complete the following questionnaires:
   a. QSU-Brief questionnaire (Appendix 4).
   b. MNWS questionnaire (Appendix 5).
2. Review study treatment diary to verify dosing up to time of visit.
3. Assess for AEs and any changes to concomitant medications.
4. Vital signs, including weight.
5. Review study treatment Week 2 pack for compliance and collect the Week 1 pack (which should be empty if all doses were taken as expected). Confirm that the subject has the Week 3 pack and provide a study treatment Week 4 pack.
6. Provide subject with behavioral support information that includes counseling (Appendix 7). NOTE: At this time, it should be stressed to subjects that they must maintain their dosing schedule throughout the Treatment Period even if they have quit smoking. In addition, subjects are to be encouraged to continue trying to quit even if they are smoking or have a lapse after they have quit smoking.
7. Blood for cotinine testing.
8. Expired CO.

9. Record the following:
    a. Has the subject smoked any cigarettes since the last clinic (Day 7) visit?
    b. If subject has smoked, subject should report the total number of cigarettes smoked since the last clinic visit.
    c. Has the subject used any non-cigarette nicotine products, including vaping, since the last clinic (Day 7) visit? If yes, record what was used and remind subject such products should not be used during the study.
10. Remind subject of their Day 21 (Week 3) appointment date and time and that they must bring with them all study treatment packs.

Treatment Day 21/Week 3 (±1 day)

1. Subject to complete the following questionnaires:
    a. QSU-Brief questionnaire (Appendix 4).
    b. MNWS questionnaire (Appendix 5).
2. Review study treatment diary to verify dosing up to time of visit.
3. Assess for AEs and any changes to concomitant medications.
4. Vital signs, including weight.
5. Review study treatment Week 3 pack for compliance and collect the Week 2 pack (which should be empty if all doses were taken as expected). Confirm that the subject has the Week 4 pack and provide a study treatment Week 5 pack.
6. Provide subject with behavioral support information that includes counseling (Appendix 7). NOTE: At this time, it should be stressed to subjects that they must maintain their dosing schedule throughout the Treatment Period even if they have quit smoking. In addition, subjects must be counseled to be honest with their smoking status information and encouraged to continue trying to quit even if they are smoking or have a lapse after they have quit smoking.
7. Expired CO.
8. Record the following:
    a. Has the subject smoked any cigarettes since the last clinic (Day 14) visit?
    b. If subject has smoked, subject should report the total number of cigarettes smoked since the last clinic visit.
    c. Has the subject used any non-cigarette nicotine products, including vaping, since the last clinic (Day 14) visit? If yes, record what was used and remind subject such products should not be used during the study.
9. Remind subject of their Day 28 (Week 4) appointment date and time and that they must bring with them their study treatment packs.

Treatment Day 28/Week 4 (±1 day)

1. Subject to complete the following questionnaires:
    a. QSU-Brief questionnaire (Appendix 4).
    b. MNWS questionnaire (Appendix 5).
2. Review study treatment diary to verify dosing up to time of visit.
3. Assess for AEs and any changes to concomitant medications.
4. Vital signs, including weight.
5. Review study treatment Week 4 pack for compliance and collect Week 3 pack (which should be empty if all doses were taken as expected). Confirm that the subject has the Week 5 pack and provide a study treatment Week 6 pack, which will be the last pack in first carton (Carton #1) assigned at randomization.
6. Provide subject with behavioral support information that includes counseling (Appendix 7). NOTE: Again it should be stressed to subjects that they must maintain their dosing schedule throughout the Treatment Period even if they have quit smoking. In addition, subjects must be counseled to be honest with their smoking status information and encouraged to continue trying to quit even if they are smoking or have a lapse after they have quit smoking.
7. Blood for cotinine testing.
8. Urine pregnancy for all female subjects, excluding those that are surgically sterile (hysterectomy or tubal ligation) or >2 years post-menopausal.
9. Expired CO.
10. Record the following:
    a. Has the subject smoked any cigarettes since the last clinic (Day 21) visit?
    b. If subject has smoked, subject should report the total number of cigarettes smoked since the last clinic visit.
    c. Has the subject used any non-cigarette nicotine products, including vaping, since the last clinic (Day 21) visit? If yes, record what was used and remind subject such products should not be used during the study.
11. Remind subject of their Day 35 (Week 5) appointment date and time and that they must bring with them their study treatment packs.

Treatment Day 35/Week 5 (±1 day)

1. Subject to complete the following questionnaires:
    a. QSU-Brief questionnaire (Appendix 4).
    b. MNWS questionnaire (Appendix 5).
2. Review study treatment diary to verify dosing up to time of visit.
3. Assess for AEs and any changes to concomitant medications.
4. Vital signs, including weight.

5. Review study treatment Week 5 pack for compliance and collect Week 4 pack (which should be empty if all doses were taken as expected). Confirm that the subject has the Week 6 pack.
6. Obtain the study treatment carton #2 via IRT, which will contain study treatment packs for Weeks 7-12. Provide subject with a Week 7 pack from Carton #2.
7. Provide subject with behavioral support information that includes counseling (Appendix 7). NOTE: Again it should be stressed to subjects that they must maintain their dosing schedule throughout the Treatment Period even if they have quit smoking. In addition, subjects must be counseled to be honest with their smoking status information and encouraged to continue trying to quit even if they are smoking or have a lapse after they have quit smoking.
8. Expired CO.
9. Record the following:
    a. Has the subject smoked any cigarettes since the last clinic (Day 28) visit?
    b. If subject has smoked, subject should report the total number of cigarettes smoked since the last clinic visit.
    c. Has the subject used any non-cigarette nicotine products, including vaping, since the last clinic (Day 28) visit? If yes, record what was used and remind subject such products should not be used during the study.
10. Remind subject of their appointment date and time for the Day 42 (Week 6) visit and that they must bring with them their study treatment packs.

Treatment Day 42/Week 6 (±1 day)

1. Administer and assess suicidal ideation/risk using the "Since Last Visit" C-SSRS questionnaire (refer to Appendix 1).
2. Subject to complete the following questionnaires:
    a. QSU-Brief questionnaire (Appendix 4).
    b. MNWS questionnaire (Appendix 5).
    c. HADS questionnaire (Appendix 6).
3. Review study treatment diary to verify dosing up to time of visit.
4. Assess for AEs and any changes to concomitant medications.
5. Vital signs, including weight.
6. Review study treatment Week 6 pack for compliance and collect the Week 5 pack (which should be empty if all doses were taken as expected). Confirm that the subject has the Week 7 pack and provide a study treatment Week 8 pack from Carton #2.
7. Provide subject with behavioral support information that includes counseling (Appendix 7). NOTE: Again it should be stressed to subjects that they must maintain their dosing schedule throughout the Treatment Period and to be honest with their smoking status information.
8. Blood for hematology, serum chemistry and cotinine testing.

9. 12-lead ECG.
10. Expired CO.
11. Record the following:
    a. Has the subject smoked any cigarettes since the last clinic (Day 35) visit?
    b. If subject has smoked, subject should report the total number of cigarettes smoked since the last visit.
    c. Has the subject used any non-cigarette nicotine products, including vaping, since the last clinic (Day 35) visit? If yes, record what was used and remind subject such products should not be used during the study.
12. Remind subject of their Day 49 (Week 7) appointment date and time and that they must bring with them their study treatment packs.

Treatment Day 49/Week 7 (±1 day)

1. Subject to complete the MNWS questionnaire (Appendix 5).
2. Review study treatment diary to verify dosing up to time of visit.
3. Assess for AEs and any changes to concomitant medications.
4. Vital signs, including weight.
5. Review study treatment Week 7 pack for compliance and collect the Week 6 pack (which was the last pack in Carton #1 and should be empty if all doses were taken as expected). Retain Carton #1 and all weekly packs for drug accountability by the study monitor. Confirm that the subject has the Week 8 pack and provide a study treatment Week 9 pack from Carton #2.
6. Provide subject with behavioral support information that includes counseling (Appendix 7). NOTE: Again it should be stressed to subjects that they must maintain their dosing schedule throughout the Treatment Period and to be honest with their smoking status information.
7. Expired CO.
8. Record the following:
    a. Has the subject smoked any cigarettes since the last clinic (Day 42) visit?
    b. If subject has smoked, subject should report the total number of cigarettes smoked since the last clinic visit.
    c. Has the subject used any non-cigarette nicotine products, including vaping, since the last clinic (Day 42) visit? If yes, record what was used and remind subject such products should not be used during the study.
9. Remind subject of their Day 56 (Week 8) appointment date and time and that they must bring with them their study treatment packs.

Treatment Day 56/Week 8 (±1 day)

1. Review study treatment diary to verify dosing up to time of visit.
2. Assess for AEs and any changes to concomitant medications.
3. Vital signs, including weight.
4. Review study treatment Week 8 pack for compliance and collect Week 7 pack (which should be empty if all doses were taken as expected). Confirm that the subject has the Week 9 pack and provide a study treatment Week 10 pack from Carton #2.
5. Provide subject with behavioral support information that includes counseling (Appendix 7). NOTE: it should be stressed to subjects that they must maintain their dosing schedule throughout the Treatment Period and to be honest with their smoking status information.
6. Blood for cotinine testing.
7. Urine pregnancy for all female subjects, excluding those that are surgically sterile (hysterectomy or tubal ligation) or >2 years post-menopausal.
8. Expired CO.
9. Record the following:
    a. Has the subject smoked any cigarettes since the last clinic (Day 49) visit?
    b. If subject has smoked, subject should report the total number of cigarettes smoked since the last clinic visit.
    c. Has the subject used any non-cigarette nicotine products, including vaping, since the last clinic (Day 49) visit? If yes, record what was used and remind subject such products should not be used during the study.
10. Remind subject of their Day 63 (Week 9) appointment date and time and that they must bring with them their study treatment packs.

Treatment Day 63/Week 9 (±1 day)

1. Review study treatment diary to verify dosing up to time of visit.
2. Assess for AEs and any changes to concomitant medications.
3. Vital signs, including weight.
4. Review study treatment Week 9 pack for compliance and collect the Week 8 pack (which should be empty if all doses were taken as expected). Confirm that the subject has the Week 10 pack and provide a study treatment Week 11 pack from Carton #2.
5. Provide subject with behavioral support information that includes counseling (Appendix 7). NOTE: Stress to subjects that they must maintain their dosing schedule for the remaining Treatment Period and to be honest with their smoking status information.

6. Expired CO.
7. Record the following:
    a. Has the subject smoked any cigarettes since the last clinic (Day 56) visit?
    b. If subject has smoked, subject should report the total number of cigarettes smoked since the last clinic visit.
    c. Has the subject used any non-cigarette nicotine products, including vaping, since the last clinic (Day 56) visit? If yes, record what was used and remind subject such products should not be used during the study.
8. Remind subject of their Day 70 (Week 10) appointment date and time and that they must bring with them their study treatment packs.

Treatment Day 70/Week 10 (±1 day)

1. Review study treatment diary to verify dosing up to time of visit.
2. Assess for AEs and any changes to concomitant medications.
3. Vital signs, including weight.
4. Review study treatment Week 10 pack for compliance and collect the Week 9 pack (which should be empty if all doses were taken as expected). Confirm that the subject has the Week 11 pack and provide the last study treatment Week 12 pack from Carton #2.
5. Provide subject with behavioral support information that includes counseling (Appendix 7). NOTE: Stress to subjects that they must maintain their dosing schedule for the remaining Treatment Period and to be honest with their smoking status information.
6. Blood for cotinine testing.
7. Expired CO.
8. Record the following:
    a. Has the subject smoked any cigarettes since the last clinic (Day 63) visit?
    b. If subject has smoked, subject should report the total number of cigarettes smoked since the last clinic visit.
    c. Has the subject used any non-cigarette nicotine products, including vaping, since the last clinic (Day 63) visit? If yes, record what was used and remind subject such products should not be used during the study.
9. Remind subject of their Day 77 (Week 11) appointment date and time and that they must bring with them their study treatment packs.

Treatment Day 77/Week 11 (±1 day)

1. Review study treatment diary to verify dosing up to time of visit.
2. Assess for AEs and any changes to concomitant medications.
3. Vital signs, including weight.
4. Review study treatment Week 11 pack for compliance and collect the Week 10 pack (which should be empty if all doses were taken as expected). Confirm that the subject has the last Week 12 pack.
5. Provide subject with behavioral support information that includes counseling (Appendix 7). NOTE: Stress to subjects that they must maintain their dosing schedule for the remaining week and to be honest with their smoking status information.
6. Expired CO.
7. Record the following:
    a. Has the subject smoked any cigarettes since the last clinic (Day 70) visit?
    b. If subject has smoked, subject should report the total number of cigarettes smoked since the last clinic visit.
    c. Has the subject used any non-cigarette nicotine products, including vaping, since the last clinic (Day 70) visit? If yes, record what was used and remind subject such products should not be used during the study.
8. Remind subject of their Day 84 (Week 12) appointment date and time and that they must bring with them their study treatment packs.

Treatment Day 86/ Week 12 (Assessment Day 86±1)

Note: The final day of treatment should be on Day 84. In order to ensure all subjects have completed treatment prior to assessments, the Week 12 visit is to be scheduled on Day 86±1 day.

1. Administer and assess suicidal ideation/risk using the "Since Last Visit" C-SSRS (refer to Appendix 1).
2. Subject to complete the HADS questionnaire (Appendix 6).
3. Review study treatment diary to verify dosing through Week 12.
4. Assess for AEs and any changes to concomitant medications.
5. Vital signs, including weight.
6. Review study treatment Week 12 pack for compliance and collect both Weeks 11 and 12 packs (which should be empty if all doses were taken as expected).
7. Provide subject with behavioral support information that includes counseling (Appendix 7).
8. Blood for hematology, serum chemistry and cotinine testing.
9. Urine pregnancy for all female subjects, excluding those that are surgically sterile (hysterectomy or tubal ligation) or >2 years post-menopausal.
10. 12-lead ECG.

11. Expired CO.
12. Record the following:
    a. Has the subject smoked any cigarettes since the last clinic (Day 77) visit?
    b. If subject has smoked, subject should report the total number of cigarettes smoked since the last clinic visit.
    c. Has the subject used any non-cigarette nicotine products, including vaping, since the last clinic (Day 77) visit? If yes, record what was used and remind subject such products should not be used during the study.
13. All subjects, regardless of smoking status, are to be scheduled for their Week 16 (±3 days) follow-up visit.

12.2.4. Follow Up Period for Smoking Cessation Assessments

Week 16 (±1 week)

1. Record the following:
    a. Has the subject smoked any cigarettes since the last (Day 86/Week 12) clinic visit?
    b. Has the subject smoked any cigarettes over the past 7 days?
    c. If subject has smoked, subject should report the total number of cigarettes smoked.
    d. Has the subject used any non-cigarette nicotine products, including vaping, since the last clinic (Day 86/Week 12) visit? If yes, record what was used and remind subject such products should not be used during the study.
2. Assess for AEs.
3. Blood for cotinine testing.
4. Expired CO.
5. Provide subject with abbreviated behavioral support based on issues/concerns/questions raised (Appendix 7).
6. All subjects regardless of smoking status are to be scheduled for their Week 20 (±3 days) follow-up visit.

Week 20 (±1 week)

1. Record the following:
    a. Has the subject smoked any cigarettes since the last clinic (Week 16) visit?
    b. Has the subject smoked any cigarettes over the past 7 days?
    c. If subject has smoked, subject should report the total number of cigarettes smoked.
    d. Has the subject used any non-cigarette nicotine products, including vaping, since the last clinic (Week 16) visit? If yes, record what was used and remind subject such products should not be used during the study.
2. Assess for AEs.
3. Blood for cotinine testing.
4. Expired CO.

5. Provide subject with abbreviated behavioral support based on issues/concerns/questions raised (Appendix 7).
6. All subjects, regardless of their smoking status, should be scheduled for their Week 24 (±3 days) follow-up visit.

Week 24 (±1 week)

1. Record the following:
    a. Has the subject smoked any cigarettes since the last clinic (Week 20) visit?
    b. Has the subject smoked any cigarettes over the past 7 days?
    c. If subject has smoked, subject should report the total number of cigarettes smoked.
    d. Has the subject used any non-cigarette nicotine products, including vaping, since the last clinic (Week 20) visit? If yes, record what was used and remind subject such products should not be used during the study.
2. Assess for AEs.
3. Blood for cotinine testing.
4. Expired CO.
5. Provide subject with abbreviated behavioral support based on issues/concerns/questions raised (Appendix 7).
6. Discharge subject from study.

12.2.5. Subject Diaries

A 7-day smoking diary will be collected during the screening period in order to capture the number of cigarettes smoked daily for 7 consecutive days. These data will be used to calculate the average number of cigarettes smoked per day in order to support Inclusion Criteria #2.

In addition, a study treatment diary must be maintained by each subject to record date and timing of study drug administrations during the Treatment Period. The diary will be configured into specific sections to support the above reporting by the subject. Staff must review entries for completeness with the subject at each clinic visit.

12.2.6. Behavioral Support

Each participating site must have a minimum of two staff members assigned to provide smoking cessation counseling. For this study, site counselors are required to complete an on-line training course identified by Achieve Life Sciences and pass the associated examination. Evidence of completion (certificate issued by the training course administrator) must be provided prior to site activation. The site counselors will be provided additional study-specific training prior to or during site initiation.

All subjects will receive up to 15 behavioral support sessions by a qualified study site staff member, starting prior to randomization at the Screening Visit #2 when the subject sets their Quit Date, again at randomization and continuing through the Week 12 (Day 86±1 day) visit as outlined in Table 4. Each behavioral session will be subject-driven and must include direct engagement with the subject about their attempt to quit smoking. Each session should last approximately 10 minutes (Refer to Appendix 7).

Site counselor(s) are to encourage subjects to continue study drug as scheduled even if they quit smoking as planned or if they lapse and have a cigarette after their quit date during the Treatment Period. It is important for subjects to keep trying to quit as planned. It is also important to stress to subjects that they should be honest when reporting cigarette smoking status and to remind them that all timepoints from Week 2 through Week 12 during the Treatment Period will be verified using CO.

Subjects will receive additional abbreviated support (based on issues/concerns/questions raised by the subject) during the Follow-up Period.

13. EFFICACY CRITERIA

This study will follow general criteria that are applicable to previous and current trials of cessation aids where participants have a defined target quit date and there is face-to-face contact with researchers or clinic staff.[17] Endpoint analyses for abstinence (4 weeks abstinence documented during the last 4 weeks of treatment) and continuous abstinence (continually documented to Week 24 post-randomization) will include the following criteria:

1. Self-report of smoking abstinence since the last clinic visit at each clinic assessment.
2. Biochemical verification of abstinence by expired CO at each clinic visit.
3. Use of an 'intention-to-treat' approach in which data from all randomized smokers are included in the analysis.
4. Subjects with an unknown smoking status at the Week 6, Week 12 and Week 24 assessments or lost to follow up will be classified as failed to quit.
5. Self-report of smoking abstinence during the follow up period only (Week 12 to Week 24) will follow the Russell Standard.[17]
6. Continually blinded to treatment allocation during collection of follow-up data to Week 24.

Refer to Section 16.3 and Section 16.4 for the specific criteria in determining the primary and secondary efficacy outcomes, respectively.

13.1. Laboratory Assessments for Efficacy

13.1.1. Expired Air Carbon Monoxide (CO)

Expired CO will be obtained using a calibrated instrument (eg, the Bedfont Micro+ Smokerlyzer®) provided by the sponsor and maintained by the clinical site for this study. Each clinical site must have documentation of instrument used and current calibration. CO values are to be reported in parts per million (ppm) at Week 2, weekly through Week 12, and at Weeks 16, 20 and 24.

13.1.2. Serum Cotinine Levels

Serum samples will be collected as additional laboratory efficacy assessments with cotinine levels determined at Weeks 2, 4, 6, 8, 10, 12, 16, 20 and 24. Baseline cotinine testing will use

frozen serum collected at the SV1 visit for subjects that are randomized. Cotinine levels will be determined at a central laboratory.

14. SAFETY ASSESSMENTS

All subjects will be monitored for adverse events starting at screening (pre-existing), by telephone contact on Day 1, at clinic visit on Day 7 , then weekly throughout the Treatment Period (Weeks 2 through 12) and monthly during the Follow-up Period (see Table 4 and Table 5). 12-lead ECG evaluations will be obtained on Week 6 and Week 12. Laboratory (hematology and chemistry) evaluations will be performed at the Week 1, Week 6, and Week 12 clinic visits using a central laboratory.

Safety will be assessed by consideration of all adverse events reported by or elicited from the subject and clinically significant abnormalities detected on 12-lead ECG or hematology and serum chemistry tests. Worsening of other preexisting medical conditions and any changes to concomitant medications/treatments will also be taken into account in this evaluation.

In addition to the planned times, safety procedures can be performed at any time when considered necessary by the Principal Investigator or attending Research Physician.

In the event of any clinically significant abnormalities identified by the investigating physician, subjects will be followed until:

- It has resolved/returned to normal or baseline.
- The event has stabilized at a level acceptable to the Investigator and is not considered to be clinically significant.
- It has been shown to be chronic during follow-up assessment.

All adverse events (serious and non-serious) beginning at randomization (prior to dosing) through the Week 24 visit will be recorded in the subject's CRF.

14.1. Definitions

An **Adverse Event** (AE) is defined as any untoward medical occurrence in a clinical trial subject administered a medicinal product and which does not necessarily have attribution with the treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to the investigational medicinal product.

An **Adverse Drug Reaction** (ADR) means all untoward and unintended responses to a medicinal product related to any dose administered. The phrase 'response to a medicinal product' means that attribution has at least a reasonable possibility, ie, the relationship cannot be ruled out and is judged by the investigator as at least possible (see definition below).

An **Unexpected Adverse Drug Reaction** (UADR)/**Unexpected Adverse Event** (UAE) means an adverse reaction/event, the nature or severity of which is not consistent with the applicable product information, namely in the Investigator Brochure for an unauthorized investigational product or in the SmPC for an authorized product.

The expected/unexpected status should be evaluated and assessed, by the Sponsor, based on the reference safety information available since expectedness in Pharmacovigilance refers strictly to the information listed or mentioned in the applicable reference safety information and not to event(s) that might be anticipated from knowledge of the pharmacological properties of a substance or because it was foreseeable due to the health status (eg, age, medical history) of the study subjects.

A **Serious Adverse Event** (SAE) or **Serious Adverse Reaction** (SAR) is defined as an AE that results in any of the following:

- Results in death.
- Is life-threatening.
- Requires hospitalization or prolongs existing inpatient's hospitalization.
- Results in persistent or significant disability or incapacity.
- Results in a congenital abnormality or birth defect.
- Is an important medical event which requires medical intervention to prevent any of the above outcomes.

SUSARs: AEs which meet all of the following criteria will be classified as suspected unexpected serious adverse reactions (SUSARs):

- Serious.
- Unexpected (ie, is not consistent with the applicable product information eg, Investigator's brochure for an unapproved IMP or SmPC for an authorised product).
- There is at least a reasonable possibility that there is attribution between the event and the medicinal product.

Important medical events are those which may not be immediately life-threatening, but may jeopardize the subject and may require intervention to prevent one of the other serious outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, or blood dyscrasias or convulsions that do not result in hospitalization.

The term **"life-threatening"** in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. For example, drug-induced hepatitis that resolves without evidence of hepatic failure would not be considered life threatening even though drug-induced hepatitis can be fatal.

Inpatient **hospitalization** or prolongation of existing hospitalization means that hospital inpatient admission and/or prolongation of hospital stay were required for treatment of AE or occurred as a consequence of the event. It does not refer to pre-planned elective hospital admission for treatment of a pre-existing condition that has not significantly worsened, or to diagnostic procedures.

14.2. Recording of Adverse Events

All of the following details will be recorded in the subject's CRF for each AE:

- Full description of AE.
- Date and time of onset.
- Date and time of resolution.
- Severity of event, to be assessed by an Investigator, or their delegate, in accordance with the definitions below.
- Relationship to study drug to be assessed by an Investigator, or their delegate, in accordance with the definitions below.
- Action taken (if any).
- Outcome and details of any further follow-up.

Adverse events documented in the CRF without a stop date at the Week 24 visit must be followed until final resolution or until it is medically justifiable to stop further follow up (eg, a chronic condition has been reached.) Documentation of adverse events should be updated as necessary.

14.2.1. Grading Adverse Event Severity

The following grades will be used by an Investigator to describe the severity of all AEs (including clinically-significant laboratory AEs) as shown in Table 6. Only 1 severity grade will be used for each AE (eg, mild - moderate is not acceptable).

Table 6: Adverse Event Severity

Severity of AE	Definition
Mild	No interference with activity
Moderate	Some interference with activity requiring no or minimal medical intervention
Severe	Prevents daily activity and requires medical intervention

If an adverse event has multiple aspects, the aspect in the highest intensity will be graded. It is emphasized that the term severe is a measure of intensity; thus a severe AE is not necessarily serious. For example, itching for several days may be rated as severe; however, may not be clinically serious.

14.2.2. Assessment of Attribution

The attribution between an adverse event and study drug will be determined and documented by the responsible Investigator, or their delegate, according to best medical judgment as shown in Table 7.

Table 7: Assessment of Attribution to Study Drug

Category	Description
Not Related	The event is definitely not associated with study drug.
Unlikely	The event was most probably produced by other factors such as the subject's clinical state, therapeutic intervention or concomitant therapy, and does not follow a known response pattern to study drug.
Possible	The event follows a reasonable temporal sequence from the time of study drug administration, and/or follows a known response pattern to the investigational product, but could have been produced by other factors such as the subject's clinical state, therapeutic intervention or concomitant therapy.
Probable	The event follows a reasonable temporal sequence from the time of study drug administration, and/or follows a known response pattern to the investigational product, and could not have been produced by other factors such as the subject's clinical state, therapeutic intervention or concomitant therapy.
Definite	The event follows a reasonable temporal sequence from the time of study drug administration, and/or follows a known response pattern to the investigational product, and could not have been produced by other factors such as the subject's clinical state, therapeutic intervention or concomitant therapy, and either occurs immediately following study drug administration, or improves on stopping the study drug.

14.2.3. Reporting of Serious Adverse Events

Any SAE that occurs during the AE reporting period (randomization to Week 24) must be recorded and reported immediately. All SAEs including those that are ongoing at the end of the Week 24 visit will be followed until each event resolves or is assessed as chronic.

In order to satisfy regulatory requirements, any Serious Adverse Event, whether deemed study drug-related or not, must be reported to the Sponsor or designee as soon as possible after the Investigator (or delegate) has become aware of its occurrence. SAE form completion and reporting must not be delayed, even if all of the information is not available at the time of the initial contact.

SAEs must be reported within 24 h of knowledge of the event by submitting an initial SAE report via email, telephone or fax.

[redacted]

Additional information (follow-up) about any SAE unavailable at the initial reporting should be forwarded by the site within 24 hours of the information becoming available.

The following information should be provided to accurately and completely record the event:

- Investigator name and center number.
- Subject number.
- Subject initials.

- Subject demographics.
- Clinical event:
  - Description.
  - date of onset.
  - severity.
  - treatment.
  - relationship to study drug (attribution).
  - action taken regarding study drug.
- If the AE resulted in death:
  - cause of death (whether or not the death was related to study drug).
  - autopsy findings (if available).
- Medical history case report form (copy).
- Concomitant medication case report form (copy).
- Any relevant reports (laboratory, discharge, x-ray, etc.).

Subjects who have had an SAE during the AE reporting period (randomization through to Week 24 visit) must be followed clinically until all parameters (including laboratory) have either resolved or been assessed as chronic.

SUSARs should be reported to the IRB (if applicable) and to the FDA in accordance with applicable regulatory requirements for expedited reporting. It is the Site's responsibility to report any SUSAR to their IRB and it is the Sponsor's responsibility to report any SUSAR to the FDA.

Full details of SAE handling and SUSAR reporting will be documented in a study specific reference manual prior to the start of dosing.

14.2.4. Reporting of a Pregnancy during Study Treatment

If a pregnancy occurs in a randomized subject (or the partner of an enrolled subject) during the study treatment period or during the follow-up period, the Investigator must complete the Pregnancy Notification Form and submit to the CRO Pharmacovigilance Associate. Although not considered an SAE, the CRO PV Group will process pregnancy notifications using the same guidelines as for SAE reports above [ie, will acknowledge receipt of any pregnancy notification (initial or follow up) within 24 hours of receipt to the site with a copy to the Medical Monitor and Sponsor for their awareness].

Since there may be unknown risks to a pregnancy, embryo, or fetus (Section 2.1.3), the pregnant subject should discontinue study drug treatment while remaining on the study for continued safety assessments and other study evaluations.

The CRO PV Group will also follow up with the Investigator after completion of the study on the monitoring of the subject for the duration of the pregnancy and until 28 days after the child is

born. Any serious adverse events of the subject during the pregnancy or of the child at birth need to be recorded and CRO PV Group notified accordingly.

14.2.5. Reporting of COVID-19 Positive cases and COVID-19 vaccinations as Adverse Events of Special Interest

Subjects known to be COVID-19 positive during the study will be documented under adverse event reporting as AEs of special interest. In addition, any COVID-19 vaccinations received during the study should be documented as concomitant medications and any side effects immediately following a COVID-19 vaccination should be documented under adverse event reporting as AEs of special interest.

Any effects of the COVID-19 pandemic on the conduct of the study or any specific effects of COVID-19 infections or vaccinations on treatment arm results will be assessed.

14.3. Laboratory Assessments for Safety

14.3.1. Hematology and Chemistry Assessments

Routine laboratory safety samples will be analyzed at screening and at clinic visits as identified in Table 4 for each subject by a central laboratory. A decision regarding whether a result outside the reference range is of clinical significance or not shall be made by an Investigator and the report will be annotated accordingly. Clinically significant abnormalities occurring during the study will be recorded on the AE CRF. The reference ranges for laboratory parameters will be filed in the TMF and the Investigator site file.

Hematology: Hemoglobin, red blood cells, white blood cells, neutrophils, lymphocytes, monocytes, eosinophils, basophils and platelets.

Chemistry: Total protein, albumin, total bilirubin, SGPT (ALT), SGOT (AST), alkaline phosphatase, glucose, sodium, potassium, calcium, creatinine and urea.

14.4. Vital Signs

Systolic/diastolic blood pressure, pulse rate, and oral temperature measurements will be recorded in a seated position. Body weight will also be recorded. Clinically significant abnormalities occurring during the study will be recorded on the AE CRF. Height is to be recorded at Screening Visit #1 for BMI calculation.

14.5. Physical Examination

A physical examination will be performed by an Investigator. The examination will include general appearance, head, ears, eyes, nose, throat, neck, skin, cardiovascular system, respiratory system, gastrointestinal system, central nervous system, lymph nodes and musculoskeletal. An Investigator can examine other body systems if required, at their discretion.

15. SAFETY MONITORING

15.1. Independent Data Safety Monitoring Committee

Safety monitoring will be performed by an independent Data Safety Monitoring Committee (DSMC) who will be appointed for this study. The DSMC will be composed of at least 2 independent experts in the relevant therapeutic field and a third relevant expert such as a statistician.

The DSMC governance and operating procedures are described in a separate DSMC Charter. Meetings will be held via telecommunications equipment and will meet regularly in order to assess safety and trial status. Regular DSMC meetings will be planned approximately every 2 months during enrollment and while treatment is ongoing. Additional meetings will be at the discretion of the DSMC and the meeting schedule may be altered at the request of the Sponsor or at the discretion of the DSMC Chairperson. Meetings will typically begin with an open session. DSMC members, representatives of the Sponsor and other individuals as needed may be present during the open session. The open session will be followed by a closed session. Only DSMC members, and other individuals, as needed by the DSMC, will be in attendance at the closed session.

The primary responsibility of the DSMC will be to monitor for any unexpected safety risk for subjects on the protocol. The DSMC will:

- Review all SUSARs and SAEs reported to the Sponsor. The Sponsor will provide the DSMC with a copy of any unexpected study drug-related SAE Report Form within 7 business days of receipt by the Sponsor. The Medical Monitor (or designee) will also provide the DSMC with copies of all expedited SAE reports submitted to regulatory agencies.
- Perform periodic reviews of overall safety data for the study (eg, moderate or severe adverse events).

The DSMC may request unblinding of study treatment based on a safety concern or specific SUSARs or SAE. All unblinding and the reason for unblinding will be documented by the DSMC. The Sponsor and sites will not be unblinded unless the DSMC requests that individual or other unblinding occurs due to a safety concern.

The Sponsor may also request unblinding of any serious or unexpected adverse event (regardless of relationship to study drug) that the sponsor deems should be further assessed by the DSMC.

The DSMC Chairperson will communicate with the sponsor in regard to issues resulting from the conduct and clinical aspects of the trial. The sponsor will work closely with the committee to provide the necessary data for review.

16. STATISTICAL CONSIDERATIONS

A major design feature of this study is blinding. The study will be unblinded only after database lock and at the time of final study analyses (ie, when unblinding cannot induce bias in collection of data and interpretation of results).

Detailed statistical specifications are documented in the Statistical Analysis Plan (SAP) and the SAP will be final prior to initiation of any study unblinding.

16.1. Statistical Design

The overall study type I error probability will be one-sided 0.025 conditional on evidence of a favorable outcome for cytisinicline. Subjects will be randomized with equal probability to one of three arms (groups), one of two experimental arms or a control arm. The intended dosing regimens in these three arms are placebo for 12 weeks (Arm A), 3 mg cytisinicline for 6 of 12 weeks (Arm B) and 3 mg cytisinicline for 12 weeks (Arm C). The details of the interventions are specified in Section 7.1 and Section 7.2.

Two primary study objectives are specified in Section 6.1. These two primary objectives specify that the outcomes for each of the two experimental arms are to be compared to the control arm. The study size is based on a one-sided type I error probability of 0.0125 for each comparison of an experimental arm to the control (placebo) arm. Study success will be assessed using the Hochberg method for the two comparisons and the overall study type I error probability of one-sided 0.025; the outcomes are assumed to be positively correlated.

16.2. Analysis Sets

Screening Analysis Set: The Screening Analysis Set is defined as all subjects who give written informed consent and have entered screening but are not randomized. Analyses in this population will be restricted to presentation of baseline data and reasons for non-participation only.

Safety Analysis Set: The Safety Analysis Set (SAS) is defined as all randomized subjects who take at least one dose of study drug. All safety analyses will be performed on the Safety Analysis Set.

Efficacy Analysis Set: The All Randomized Analysis Set (ARS) is based on the ‘intention-to-treat’ principle and will include data from all randomized subjects.

16.3. Primary Outcome for Subjects

The primary efficacy outcome (biochemically verified abstinence for the last 4 weeks of cytisinicline treatment) for each subject is binary: success versus failure. Success is defined for the subject as having reported smoking abstinence (no cigarettes since the last clinic visit) at each clinic assessment from Week 3 to Week 6 (Arm B) and Week 9 to Week 12 (Arm C) with biochemical verification at each assessment. Biochemical verification will be defined by a carbon monoxide concentration in exhaled breath of less than 10 ppm. Similar timeframe and analyses will occur for Arm A placebo subjects.

Any other outcome is regarded as a failure. There are therefore two types of failure for the subject: (1) subjects with adequate data that they are smoking at any time (either by the subject’s self-report or CO ≥10 ppm) and (2) subjects having insufficient data to be determined as a

success for smoking cessation. This definition of primary outcome means that all subjects will have a realization of the primary outcome and therefore this endpoint is amenable to intent-to-treat (ITT) analyses.

16.3.1. Analysis of Primary Outcome

The outcome for each arm will be the proportion of subjects classified as a success. Each of the two experimental arms will be compared separately to the control arm (Arm A) at the appropriate timeframes. All randomized subjects will be included in the comparisons according to their randomized arm (ITT analysis). The statistical significance of each comparison will be based on the odds ratio using exact computations for stratified 2×2 frequency tables and using Monte Carlo estimation if necessary. The stratifier will be clinical site, with the possibility of pooling clinical sites having a small contribution. If cytisinicline is not favored by the effect size point estimate then the comparison will be designated as not statistically significant.

The estimated common odds ratio and its exact confidence interval will be reported. In addition, the estimated odds ratio and exact confidence interval for the marginal 2x2 table across sites (unadjusted odds ratio), and the estimated difference in proportions and the associated derived exact confidence interval using the exact confidence interval on the odds ratio will be reported. The exact difference in proportion confidence interval is derived using the method of Thomas (1971 and 1977).[18,19]

The primary comparisons will be presented in the context of a tipping point analysis.[20] Other supporting and sensitivity analyses challenging the results as well as analyses designed to assess homogeneity of effect are planned and described in the SAP.

16.4. Secondary Outcome for Subjects

The secondary efficacy outcome 1 and 2 (continued biochemically verified abstinence to Week 24) for each subject is binary: success versus failure. Success is defined for the subject as having reported smoking abstinence since the last clinic visit at each clinic assessment from Week 6 (Arm B) or Week 12 (Arm C) to Week 24 with biochemical verification at each assessment. Biochemical verification will be defined by a carbon monoxide concentration in exhaled breath of less than 10 ppm. During the Follow-up Smoking Cessation Assessment Period between Weeks 12 to 24, self-report of smoking abstinence will be according to the Russell Standard.[17]

The secondary efficacy outcome 3 is success with respect to being without relapse at Week 24. The secondary efficacy outcome 3 (reduction in risk of relapse from Week 6 to Week 24 in Arm C vs Arm B) will be assessed in each subject (in both Arms C and B). Subjects not abstinent at Week 6 will be regarded as having relapsed.

The considerations relative to the definition of these secondary efficacy endpoints are similar. The analyses associated with these three objectives will be done as Intent-to-Treat (ITT) analyses. The statistical model used for secondary objectives will be the same statistical model used for the analysis of the primary objectives.

16.4.1. Analysis of Secondary Outcomes

There are 3 secondary efficacy objectives, 2 objectives for continuous abstinence and 1 objective for reduction in risk of relapse. The continuous abstinence through Week 24 success outcome (secondary objectives 1 and 2) and relapse-free through Week 24 (secondary objective 3) must be defined separately for each of the three associated comparisons because of differences in the primary evaluation timing, that is, Weeks 3-6 for the Arm A versus Arm B comparison and Weeks 9-12 for Arm A versus Arm C comparison, and a mixed primary evaluation time for the Arm B versus Arm C comparison. It is important to note that the data collected and the schedule of collection are identical for all arms.

The following operational details are applicable to these secondary comparisons:

- Being abstinent requires meeting both a self-reported criterion and a biochemical verification. The beginning of self-reported abstinence is Week 3 to Week 6 for comparisons of Arm A and Arm B and Week 9 to Week 12 for comparison of Arm A and Arm C. For comparison of Arm B to Arm C, the failure of self-reported abstinence starts at Week 6 for both Arms B and C.
- Self-reported abstinence over the Follow-up Weeks 16-24 period will be assessed using the Russell Standard[17] to be regarded as abstinent or without relapse.
- Biochemical verification of non-smoking status is defined by a carbon monoxide concentration in exhaled breath of less than 10 ppm.

Subjects not observed to meet all success criteria will be regarded as non-success relative to the secondary efficacy outcome. Non-success will have two types: (1) subjects with adequate data that fail to meet the above criteria, and (2) subjects having insufficient data to be assessed as a success.

16.5. Study Size

In the 2011 published TASC Phase 3 study that evaluated cytisine versus placebo in 740 primarily moderate-to-heavy smokers treated for 25 days in Poland, the sustained 6-month abstinence rate was 10.0% in the cytisinicline arm compared to 3.5% in the placebo arm ($P<0.001$). In the 2014 published Phase 3 study that evaluated cytisinicline for 25 days versus nicotine replacement therapy (NRT) for 8 weeks in 1,310 adult daily smokers in New Zealand, the continuous six-month abstinence rate was 22% in the cytisinicline arm compared to 15% in the NRT arm ($P=0.002$).

Data from the international EAGLES trial (N=8120) were used to assess predictors for continuous smoking abstinence outcomes from Weeks 9-24. These analyses provided clear evidence that US origin was associated with lower success rates of stopping, regardless of treatment (varenicline, bupropion, or NRT). The continuous abstinence rates from 9-24 weeks in the US were 16.1%, 11.4% and 10.6% for varenicline, bupropion, or NRT, respectively, compared to 6.7% (95% CI: 5.3-8.4%) for placebo treatment. The odd ratios (OR) for these treatments in the US were 2.66, 1.78, and 1.64, respectively. The lower success rate in US smokers supports the view that smokers in the US may have particular characteristics that make it more difficult for them to stop smoking.

The trial size for this study is specified as 250 subjects per arm. The assumed control arm probability of success (continued abstinence to Week 24) is 0.07 (7%). The hypothesized experimental arm minus control arm probability difference is specified as 0.12 (12 points), corresponding to a hypothesized odds ratio of 3.116 (eg, 7% for placebo vs 19% for cytisinicline treatment). The significance level to be used is adjusted from the overall type I error probability of one-sided 0.025 to one-sided 0.0125 using the Bonferroni method to control for multiplicity. The statistical operating characteristics for each comparison are illustrated using simulation of Fisher's exact test with 10,000 replicates. These specifications are consistent with 95.7% power for each comparison with, conditional on 0.07 control arm probability outcome, an odds ratio critical region of ≥1.83, corresponding to a critical difference of ≥0.051 (7% for placebo vs 12% for cytisinicline treatment).

The study size is designated for approximately 750 subjects (250 subjects per arm). However, if higher than expected early treatment discontinuations (>5%) occur before completion of 6 weeks study treatment due to reasons other than adverse events, additional enrollment may be allowed up to 10% or 75 subjects.

16.6. Other Objectives

Other objectives beyond the designated primary and secondary objectives will be exploratory. There will be no multiplicity protection scheme for these analyses, and the results of these analyses will be labeled as exploratory.

16.7. Safety Objectives

Safety assessments include reported adverse events, laboratory tests results, and vital signs. Safety variables will be summarized for the Safety Analysis Set (SAS), defined as all randomized subjects who take at least one dose of study drug.

Adverse events will be coded using the MedDRA dictionary. Coding includes system organ class (SOC) and preferred term (PT). All verbatim descriptions and coded terms will be listed for all AEs.

Safety summaries are described in the SAP.

17. REGULATORY AND ETHICS CONSIDERATIONS

17.1. Institutional Review Board (IRB)

This study protocol must be submitted to an IRB for review and approval prior to initiation. As this study will be conducted at multiple sites, it is expected that each site must submit and obtain approval from their designated IRB with preference towards use of a central IRB when at all possible. Before the investigational product can be shipped to the investigative site and before the consenting and screening of subjects at the site can begin, all required regulatory documents (Section 18.1) must be in place. In addition, the protocol, any protocol amendments, the consent form, any advertising materials, any materials to be provided to the subjects for the proposed clinical study, and any other documents required by the IRB must be submitted by the Investigator (or representative) for review and approval by the IRB. The Investigator must also

ensure that the IRB reviews the progress of the study, if necessary, and renews its approval of the study (if ongoing) on an annual basis. Any member of the IRB who is directly affiliated with this study as an Investigator or as participating site personnel must abstain from the IRB vote on the approval of the protocol and associated documents.

All amendments or revisions to the protocol must undergo review by appropriate IRBs. Amendments/revisions will be circulated to all participating sites with clear instructions regarding IRB review. Amendments will be submitted by the Sponsor to the Food and Drug Administration (FDA) prior to central implementation to the study, and by IRBs prior to local implementation, EXCEPT when the amendment eliminates an immediate hazard to clinical trial subjects or is of a purely administrative nature.

A copy of the IRB approval letter must be forwarded to the Sponsor or Sponsor's representative before the study is implemented. The approval letter must clearly state the protocol title and version that was reviewed, as well as any associated documents. The Investigator also must forward copies of subsequent amendment approval letters upon receipt.

17.2. Ethical Conduct of the Study

This trial will be conducted in accordance with the Declaration of Helsinki, as well as the ICH Guidelines on GCP, the US Code of Federal Regulations, and local requirements regarding IRB committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research. Study plans may be adjusted in response to COVID-19 public health control measures and in accordance with regulatory guidelines to ensure subject safety, data integrity and study continuity occurs.

17.3. Informed Consent

The informed consent forms used for the study must comply with the Declaration of Helsinki and its updates and the International Conference on Harmonization (ICH) Guidelines and must have been approved by the Sponsor or Sponsor's representatives (prior to review by the site's IRB) and the Investigator's IRB. The Investigator or an authorized associate, must explain the nature of the study and the treatment in such a manner that the subject is aware of his/her rights and responsibilities, as well as potential benefits and risks. The Investigator is also responsible for answering any questions the subject may have throughout the study and sharing any new information, in a timely manner, that may be relevant to the subject's willingness to continue his/her participation in the trial.

Subjects must also be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice to their current or future care. Documentation of the discussion and the date of informed consent should be recorded in the subject's medical record or a study/clinic chart. Once all of their questions have been answered and they have voluntarily agreed to participate in the study, subjects will be asked to sign and date the Informed Consent Form.

Subjects, or their legally authorized representatives, must give informed consent in writing prior to the performance of any protocol-specific procedure. Subjects who cannot give informed consent (ie, mentally incompetent subjects or those physically incapacitated such as comatose subjects) are not to be recruited into the study. Subjects who are competent but physically unable

to sign the consent form may have the document signed by their nearest relative or legal guardian. A copy of the signed Informed Consent Form will be provided to the subject.

17.4. Subject Confidentiality

The Investigator must attempt to assure that the subjects' confidentiality will be maintained within the limit of the law. Subjects will be identified by subject number and initials (or other code) on all documents submitted to the Sponsor. Subjects will not be identified by name.

All records will be kept in a secure place in the clinical research site. Computer data entry and data review programs will be done using subject numbers and initials (or other code) only. Clinical information will not be released without written permission of the subject, as outlined in the subject consent form.

The Investigator must maintain a log of subject names and identification codes.

18. DOCUMENTATION

18.1. Study File and Site Documents

Prior to the activation of the study, at a minimum, the following items must be received by the Sponsor from the site:

1. Confidential Disclosure Agreement.
2. Signed protocol, and amendment(s) page(s).
3. The Principal Investigator's curriculum vitae and current medical license. Note: Principal Investigator or a Co-Investigator must be a medical doctor (MD).
4. Documentation of required training for designated smoking cessation behavioral counselors.
5. Signed Clinical Study Agreement/Contract.
6. Signed Financial Disclosure Form from the relevant site personnel.
7. IRB written approval for the protocol, amendment(s), Informed Consent Form, Smoking cessation information and advertisements (if applicable).
8. IRB Membership list or an official statement from the IRB stating the IRB is in compliance with Good Clinical Practice (GCP).
9. FDA Form 1572

18.2. Study Documents Supplied by the Sponsor

The Sponsor will supply the investigator with the following items:

1. Current version of the Investigator's Brochure
2. Current version of study protocol
3. Master CRF

4. Informed Consent Form template
5. Study Procedure Manual
6. Laboratory Manual (if applicable)

18.3. Maintenance and Retention of Records

It is the responsibility of the investigator to maintain a comprehensive and centralized filing system of all relevant documentation.

Investigators will be instructed to retain all study records required by the Sponsor and regulatory authorities in a secure and safe facility with limited access for one of the following time periods based on notification from the Sponsor:

1. For a period of at least 2 years from the **last** marketing approval worldwide.
2. Or a period of at least two years after discontinuation of clinical development of the investigational product as confirmed by the Sponsor.

The investigator will be instructed to consult with the Sponsor before disposal of any study records and to provide written notification to the Sponsor of any change in the location, disposition, or custody of the study files.

19. ADMINISTRATIVE PROCEDURES

19.1. Sponsor Responsibilities

The study will be monitored by representatives of the Sponsor and/or designated contract research organizations (CROs). On-site and remote monitoring will be performed. Routine monitoring visits will be conducted to (at a minimum):

1. Assure compliance with the study protocol.
2. Verify that the research facilities, including laboratories and equipment, are adequate to safely and properly conduct the study.
3. Verify that the investigational product is stored properly and under the proper conditions, is in sufficient supply, and that receipt, use, and destruction or return of investigational product at the study sites are controlled and documented adequately.
4. Verify that written informed consent was obtained before any protocol-specific screening procedures are performed solely for the purpose of determining eligibility for the clinical study and/or prior to the provision of study drug.
5. Review the subject CRFs and source documents to ensure that reported study data are accurate, complete, and verifiable from source documents.
6. Verify that the Investigator and study site personnel are adequately qualified throughout the study.
7. Verify that the safety information and amendments are submitted to the IRBs.

19.2. Investigator Responsibilities

All requested study data must be entered on the CRFs for the study. An explanation should be provided for all missing data. Correction of data on a CRF will be made with identification of the individual making the correction and date of the correction. Only individuals who are identified on the Delegation of Responsibility Form(s) may correct data on the CRF. For those subjects who withdraw before completion of their specified treatment regimen, all available efficacy and safety data must be entered in the CRF. The reason for withdrawal must be specified. Incomplete or inconsistent data on the CRFs will result in data queries that will be returned to the Investigator for resolution.

The Investigator must maintain adequate and accurate source documents upon which CRFs for each subject are based. The source documents are to be separate and distinct from the CRFs, except for cases in which the Sponsor has predetermined that direct entry into specified pages of the subject's CRF is appropriate. The documents to be maintained must include, but are not limited to, detailed notes on:

1. The medical history prior to participation in the study.
2. The basic identifying information, such as demographics, that link the subject's source documents with the CRFs.
3. The results of all diagnostic tests performed, diagnoses made, therapy provided, and any other data on the condition of the subject.
4. The subject's exposure to study treatment.
5. All AEs.
6. The subject's exposure to any concomitant therapy, including dates of administration.
7. All relevant observations and data on the condition of the subject throughout the study.
8. The oral and written communication with the subject regarding the study treatment, including the risks and benefits of the study. The date of informed consent must be recorded in the source documentation.

19.3. Regulatory Compliance

Quality Assurance representatives from the Sponsor or their delegate, and the FDA as required will be allowed to periodically visit the Investigators to discuss the conduct of the trial and, upon request, to inspect the records of the trial. These reviews are necessary to ensure that the study is conducted according to standards consistent with the ICH GCP Guidelines.

The Investigator agrees to discuss and correct, if necessary, any problems or deficiencies that are found during the course of these reviews.

19.4. Protocol Modification/Premature Termination

All protocol amendments must be written and approved by the Sponsor. Each IRB will review and approve amendments prior to their implementation in the study. IRB approval need not be obtained prior to removal of an immediate hazard to subjects.

The Sponsor may suspend or terminate the protocol early if safety or other issues occur. Furthermore, the study may also be terminated prematurely by the Sponsor for important corporate reasons, or due to instruction of the FDA due to safety reasons.

The Principal Investigator may terminate participation at his/her site at any time but must provide all study data for subjects randomized.

Following a decision of temporary suspension or discontinuation, it is a responsibility of the Principal Investigator to inform the study subjects and IRB stating the reasons for premature termination. The Sponsor shall be responsible for expedited reporting and/or notification to the FDA, as applicable.

19.5. Policy for Publication and Data Presentation

The Sponsor encourages the scientific publication of data from clinical research trials. However, Investigators may not present or publish partial or complete study results individually. The Principal Investigators and the Sponsor may propose appropriate scientific manuscripts or abstracts from the study data. Any manuscript or abstract proposed by the Investigators must be reviewed to ensure accuracy of data represented and commented upon in writing by the Sponsor prior to submission for publication. Investigators agree to consider the comments of the Sponsor in good faith and the Sponsor agrees in good faith not to impose limitations on access to the complete study data or unreasonable or inappropriate restrictions on publication of the study results. In case of publication, confidentiality of the study volunteers will be maintained.

Protocol No. ACH-CYT-04 (ORCA-3)

20. INVESTIGATOR'S AGREEMENT

I have carefully read the foregoing protocol including all appendices and agree that it contains all the necessary information for conducting the study safely.

I will conduct this study in strict accordance with this protocol and according to the current GCP guidelines and will attempt to complete the study within the time designated.

I will provide copies of the protocol and all other information submitted by the Sponsor relating to non-clinical and prior clinical experience to all personnel for whom I am responsible that participate in the study. I will discuss this information with them to assure that they are adequately informed regarding the drug and conduct of the study.

I agree to keep records on all subject information (case report forms, shipment and drug return/destruction forms and all other information collected during the study) in accordance with the current GCP and local regulations.

_____

Site Principal Investigator's name

_____

Signature/Date

_____

Institution

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APPENDIX 1. COLUMBIA - SUICIDE SEVERITY RATING SCALE (C-SSRS)

The Columbia Suicide Severity Rating Scale (C-SSRS) provides a standardized method to assess both suicidal ideation and behaviour to identify those at risk for suicide.[21] The questionnaire must be administered by trained study staff* at Screening and again at the Week 6 (Day 42) and Week 12 (Day 86) study visits. Assessments at Screening will utilize the "Screening" version of the form with ideation to be assessed in the past 3 months and suicidal behaviour within lifetime (the later assessment timing helps to discern if later positive assessments are possibly treatment emergent). Any "Yes" to question 4 or 5 OR "Yes" to any suicidal behaviour question with clear suicidal intent or previous attempt will be considered exclusionary for this study. Assessments at Week 6 (Day 42) and Week 12 (Day 86) study visits will utilize the "Since Last Visit" version of the form with timeframe to be "since last assessment". Any "Yes" to question 4 or 5 OR "Yes" to any suicidal behaviour question at the Week 6 (Day 42) or Week 12 (Day 86) study visits requires reporting as an AE as well as referral to a qualified Mental Health Professional for follow-up.

*Training by study staff is to be documented via certification in past 1 year on the C-SSRS. Training can be obtained on-line (www.cssrs.columbia.edu/training/training-research-setting).

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Screening

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

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

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

C-SSRS-Screening - United States/English - Mapi.
ID040351 / C-SSRS-Screening_AU5.1_eng-USori.doc

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Past 3 Months

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
Yes ☐ No ☐
If yes, describe:

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan.
Have you actually had any thoughts of killing yourself?
Yes ☐ No ☐
If yes, describe:

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it."*
Have you been thinking about how you might do this?
Yes ☐ No ☐
If yes, describe:

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
Yes ☐ No ☐
If yes, describe:

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
Yes ☐ No ☐
If yes, describe:

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.

Most Severe Ideation: ____ _____

Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply
____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe:	Yes ☐ No ☐ Total # of Attempts ____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted ____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted ____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* ____	*Enter Code* ____	*Enter Code* ____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* ____	*Enter Code* ____	*Enter Code* ____

 C-SSRS—Screening (Version 1/14/09) Page 2 of 2

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

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

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Assessment**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it".* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION	
The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Assessment**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** ☐ **No** ☐ Total # of Attempts _____ **Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐
Suicide:	**Yes** ☐ **No** ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage, *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

APPENDIX 2. FAGERSTRÖM TEST OF NICOTINE DEPENDENCE

The Fagerström Test of Nicotine Dependence (FTND) has been shown to be a reliable and valid measure of nicotine dependence[22] and will be administered at the randomization visit only. Analysis of results is outlined in the study Statistical Analysis Plan.

Question	Response	
How soon after you wake up do you smoke your first cigarette?	Within 5 minutes	
	6-30 minutes	
	31-60 minutes	
	After 60 minutes	
Do you find it difficult to refrain from smoking in places where it is forbidden (for example in church, at the library, in a cinema, etc.)?	Yes	
	No	
Which cigarette would you hate most to give up?	The first one in the morning	
	All others	
How many cigarettes/day do you smoke?	10 or less	
	11-20	
	21-30	
	31 or more	
Do you smoke more frequently during the first hours after waking than during the rest of the day?	Yes	
	No	
Do you smoke if you are so ill that you are in bed most of the day?	Yes	
	No	

APPENDIX 3. SMOKING SELF-EFFICACY QUESTIONNAIRE (SEQ-12)

The Smoking Self-Efficacy Questionnaire (SEQ-12)[23] is a validated instrument to assess baseline situations in which people might be tempted to smoke and will be administered at the randomization visit only. Analysis of results is outlined in the study Statistical Analysis Plan.

The following are some situations in which certain people might be tempted to smoke. Please indicate whether you are sure that you could refrain from smoking in each situation using one of the following answers:	**1 = Not at all sure**	**2 = Not Very Sure**	**3= More or less sure**	**4 = Fairly Sure**	**5 = Absolutely Sure**
1. When I feel nervous	1	2	3	4	5
2. When I feel depressed	1	2	3	4	5
3. When I am angry	1	2	3	4	5
4. When I feel very anxious	1	2	3	4	5
5. When I want to think about a difficult problem	1	2	3	4	5
6. When I feel the urge to smoke	1	2	3	4	5
7. When having a drink with friends	1	2	3	4	5
8. When celebrating something	1	2	3	4	5
9. When drinking beer, wine, or other spirits	1	2	3	4	5
10. When I am with other smokers	1	2	3	4	5
11. After a meal	1	2	3	4	5
12. When having coffee or tea	1	2	3	4	5

APPENDIX 4. BRIEF QUESTIONNAIRE OF SMOKING URGES (QSU-BRIEF)

The 10-question Brief Questionnaire of Smoking Urges (QSU-Brief) has been validated as a self-report instrument to measure tobacco craving/urges[24,25] and will be administered to study subjects at randomization and clinic visits on Day 7, 14, 21, 28, 35, and 42. Analysis of results is outlined in the study Statistical Analysis Plan.

We are interested in how you are thinking or feeling right now as you are filling out the questionnaire:

Question	**Response**						
	Strongly Disagree……..Strongly Agree						
	1	2	3	4	5	6	7
I have a desire for a cigarette right now.	◯	◯	◯	◯	◯	◯	◯
Nothing would be better than smoking a cigarette right now.	◯	◯	◯	◯	◯	◯	◯
If it were possible, I probably would smoke now.	◯	◯	◯	◯	◯	◯	◯
I could control things better right now if I could smoke.	◯	◯	◯	◯	◯	◯	◯
All I want right now is a cigarette.	◯	◯	◯	◯	◯	◯	◯
I have an urge for a cigarette.	◯	◯	◯	◯	◯	◯	◯
A cigarette would taste good now.	◯	◯	◯	◯	◯	◯	◯
I would do almost anything for a cigarette now.	◯	◯	◯	◯	◯	◯	◯
Smoking would make me less depressed.	◯	◯	◯	◯	◯	◯	◯
I am going to smoke as soon as possible.	◯	◯	◯	◯	◯	◯	◯

APPENDIX 5. MINNESOTA WITHDRAWAL SCALE (MNWS)

Several versions of the Minnesota Withdrawal Scale (MNWS) have been used since 1986. The version used in this study has been shown to provide specific assessment of nicotine withdrawal using 9 specific items.[26,27] The questionnaire will be administered to all study subjects at randomization and then weekly starting on Week 1 through Week 7 clinic visits. Analysis of results is outlined in the study Statistical Analysis Plan.

For each of the following, please rate yourself on how you have been feeling over the past 24 hours. Mark the number that applies to you:

Question	Response				
	Not at all	Slight	Moderate	Quite a bit	Extreme
Urge to smoke item 1	0	1	2	3	4
Depressed mood item 2	0	1	2	3	4
Irritability, frustration, or anger item 3	0	1	2	3	4
Anxiety item 4	0	1	2	3	4
Difficulty concentrating item 5	0	1	2	3	4
Restlessness item 6	0	1	2	3	4
Increased appetite item 7	0	1	2	3	4
Difficulty going to sleep item 8	0	1	2	3	4
Difficulty staying asleep item 9	0	1	2	3	4

APPENDIX 6. HOSPITAL ANXIETY AND DEPRESSION SCALE (HADS)

The HADS questionnaire[28] has been validated as a self-report instrument to measure levels of anxiety and depression and will be administered to study subjects. This questionnaire must be completed by all potential study subjects (completed = each of the 14 questions must be answered by the subject) during screening. The HADS questionnaire must be reviewed by clinic staff and a summation score calculated by totalling the numbers circled for each question at Screening Visit #1. A score ≥11 **(total of Depression "D" Questions only)** indicates current symptoms of moderate to severe depression and will be considered exclusionary for this study. The HADS questionnaire is to also be completed at Day 42 (Week 6) and again at Day 86 (Week 12). Analysis of results is outlined in the study Statistical Analysis Plan.

A	**I feel tense or 'wound up':**
3	Most of the time
2	A lot of the time
1	From time to time, occasionally
0	Not at all
D	**I still enjoy the things I used to enjoy:**
0	Definitely as much
1	Not quite so much
2	Only a little
3	Hardly at all
A	**I get a sort of frightened feeling as if something awful is about to happen:**
3	Very definitely and quite badly
2	Yes, but not too badly
1	A little, but it doesn't worry me
0	Not at all
D	**I can laugh and see the funny side of things:**
0	As much as I always could
1	Not quite so much now
2	Definitely not so much now
3	Not at all
A	**Worrying thoughts go through my mind:**
3	A great deal of the time
2	A lot of the time
1	From time to time, but not too often
0	Only occasionally
D	**I feel cheerful:**
3	Not at all
2	Not often
1	Sometimes
0	Most of the time

D	**I feel as if I am slowed down:**
3	Nearly all the time
2	Very often
1	Sometimes
0	Not at all
A	**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0	Not at all
1	Occasionally
2	Quite Often
3	Very Often
D	**I have lost interest in my appearance:**
3	Definitely
2	I don't take as much care as I should
1	I may not take quite as much care
0	I take just as much care as ever
A	**I feel restless as I have to be on the move:**
3	Very much indeed
2	Quite a lot
1	Not very much
0	Not at all
D	**I look forward with enjoyment to things:**
0	As much as I ever did
1	Rather less than I used to
2	Definitely less than I used to
3	Hardly at all
A	**I get sudden feelings of panic:**
3	Very often indeed
2	Quite often
1	Not very often
0	Not at all

A	I can sit at ease and feel relaxed:
0	Definitely
1	Usually
2	Not Often
3	Not at all

D	I can enjoy a good book or radio or TV program:
0	Often
1	Sometimes
2	Not often
3	Very seldom

Note: The actual questionnaire will not indicate the category (A=anxiety, D=depression) or the points, which are provided here to show how responses will be scored for analysis.

APPENDIX 7. BEHAVIORAL SUPPORT

Each participating site must have a minimum of two staff members assigned to provide smoking cessation counseling. For this study, site counselors are required to complete an on-line training course identified by Achieve Life Sciences and pass the associated examination. Evidence of completion (certificate issued by the training course administrator) must be provided prior to site activation. The site counselors will be provided additional study-specific training prior to or during site initiation.

All subjects will receive up to 15 behavioral support sessions by a qualified study site staff member, starting prior to randomization at the Screening Visit #2 when the subject sets their Quit Date, again at randomization and continuing through the Week 12 (Day 86±1 day) visit. Each behavioral session will be subject-driven and must include direct engagement with the subject about their attempt to quit smoking. Each session should last approximately 10 minutes. Ideally, one counselor should be assigned to support a given subject throughout their smoking cessation journey during the study in order to establish a trusting and supportive relationship.

Site counselor(s) are to encourage subjects to continue study drug as scheduled even if they quit smoking as planned or if they lapse and have a cigarette after their quit date during the Treatment Period. It is important for subjects to keep trying to quit as planned. It is also important to stress to subjects that they should be honest when reporting cigarette smoking status and to remind them that all timepoints from Week 2 through Week 12 during the Treatment Period will be verified using CO.

Subjects will be given the National Cancer Institute, “Clearing the Air” booklet, American Heart Associate “Managing Stress” handout, and the American Thoracic Society, “What is Second and Third Hand Smoking?” handout at the randomization visit.

Subjects will be given a list of 2-3 U.S. websites (eg, www.smokefree.gov, www.cancer.org/healthy/stay-away-from-tobacco/guide-quitting-smoking, www.heart.org/en/healthy-living/healthy-living-lifestyle/quit-smoking-tobacco) as resources.

Subjects may receive additional abbreviated support (based on issues/concerns/questions raised by the subject) during the Follow-up Period.

Each behavioral session will be subject-driven and must include direct engagement with the subject about their attempt to quit smoking. Counselors must be warm, empathetic, and genuine so that the subject is comfortable and will share issues and challenges that can be discussed further. In addition, the counselor is to be well-versed on study drug administration and expected side effects of cytisinicline and able to clearly review and discuss these topics with the study subject. Subjects will be encouraged to “keep trying” if they experience set-backs or a “lapse” during treatment. Each session should last approximately 10 minutes.

Practical counseling (problem solving/skills training) should be given. Topics include, but are not limited to, the following:

- Abstinence–Striving for total abstinence is essential. Not even a single puff after the quit date.
- Past quit experience–Identify what helped and what hurt in previous quit attempts. Build on past success.

- Anticipate triggers or challenges in the upcoming attempt–Discuss challenges/triggers and how the subject will successfully overcome them (eg, avoid triggers, alter routines).
- Alcohol–Because alcohol is associated with relapse, the subject should consider limiting/abstaining from alcohol while quitting. (Note that reducing alcohol intake could precipitate withdrawal in alcohol-dependent persons).
- Other smokers in the household–Quitting is more difficult when there is another smoker in the household. Subjects should encourage housemates to quit with them or to not smoke in their presence.
- Recognize danger situations–Identify events, internal states, or activities that increase the risk of smoking or relapse (ie, smoking cues and availability of cigarettes, experiencing urges)
- Develop coping skills–Identify and practice coping or problem solving skills. Typically, these skills are intended to cope with danger situations (ie, learning to avoid temptation and triggers)
- Provide basic information–Provide basic information about smoking and successful quitting.

Worksheets containing questions will be provided and may be administered by the counselor to initiate/foster open conversation with the subject and may be used at the start or during the study. These questions do not need to be used at every visit. They are provided as guidance if the subject has difficulty opening up a discussion.

Potential questions are:

- What is my motivation for quitting?
- Why is it important for me to quit right now?
- What are the biggest barriers I will encounter without a cigarette?
- What are some alternatives I can do when I face these barriers instead of smoking?
- What are my stress triggers for cravings?
- How will I deal with these stressors instead of smoking?
- What are your biggest concerns/fears about quitting smoking?

At the end of each visit, the subject will be reminded of supplementary information for additional support including: study staff contact information, Quitline information (1-800-QUIT-NOW), or additional websites.

Any questions regarding the medication or protocol must be answered by qualified study staff. Documentation of the behavioral support must be captured in the subject's source document.