Protocol ACH-CYT-09

A Multicenter, Double-blind, Randomized, Placebo-controlled Phase 2b Trial of Cytisine in Adult Smokers

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Version 3.0

CONFIDENTIAL

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SYNOPSIS

Protocol Number: ACH-CYT-09
Sponsor: Achieve Life Sciences
Title of Study: A Multicenter, Double-blind, Randomized, Placebo-controlled Phase 2b Trial of Cytisine in Adult Smokers
Clinical Phase: Phase 2b
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, isolated from seeds of *Cytisus laburnum* (Golden chain), that is believed to reduce the severity of nicotine withdrawal symptoms while inhibiting nicotine's effects by targeting nicotinic acetylcholine receptors (nAChRs) in the brain. Cytisine administered at the 1.5 mg dose has been used as a smoking cessation drug since the 1960's in Central and Eastern European countries. Previous studies dating from decades ago to support use in Central and Eastern Europe, and more recent studies conducted to Good Clinical Practice (GCP), have shown that cytisine can be effective in helping smokers to stop smoking. The titration schedule for the commercial product comprises a gradual reduction in the number of tablets per day from 6 tablets to 1 tablet over a 25-day treatment period. However, no studies are available evaluating how alternative dose exposure and administration impacts outcomes within the treatment period. The intent of this Phase 2b trial is to test the logistics and planned Phase 3 procedures, including compliance using various blister packaging, as well as the general effectiveness of cytisine treatment and the intended behavioral support in overall smoking cessation rates for subsequent Phase 3 sample size determinations. This Phase 2b trial is being conducted at sites within the United States (US) to evaluate cytisine dosage and administration schedules within a 25-day treatment period. Study arms will consist of the commercial 1.5 mg dose/titration schedule that is marketed in European countries, a higher dose of 3.0 mg following the marketed titration schedule, 1.5 mg and 3.0 mg doses using an initial three times a day (tid) schedule and respective placebo arms for either schedule. The study will evaluate efficacy based on the overall reduction in the number of cigarettes smoked during the various study treatment dosing/schedules as well as evaluate general compliance and safety profiles compared to the respective placebo arms (i.e. the marketed titration schedule or a simplified tid schedule). Results will also be used to aid defining Phase 3 sample size calculations when using the planned behavioral support and timing of study evaluations for the Phase 3 primary endpoint of abstinence from Week 5 to Week 8 post-randomization.

Objectives:

Efficacy Objectives:

1. Assess whether subjects randomized to cytisine, administered using the commercial titration schedule, have a greater overall reduction in cigarette smoking during the study treatment period (Day 1 – 25) compared to subjects randomized to the same titration schedule of a placebo.
2. Assess whether subjects randomized to cytisine, using a simplified tid schedule, have a greater overall reduction in cigarette smoking during the study treatment period (Day 1 - 25) compared to subjects randomized to the same tid schedule of a placebo.

Other Efficacy Objectives

(to include comparisons for 1.5 mg or 3.0 mg doses versus placebo when given as the commercial 25-day titration schedule and for the tid treatment schedule as well as comparisons between the commercial 25-day titration versus tid treatment schedules):

1. Assess the probability of abstinence from Week 5 to Week 8 post-randomization in subjects randomized to cytisine as compared to subjects randomized to placebo.
2. To compare cytisine and placebo arms on initial quit rates during study treatment, at Week 4 (End of Treatment) and on 7-day point prevalence abstinence at Week 5, Week 6, Week 7, and Week 8.
3. Among subjects abstinent at Week 4, compare time to failure to maintain abstinence through Week 8 between arms.
4. To explore potential relationships between subject-reported outcomes (e.g. anxiety, withdrawal symptoms, depression, tobacco craving, alcohol use) with the reduction in cigarette smoking during the study Treatment Period, as well as smoking cessation outcomes at Week 4 (End of Treatment) and from Week 5 to Week 8 post-randomization.
5. To explore a potential correlation for subject's nicotine metabolite ratio (NMR) with the reduction in cigarette smoking and smoking cessation outcomes.

Safety Objectives:

To evaluate overall safety profiles of cytisine when administered at 1.5 mg or 3.0 mg, using the 25-day commercial titration or simplified tid schedules, compared to placebo.

Study Design:

This will be a six-arm, multi-center, double-blind, randomized, placebo-controlled, Phase 2b 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 5-7 days after the start of treatment. The study will be double-blinded to dose but not to the administration schedule. Study treatment will start the day after randomization.

Subjects must meet all requirements outlined in the inclusion and exclusion criteria. Subjects will be stratified at randomization by BMI class (18.5 to <25 kg/m^2; 25 to <30 kg/m^2; 30 to <35 kg/m^2). A total of approximately 250 subjects will be randomly assigned 2:1 to cytisine treatment and the respective placebo treatment as designated by the defined schedule (i.e. the commercial titrated schedule or the simplified tid schedule). The intended six treatment arms are as follows:

Arm A N=50
1.5 mg cytisine dose using the commercial 25-day titration schedule+behavioral support

Arm B N=50
3.0 mg cytisine dose using the commercial 25-day titration schedule+behavioral support

Arm C N=25
Placebo tablets using the commercial 25-day titration schedule+behavioral support

Arm D N=50
1.5 mg cytisine dose for 25 days using a simplified tid schedule+behavioral support

Arm E N=50
3.0 mg cytisine dose for 25 days using a simplified tid schedule+behavioral support

Arm F N=25
Placebo tablets for 25 days using a simplified tid schedule+behavioral support

Each randomized subject will receive twenty-five (25) days treatment either using the commercial titration schedule (i.e. decreasing daily tablets over the 25 days) or a simplified tid version of the schedule. Smoking status assessments will begin on Day 1 and will continue through study treatment by recording the number of cigarettes smoked daily during treatment and at the End-of-Treatment visit on Week 4 (Day 27±2 day post-randomization). Smoking cessation status will then be assessed weekly over a 4-week follow-up period by the subject's self-report of abstinence with biochemical verification (expired CO) documented at Week 5, 6, 7 and 8.
Safety assessments will occur during study treatment, at the Week 4 End-of-Treatment clinic visit, and at the Week 5, 6, 7 and 8 clinic visits. The end of study is defined as the last follow-up visit (at Week 8 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 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 that will be 5-7 days after 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, comply with dosing schedule, and sign the Informed Consent Form.

Exclusion criteria:

1. Known hypersensitivity to cytisine or any of the excipients.
2. Positive urinary drugs of abuse screen, determined within 28 days before the first dose of cytisine.
3. Clinically significant abnormal serum chemistry or hematology values within 28 days of randomization (i.e. requiring treatment or monitoring).
4. Clinically significant abnormalities in 12-lead ECG determined after minimum of 5 minutes in supine position within 28 days of randomization (i.e. requiring treatment or further assessment).
5. BMI classification for being underweight (<18.5 kg/m^2) or having ≥Class 2 obesity (≥ 35 kg/m^2).
6. Recent history (within 3 months) of acute myocardial infarction, unstable angina, stroke, cerebrovascular incident or hospitalization for congestive heart failure.
7. Current uncontrolled hypertension (blood pressure ≥160/100 mmHg).
8. Documented diagnosis of schizophrenia or bipolar psychiatric illness; currently psychotic; having suicidal ideation (SBQ-R score ≥7); or current symptoms of moderate to severe depression (HAD score ≥11).
9. Renal impairment defined as a creatinine clearance (CrCl) <60 mL/min (estimated with the Cockroft-Gault equation) or hepatic impairment defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.0 x the upper limit of normal (ULN).
10. Women who are pregnant or breast-feeding.
11. Male or female subjects of child bearing potential who do not agree to use acceptable methods of birth control during the study treatment period.
12. Participation in a clinical study with an investigational drug within 4 weeks of randomization.
13. Treatment with other smoking cessation medications (bupropion, varenicline, nortriptyline, or any nicotine replacement therapy [NRT]) within 4 weeks of randomization or planned use of these other smoking cessation medications during the study.

14. Use within 2 weeks of randomization or planned use during the study of non-cigarette nicotine products (e-cigarettes, pipe tobacco, cigars, snuff, chewing tobacco, hookah) or marijuana vaping or smoking.
15. 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 250 subjects will be randomized to the study. Subjects will be stratified at randomization by BMI class (18.5 to <25 kg/m^2; 25 to <30 kg/m^2; 30 to <35 kg/m^2) in order to minimize imbalanced allocation to treatment arms.

Study Treatment Dosing and Administration:

Dosing:

All subjects will receive 2 tablets at each dosing according to randomization as follows:

Specified Tablets	**Cytisine 1.5 mg Arms**	**Cytisine 3.0 mg Arms**	**Placebo Arms**
Cytisine 1.5 mg tablets	1 tablet	2 tablets	-
Placebo tablets	1 tablet	-	2 tablets

Commercial Titration Schedule:

During the 25-day Treatment Period, subjects will take 2 tablets as follows:

25-day Schedule	**Number of Daily Treatments**
Days 1 - 3	6 times daily
Days 4 - 12	5 times daily
Days 13 - 16	4 times daily
Days 17 - 20	3 times daily
Days 21 - 24	2 times daily
Day 25	1 time only

Simplified TID Schedule:

During the 25-day Treatment Period, subjects will take 2 tablets as follows:

25-day Schedule	**Number of Daily Treatments**
Days 1 - 20	3 times daily
Days 21 - 24	2 times daily
Day 25	1 time only

The reduction in the frequency of administrations starting on Day 21 is intended to match the corresponding reduction in the commercial titration schedule.

Administration

In order to facilitate accurate compliance and accountability within the clinic visit schedule, tablets will be blister packed and will be configured into 9 medication packs, regardless of the 25-day treatment scheduled assignment. Each of the 9 packs will contain the correct number of tablets for the days of treatment as follows:

Pack Number	Days of Treatment
1	1-2
2	3-4
3	5-7
4	8-10
5	11-13
6	14-15
7	16-17
8	18-21
9	22-25

Clinic staff will distribute and collect packs as the subject progresses through the clinic visits and will conduct ongoing accountability during each clinic visit by reviewing a subject's 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 25 days of treatment and then be followed for up to 8 weeks post-randomization (approximately 31 days post-treatment). Therefore, the duration of the study will be approximately 8 weeks post-randomization for each 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 5-7 days after starting treatment and treatment must begin on the day after randomization. Subjects will be randomized 2:1 (active vs. placebo) in a blinded manner to either Arm A or Arm B, versus Arm C and similarly to either Arm D or Arm E versus Arm F. 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 at various scheduled times through the Week 8 Follow-Up Period.

Compliance will be assessed during the treatment period by reviewing subject's diary (date and time of dosing) as well as ongoing drug accountability at each clinic visit (Days 2, 3, 6, 12, 16, 20, and 27).

Subjects will be assessed for efficacy (number of cigarettes smoked daily during treatment as well as smoking cessation status by self-report of abstinence with biochemical verification (expired CO) during the follow-up assessments at Week 5, 6, 7 and 8).

Subjects will be assessed for safety (vital signs, adverse event reporting and concomitant medications) at each clinic visit, starting on Day 2 of treatment and ending at the Week 8 visit (Note: clinic will contact subject via telephone on Day 1 of treatment to assess for reported adverse events). In addition to the above safety assessments, hematology and chemistry assessments will be made during treatment (Days 2, 3, 6, 12, 16, 20 and 27) and again at the Week 8 visit. Subjects presenting with clinically significant laboratory findings or any adverse event of moderate severity (or higher), regardless of attribution, on the Day 16 visit must be scheduled for an additional safety visit on Day 21 (±1 Day). 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.

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. Analyses will be restricted to presentation of baseline data and reasons for non-participation as contrasted to those randomized.

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 smokers.

Efficacy outcomes

The primary outcome Y is the percent of expected cigarettes smoked computed for each subject as follows:

Let N=total of number of cigarettes smoked each day over period from 1 to 25 days.

Let R=representation of the average number of cigarettes smoked daily over the 7-day screening period as baseline.

Let T=number of post-randomization days where number of cigarettes smoked is recorded.

Compute Y=100*N/(T*R)

The denominator is the expected number of cigarettes that would have been smoked without intervention over the days where the number of cigarettes smoked is recorded, and the numerator is 100 times the actual number of cigarettes smoked (the purpose of the 100 factor is to convert to a percent).

Statistical methods

This study will be analyzed without specific statistical criteria. The overall goal is to obtain effect and conduct estimates to inform the design of future studies.

The primary comparisons are: A versus C, B versus C, D versus F, and E versus F (comparison of active arms to the associated placebo arm).

The primary analyses will include all randomized subjects by randomized arm (intent-to-treat analysis). The four primary comparisons will be based on analysis of variance with main effects arm (2 levels for the arms to be compared) and BMI class (3 level stratification as previously specified), and with covariate of baseline cigarettes. Sensitivity analyses will include the assessment of the contribution of interaction terms and effect modification analyses.

Analyses of data associated with other objectives will be detailed in a statistical analysis plan (SAP) and will include comparisons for 1.5 mg or 3.0 mg doses versus placebo when given as the commercial 25-day titration schedule and for the tid treatment schedule as well as comparisons between the commercial 25-day titration versus tid treatment schedules.

The trial size was computed based on previous data from a Phase 1/2 trial and for achieving narrow confidence intervals for the primary comparison estimates in this trial.

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 adverse event 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
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
C_{max}	Maximum Observed Plasma Concentration
CrCl	Creatinine Clearance
CRF	Case Report Form
DSM	Data Safety Monitor
ECG	Electrocardiogram
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product (for this protocol indicates cytisine 1.5 mg film coated tablet)
MedDRA	Medical Dictionary for Regulatory Activities
NMR	Nicotine Metabolite Ratio
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SOC	MedDRA System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Events
tid	Three Times Daily
T_{max}	Time to Maximum Observed Concentration
UADR	Unexpected Adverse Drug Reaction
UAE	Unexpected Adverse Event
ULN	Upper Limit of Normal

1. INTRODUCTION AND BACKGROUND

1.1. History of the Investigational Product

(-)-Cytisine (cytisinicline) is a plant-based alkaloid isolated from seeds of *Cytisus laburnum L.* (Golden chain) and has been used as a smoking cessation drug since the 1960's in Central and Eastern Europe, marketed as [redacted]).[1] It is estimated that over 20 million smokers have been treated with [redacted]. 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.[2-4] 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 Central and Eastern Europe. This may, in part, be explained by [redacted] focus on clinical development of cytisine in its traditional markets in Central and Eastern Europe countries where the initial clinical studies were conducted and published, although not in English.[1] Two more recent Phase 3 studies have been conducted and published in 2011 and 2014 in the New England Journal of Medicine.[5,6]

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 7 million premature deaths each year worldwide.[7] It is highly addictive, with more than 95% of unaided attempts at cessation failing by 6 months.[8] Every year that a smoker delays quitting beyond the mid-30s, there is an estimated 3 months reduction in life expectancy.[9]

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.[10] 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.[11,12] Varenicline is more effective than single NRT and bupropion, although combination NRT is comparable in efficacy.[13] 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).[12] 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. Combining NRT (e.g. oral and patch) has been shown to increase effectiveness.[13] 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).[11] 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.[4] 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).[14] 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 (e.g., 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[15]) 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. RECENT EVIDENCE FOR CYTISINE AS A SMOKING CESSATION TREATMENT

Cytisine has recently been evaluated using the commercial 25-day titration schedule in two large randomized Phase 3 clinical trials that were conducted according to Good Clinical Practice (GCP) in more than 2,000 participants. The overall objectives in these trials were to confirm the efficacy and safety of cytisine according to current clinical development standards.

The Phase 3 trial ([redacted] Smoking Cessation, or TASC[5] 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.[5] 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. Compliance (assessed at End of Treatment visit) showed that 44% of subjects randomized to cytisine took all doses as directed and 33% of subjects randomized to placebo were compliant with all doses.

The second Phase 3 trial (Cytisine As a Smoking Cessation Aid, or CASCAID[6] 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 by the commercial 25-day titration schedule or vouchers for low-cost combination NRT (patch plus gum or lozenges) 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. Overall, 53% of subjects randomized to receive cytisine were in compliance with the treatment schedule (had taken 80 or more of the required 100 tablets). Subjects in the NRT group showed 67% compliance (using NRT at both 1 week and 1 month). 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 patches with gum or lozenges to help participants stop smoking and remain non-smokers for six months.[6]

Both studies are described in more detail within the Investigator's Brochure.

3. SAFETY OVERVIEW FOR CYTISINE

3.1. 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 more recent pharmacology and toxicology studies in support of the cytisine IND and in preparation for formal Phase 3 evaluation. In that regard, NCCIH has sponsored new non-clinical studies to current Good Laboratory Practice (GLP) that have included 28-day repeat dosing for toxicology assessments in rats and dogs as well as two reproductive/developmental studies in rats.

3.1.1. Summary of 28-Day Repeat Toxicology Studies

Daily oral dose administration of cytisine in Sprague Dawley rats at 5 or 20 mg/kg/day for 28 consecutive days resulted in clinical signs, such as drooling, in a dose dependent manner. Other clinical signs were only seen in the 20 mg/kg group including ruffled fur, hypoactivity, shoveling behaviors, and ataxia. Decreases in food consumption and body weight gain were observed in animals treated with 20 mg/kg of cytisine. No cytisine-related macroscopic and microscopic findings were observed. The no observed adverse effect level (NOAEL) of cytisine is considered to be approximately 2 mg/kg/day when given orally for 28 consecutive days in rats. This would calculate to an estimated Human Equivalent Dose (HED) of 0.3 mg/kg (i.e. 21 mg for a 70 kg human) when cytisine is administered for 28 consecutive days.

Daily oral dose administration of cytisine via capsules in Beagle dogs at 0.5, 1, or 2 mg/kg/day for 28 consecutive days resulted in adverse effects. The maximum tolerated dose (MTD) was considered to be greater than 1 mg/kg/day but less than 2 mg/kg/day. Although emesis, drooling and diarrhea were observed in some animals treated with 0.5 mg/kg cytisine, the severities were mostly slight and not dose-limiting clinically; therefore, the NOAEL was slightly less or at approximately 0.5 mg/kg/day following 28 days oral administration. This gives an estimated HED of 0.28 mg/kg (i.e. 20 mg for a 70 kg human) should cytisine be administered for 28 consecutive days (Note: cytisine is administered for 25 days using a descending dose titration schedule).

Based on the findings in both the 28-day rat and 28-day dog toxicology studies, the established commercial dose of 1.5 mg × 6 doses/day (maximum total exposure of 9 mg/day for the first

3 days of treatment) is approximately half that of the estimated HED of ~20 mg/day for humans. The planned higher 3 mg/dose for this study yields a maximum total exposure of 18 mg/day for the first 3 days of treatment. This again is below the calculated HED based on all of the studies as shown in Table 1.

Table 1: Calculation of Margin of Safety based on Rat and Dog Toxicology Studies

NOAEL	C_{max} (ng/mL)	AUC_{last} (ng*h/mL)	HED[a] (mg/kg/day)	HED[a] (mg/day)	Human Dose[b]	Margin of Safety based on BSA
7-day rat study: 5 mg/kg	383.5	2926	0.8	56	9 mg/day	~6X
7-day dog study: 2 mg/kg	317.5	708.5	1.1	77	9 mg/day	~8X
28-day rat study: 2 mg/kg	292.6	1071.7	0.3	21	9 mg/day	~2X
28-day dog study: 0.5 mg/kg	TBD	TBD	0.28	20	9 mg/day	~2X

[a] HED = Human Equivalent Dose
[b] Human commercial dose is 9 mg/day for the first 3 days in the 25-day schedule per commercial use.
Notes: C_{max} and AUC are determined from the NOAEL data.
HED (mg/kg/day) = rat dose divided by 6.2 and dog dose divided by 1.8.
HED (mg/day) = HED dose (mg/kg/day) x 70 kg.

3.1.2. Summary of Reproductive/Developmental Studies

The study titled "Combined Fertility and Embryofetal Development Toxicity Study in Rats with Toxicokinetics" administered oral cytisine once daily to males for 10 weeks (initiating 28 days prior to mating) and to females for 14 days prior to mating, during mating, and through Gestation Day (GD) 17. Reproductive assessment for 10 males/group included sperm assessments with sample collection for evaluation of motility and total sperm count. Females were sacrificed with caesarian section on GD 21 with uterine contents examined and any grossly abnormal cervical, thoracic and abdominal viscera noted. The placenta, amniotic sac, number of live fetuses, number of early or late resorptions, and number of corpora lutea and any abnormalities were also recorded. Fetuses were evaluated for gross, visceral, and skeletal abnormalities. This study has been completed and no treatment-related mortality or clinical signs of toxicity were observed. There was also no evidence of treatment-related effects on mating, cyclicity, impaired fertility or embryofetal development.

The study titled "Pre- and Postnatal Development Toxicity Study in Rats, Including Maternal Function" administered daily cytisine to time-mated females on Gestation Days 6 through Lactation Day (LD) 20. Once daily, during the dosing interval (GD 6 through LD 20), detailed observations were done for each maternal animal at 4 hours post-dosing. Prior to and after the dosing interval, detailed observations were done at the same time that body weights were taken. On LD 0, date of delivery, litter size, and the sex, weight, and observations of individual offspring were recorded. During lactation on LD 4, 7, 14, and 21 (weaning), general development was recorded daily for individual offspring. Maturation phase procedures on LD 22-63 were also evaluated and recorded for development of each offspring. This study has been completed. No treatment-related mortality or clinical signs of toxicity were observed, and

no evidence of treatment-related effects on mating, cyclicity, impaired fertility or embryofetal development. A slight treatment-related effect on body weight/body weight gain was seen at the 10.0 mg/kg dose level in both males and females. Systemic exposure was generally higher in females than in males regardless of dose, and C_{max} was slightly higher in females at the 10 mg/kg compared to males at the 10 mg/kg dose level.

The non-GLP study titled "Embryotoxicity and Teratogenicity Study of Cytisine [redacted] in Rabbits" administered cytisine in sexually mature female rabbits. After fertilization by a male, female rabbits were treated with cytisine daily. Fertilized animals were observed for symptoms of toxicity and weight gain. Female animals were sacrificed by anesthesia on day 28 of pregnancy and were subjected to macroscopic examination of internal organs and Caesarean section of the uterus. After visual examination of fetuses, placentas and fetal resorption remains, fetuses were weighed, examined for external anomalies as well as skeleton and brain structure development were evaluated. Treatment with cytisine did not cause clinical symptoms, death or negative influence on weight gain of pregnant rabbits. Unsuccessful pregnancies, loss of offspring or abortion associated with the effect of cytisine were not found. Increased pre- and post-implantation death of the developing fetus, as well as reduced fetal weight, was not observed. No cases of external or visceral malformations and defects in fetal development were found. Malformations in the development of the skeleton and cranial bones as well as higher incidence rate of delayed ossification and variants in groups exposed to cytisine were also not observed.

Refer to the Investigator's Brochure for more detail on GLP-conducted, non-clinical studies.

3.2. General Safety of Cytisine as a Marketed Product

Cytisine (Generic designation cytisinicline) has been marketed by [redacted], in Central and Eastern Europe for over 20 years under the brand name [redacted] is currently marketed in 20 countries and is estimated to have been administered to over 21 million subjects.

[redacted] maintains an independently-audited pharmacovigilance system overseen by a pharmacovigilance Qualified Person (QPPV). Periodic Safety Update Reports (PSURs) have been regularly provided to the relevant European authorities since 2005 ([redacted]). It is estimated that the cumulative number of exposures to cytisine since 2005, and forming the denominator in the cumulative PSURs is over 15 million cases.

The safety information in the [redacted] Core Data Sheet is regularly reviewed against new PSUR information. Sections 3.2.1 and 3.2.2 summarize the section titled "Undesirable Effects" in the latest [redacted] Core Data Sheet.

3.2.1. Summary of Safety Profile

Since cytisine has a structural similarity to nicotine and is a partial agonist of nicotine acetylcholine receptors, the possible pharmacodynamic undesirable effects are manifested mainly as nicotine effects.

In 6 placebo-controlled clinical trials (N=2,844) 1,389 subjects received cytisine. The most commonly reported adverse events in the cytisine group involved the gastro-intestinal system:

upper abdominal pain, nausea, dyspepsia, dry mouth, vomiting, constipation and diarrhea. Nervous system and psychiatric disorders were also common, most frequently headache and dizziness, as well as somnolence and insomnia. However, statistical analysis did not reveal any significant difference in the nervous system adverse events between the cytisine and placebo groups (P=0.12).

3.2.2. Tabulated List of Adverse Reactions

Adverse reactions are listed according to MedDRA system organ class (SOC) and frequency category. Frequency categories are defined using the following convention: very common (>1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 2: Adverse Events Reported From the Recent [redacted] Core Data Sheet

System Organ Class	Very Common	Common	Uncommon	Rare	Very rare	Not known
Cardiac disorders						Tachycardia Palpitations
Vascular disorders						Slight increase in blood pressure
Nervous system disorders		Headache[a] Dizziness[a]	Insomnia[a] Drowsiness[a]			Increased irritability
Respiratory, thoracic and mediastinal disorders						Dyspnea
Gastrointestinal disorders		Upper abdominal pain[a] Nausea[a] Dry mouth[a] Dyspepsia[a]	Constipation[a] Diarrhea[a] Vomiting[a]			Changes in taste and appetite Abdominal pain
Musculoskeletal and connective tissue disorders						Myalgia
Metabolism and nutrition disorders						Hyperhidrosis Weight decreased
General disorders and administration site conditions						Chest pain

[a]The frequency was estimated based on data from 6 randomized clinical trials.

Thus, from marketing safety reporting for [redacted], 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.

4. RECENT STUDIES COMPLETED BY SPONSOR

4.1. Preliminary Results from Study ACH-CYT-02 on Safety and Pharmacodynamics of Cytisine Using the Commercial 25-Day Titration Schedule

ACH-CYT-02 titled "Repeat-Dose Pharmacokinetic and Pharmacodynamic Evaluation of Cytisine in Healthy Smokers" is an open-label, randomized, multi-dose study to evaluate the PK profile and PD effect of cytisine when administered at doses of 1.5 mg and 3.0 mg following the commercialized 25-day schedule as shown in Table 3.

Table 3: ACH-CYT-02: Dose Timing and Total Daily Dose

Treatment Day	Schedule	Total Daily Dose		Approximate Interval
		1.5 mg Dose	3.0 mg Dose	
1-3	6 times daily	9.0 mg	18.0 mg	2 hours
4-12	5 times daily	7.5 mg	15.0 mg	2.5 hours
13-16	4 times daily	6.0 mg	12.0 mg	3 hours
17-20	3 times daily	4.5 mg	9.0 mg	4-5 hours
21-24	2 times daily	3.0 mg	6.0 mg	6 hours
25	Once daily	1.5 mg	3.0 mg	-

A total of 36 subjects (24 subjects aged 18-65 years and 12 subjects aged >65 years) are planned for enrollment in the study. Twenty-four (24) subjects aged 18-65 have completed the study with safety and pharmacodynamics results presented in this section.

Subject demographics are summarized for the 24 subjects (18-65 years) in Table 4. Twelve (12) (8 male: 4 female) were randomized to 1.5 mg cytisine doses and 12 (7 male: 5 female) were randomized to 3 mg cytisine doses. All 12 subjects in the 1.5 mg and all 12 subjects in the 3 mg dose groups received cytisine over a 25 day period, with 98.4% and 99.1% of planned doses administered respectively.

Table 4: ACH-CYT-02: Subject Demographics (Aged 18-65)

Parameter	Statistic	18-65 Years		
		1.5 mg Cytisine (N=12)	3.0 mg Cytisine (N=12)	Overall (N=12)
Age (yrs)	n	12	12	24
	Mean	34.5	38.6	36.5
	SD	9.60	10.25	9.93
Height (m)	n	12	12	24
	Mean	1.723	1.701	1.712
	SD	0.0763	0.1083	0.0924
Weight (kg)	n	12	12	24
	Mean	84.87	75.53	80.20
	SD	15.115	14.704	15.343
Body Mass Index (kg/m^2)	n	12	12	24
	Mean	28.47	25.98	27.23
	SD	3.922	3.699	3.938
Race:				
- White	n (%)	12 (100.0)	11 (91.7)	23 (95.8)
- Other	n (%)	0 (0.0)	1 (8.3)	1 (4.2)
Gender:				
- Male	n (%)	8 (66.7)	7 (58.3)	15 (62.5)
- Female	n (%)	4 (33.3)	5 (41.7)	9 (37.5)

A total of 42 treatment-emergent adverse events (TEAEs) were reported by 16 (66.7%) subjects during the study; the severity was mild or moderate for all events, the majority of which were related to cytisine (Table 5).

When the number of subjects reporting TEAEs were compared, the same number of subjects reported at least 1 TEAE in each dose group (66.7%). However, there was a slight tendency for a greater number of TEAE's to be reported for 3.0 mg cytisine versus 1.5 mg cytisine (24 events vs 18 events, respectively). There was also a tendency for more subjects reporting moderate events with 3.0 mg cytisine when compared to 1.5 mg cytisine (41.7% vs 16.7% respectively) (Table 5).

There were no SAEs or suspected unexpected serious adverse reactions (SUSAR). All TEAEs resolved.

Table 5: ACH-CYT-02: Overall Summary of TEAEs by Severity and Relationship – 18 to 65 Years Old (Safety Set)

	18-65 Years		
	1.5 mg Cytisine (N=12)	**3.0 mg Cytisine (N=12)**	**Overall (N=24)**
Number of TEAEs	18	24	42
Mild	13	16	29
Moderate	5	8	13
Severe	0	0	0
Number(%) of Subjects Reporting at Least 1:			
TEAE	8 (66.7)	8 (66.7)	16 (66.7)
Serious TEAE	0 (0.0)	0 (0.0)	0 (0.0)
TEAE Leading to Withdrawal of Study Drug	0 (0.0)	0 (0.0)	0 (0.0)
Number(%) of Subjects with TEAE by Severity:			
Mild	6 (50.0)	3 (25.0)	9 (37.5)
Moderate	2 (16.7)	5 (41.7)	7 (29.2)
Severe	0 (0.0)	0 (0.0)	0 (0.0)
Number(%) of Subjects with TEAE by Relationship to Cytisine:			
Definite	0 (0.0)	0 (0.0)	0 (0.0)
Probable	0 (0.0)	2 (16.7)	2 (8.3)
Possible	4 (33.3)	5 (41.7)	9 (37.5)
Unlikely	2 (16.7)	0 (0.0)	2 (8.3)
Not Related	2 (16.7)	1 (8.3)	3 (12.5)
N/A	0 (0.0)	0 (0.0)	0 (0.0)

A subject with multiple AEs was counted only once at the maximum level of severity or the highest association to cytisine.
AE = adverse events, N/A = not applicable, TEAE = treatment emergent adverse event

Nervous system disorders were the most commonly occurring SOC events (Table 6), with the most commonly occurring TEAE being headache with an overall incidence of 24 headache events in 10 subjects (41.7%). There was a slightly higher number of subjects reporting moderate headaches in the 3.0 mg vs 1.5 mg dose group (33.3% vs 16.7%) (Table 6 footnote). Gastrointestinal disorders were the next most commonly occurring SOC events, with an overall incidence of 2 nausea events in 2 subjects (8%) and 2 constipation events in 2 subjects (8%).

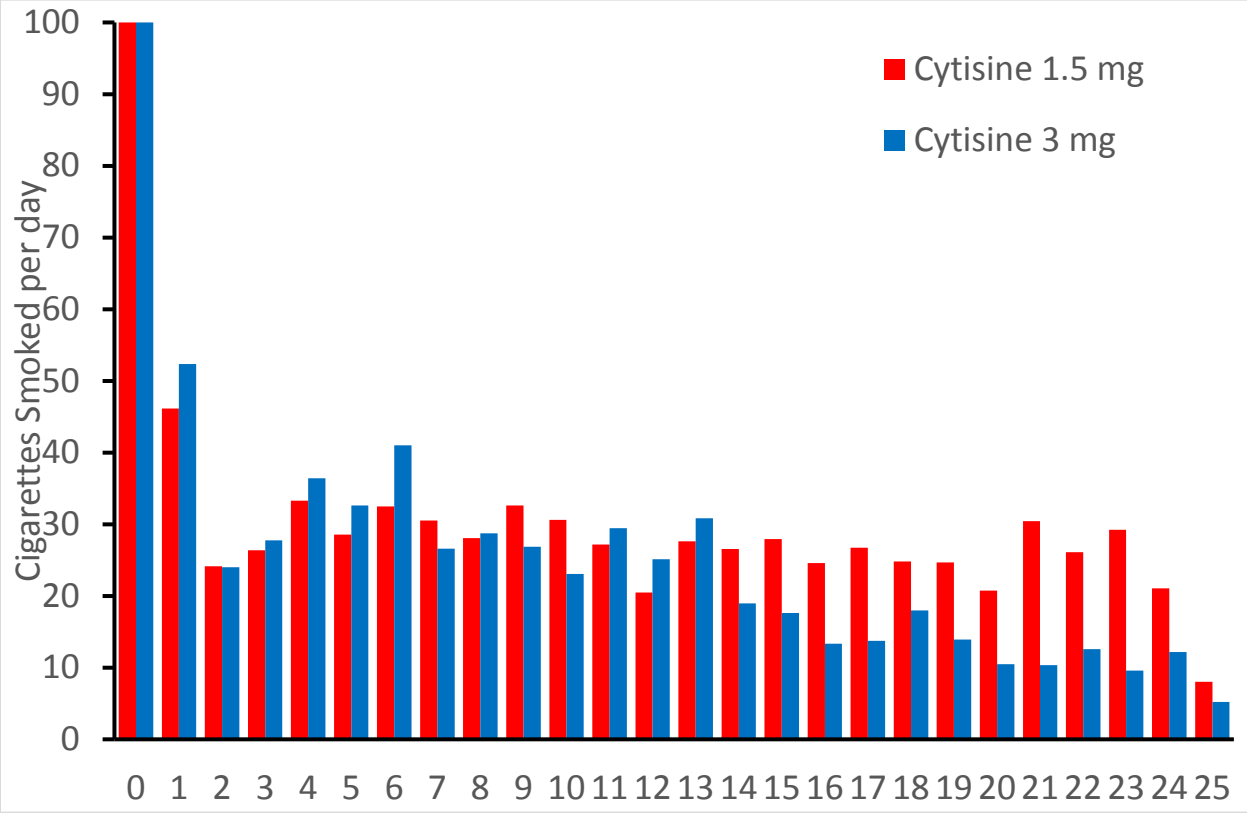
Table 6: ACH-CYT-02: Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – 18 to 65 Years Old (Safety Set)

	Number of Events/Number of Subjects (%)		
SYSTEM ORGAN CLASS:	**18-65 Years**		
Preferred Term	**1.5 mg Cytisine (N=12)**	**3.0 mg Cytisine (N=12)**	**Overall (N=24)**
GASTROINTESTINAL DISORDERS:	3 / 2 (16.7)	5 / 3 (25.0)	8 / 5 (20.8)
Constipation	1 / 1 (8.3)	1 / 1 (8.3)	2 / 2 (8.3)
Flatulence	0 / 0 (0.0)	1 / 1 (8.3)	1 / 1 (4.2)
Nausea	0 / 0 (0.0)	2 / 2 (16.7)	2 / 2 (8.3)
Tooth loss	2 / 1 (8.3)	0 / 0 (0.0)	2 / 1 (4.2)
Toothache	0 / 0 (0.0)	1 / 1 (8.3)[b]	1 / 1 (4.2)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS:	1 / 1 (8.3)	2 / 2 (16.7)	3 / 3 (12.5)
Chest discomfort	0 / 0 (0.0)	1 / 1 (8.3)	1 / 1 (4.2)
Medical device site reaction	1 / 1 (8.3)	0 / 0 (0.0)	1 / 1 (4.2)
Peripheral swelling	0 / 0 (0.0)	1 / 1 (8.3)	1 / 1 (4.2)
INFECTIONS AND INFESTATIONS:	1 / 1 (8.3)	0 / 0 (0.0)	1 / 1 (4.2)
Rhinitis	1 / 1 (8.3)	0 / 0 (0.0)	1 / 1 (4.2)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS:	2 / 2 (16.7)	0 / 0 (0.0)	2 / 2 (8.3)
Muscle strain	1 / 1 (8.3)	0 / 0 (0.0)	1 / 1 (4.2)
Procedural pain	1 / 1 (8.3)[a]	0 / 0 (0.0)	1 / 1 (4.2)
NERVOUS SYSTEM DISORDERS:	9 / 4 (33.3)	16 / 6 (50.0)	25 /10 (41.7)
Headache	9 / 4 (33.3)[a]	15 / 6 (50.0)[b]	24 /10 (41.7)
Vision blurred	0 / 0 (0.0)	1 / 1 (8.3)[b]	1 / 1 (4.2)
PSYCHIATRIC DISORDERS:	0 / 0 (0.0)	1 / 1 (8.3)	1 / 1 (4.2)
Abnormal dreams	0 / 0 (0.0)	1 / 1 (8.3)	1 / 1 (4.2)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS:	1 / 1 (8.3)	0 / 0 (0.0)	1 / 1 (4.2)
Oropharyngeal pain	1 / 1 (8.3)	0 / 0 (0.0)	1 / 1 (4.2)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS:	1 / 1 (8.3)	0 / 0 (0.0)	1 / 1 (4.2)
Rash pruritic	1 / 1 (8.3)	0 / 0 (0.0)	1 / 1 (4.2)

[a] Moderate events of headache (16.7% of subjects) and procedural pain (8.3% of subjects).
[b] Moderate events of headache (33.3% of subjects), toothache (8.3% of subjects) and blurred vision (8.3% of subjects).
A subject was counted only once per system organ class and preferred term.

Regarding preliminary pharmacodynamic results, although smokers in the study were not required to have a designated or predetermined quit date, subjects overall in the trial had a significant reduction in number of daily cigarettes smoked by the end of treatment (Figure 1). Mean baseline cigarette consumption in this 18 to 65 year age group was 16.25 (± 3.5) cigarettes per day with exhaled CO of 19.9 (± 7.3) ppm. By the end of treatment on Day 25, subjects in the 1.5 mg cytisine treatment group were smoking only 8% of the cigarettes compared to baseline cigarette smoking (i.e. a 92% reduction in daily cigarette smoking). Subjects in the 3.0 mg cytisine treatment group were smoking only 5% of the cigarettes compared to baseline cigarette smoking (i.e. a 95% reduction in daily cigarette smoking).

Figure 1: ACH-CYT-02: Percent of Cigarettes Smoked Daily During Study Treatment Compared to Baseline Number of Cigarettes Smoked (N=24)



4.2. Results from Study ACH-CYT-01 on the Effect of Food on Cytisine Bioavailability

ACH-CYT-01 titled "A Phase 1 Open Label, Randomized, Two-Way Crossover Study in Healthy Volunteers to Investigate the Effect of Food on the Bioavailability of Cytisine" evaluated 24 healthy volunteer subjects to investigate the effect of food on the bioavailability of cytisine. The primary objective was to compare the bioavailability of cytisine under fed and fasted conditions following administration of 3 mg cytisine (2×1.5 mg cytisine tablets).

Eligible subjects received a single-dose of 3 mg cytisine under fed and fasted conditions over 2 treatment periods. Pharmacokinetic (PK) samples (plasma and urine) were collected predose and up to 24 h post-dose (Day 2) during each period (17 plasma and 6 urine samples per period) for the measurement of plasma and urine cytisine concentrations.

The study enrolled 24 subjects (11 males: 13 females) with a median age of 34 years (range 19-53 years). Two of three subjects who experienced emesis during the course of the study (both under fed conditions) were excluded from statistical analysis because emesis occurred at or before 2 times the median T_{max}.

The fasted C_{max} at 29.8 ng/mL was higher than the fed C_{max} at 22.3 ng/mL. The T_{max} under fed conditions (2.75 h) was delayed when compared to the T_{max} under fasted conditions (0.75 h). However, both $AUC_{0-\infty}$ and AUC_{0-t} were comparable under fed (167.5 and 160.2 h.ng/mL) and fasted (172.6 and 165.9 h.ng/mL) conditions, respectively.

Table 7: ACH-CYT-01: Summary of Statistical Analysis of Cytisine Cmax and AUC

Parameter	Geometric LS Mean		Geometric LSMean Ratio (90% CI) fed / fasted
	3 mg Cytisine fed (N = 22)	3 mg Cytisine fasted (N = 22)	
C_{max} (ng/mL)	22.3	29.8	74.71 (66.39 - 84.08)
$AUC_{0-\infty}$ (h.ng/mL)	167.5	172.6	97.04 (94.20 - 99.98)
AUC_{0-t} (h.ng/mL)	160.2	165.9	96.52 (93.30 - 99.85)

Cytisine showed rapid absorption after oral administration with over 80% of cytisine recoverable in urine within the 24 hours post-dosing. Since cytisine using the commercial titration schedule will be administered frequently (i.e. 6 times daily, approximately every 2 hours) for the first 3 days and then administered in a decreasing frequency over the 25 day treatment course, food should not affect the overall treatment, primarily because the bioavailability measured as Area-Under-the Curve ($AUC_{0-\infty}$ and AUC_{0-t}) showed equivalence between fed and fasted states. In addition, any food restrictions for such a frequent administration would not be practical and is not necessary given the minor food effect on C_{max} and T_{max}.

Both studies are described in more detail within the Investigator's Brochure.

5. RATIONALE FOR THE STUDY

Previous studies dating decades ago and now more recent GCP studies have shown that cytisine can be effective in helping smokers to stop smoking. The recent trials have shown that cytisine was more effective than placebo as well as NRT for smoking cessation with an excellent safety profile that is consistent with the safety profile reported by [redacted] for millions of subjects who have used [redacted] (cytisine). It is not possible to effectively determine which reported adverse effects associated with cytisine treatment are an effect of the drug itself, due to nicotine withdrawal effects, or a combination of both. However, the risk/benefit for cytisine appears very acceptable. Tobacco smoking contributes to some 7 million premature deaths each year worldwide.[7] Using cytisine as a smoking cessation aid could offer far more benefit with minor risks of treatment-related adverse events when compared to the harms of continued smoking.

Achieve Life Sciences and the U.S. Food and Drug Administration (FDA) have discussed general development plans for cytisine as a new chemical entity for aiding smoking cessation in the United States (US), which ultimately led to filing an IND in 2017. The titration schedule for the commercial product comprises a gradual reduction schedule in the number of tablets per day from 6 tablets to 1 tablet over a 25 day period. However, no studies are available evaluating the dose exposure and administration schedule. This Phase 2b trial is being conducted at sites within the US to evaluate cytisine dose and administration schedules within a 25-day treatment period. Study arms will consist of the commercial 1.5 mg dose/titration schedule that is marketed in European countries, a higher dose of 3.0 mg using the marketed titration schedule, 1.5 mg and

3.0 mg doses using a three times a day (tid) schedule and respective placebo arms. The study will evaluate efficacy based on the overall reduction in the number of cigarettes smoked during the various study treatment dosing/schedules as well as compare compliance and safety profiles compared to the respective placebo arms (i.e. the marketed titration schedule or a simplified tid schedule).

Results from this study will also be used for defining Phase 3 sample size calculations when using the planned behavioral support and timing of study evaluations for the Phase 3 primary endpoint of abstinence from Week 5 to Week 8 post-randomization.

6. STUDY OBJECTIVES

6.1. Efficacy Objectives

1. Assess whether subjects randomized to cytisine, administered using the commercial titration schedule, have a greater overall reduction in cigarette smoking during the study treatment period (Day 1- 25) as compared to subjects randomized to the same placebo titration schedule.
2. Assess whether subjects randomized to cytisine, using a simplified tid schedule, have a greater overall reduction in cigarette smoking during the study treatment period (Day 1- 25) as compared to subjects randomized to the same placebo tid schedule.

6.2. Other Efficacy Objectives

Each of the following will include comparisons for 1.5 mg or 3.0 mg doses versus placebo when given as the commercial 25-day titration schedule and for the tid treatment schedule as well as comparisons between the commercial 25-day titration versus tid treatment schedules).

1. Assess the probability of abstinence from Week 5 to Week 8 post-randomization in subjects randomized to cytisine as compared to subjects randomized to placebo.
2. To compare cytisine and placebo arms on initial quit rates during study treatment, at Week 4 (End of Treatment) and on 7-day point prevalence abstinence at Week 5, Week 6, Week 7, and Week 8.
3. Among subjects abstinent at Week 4, compare time to failure to maintain abstinence through Week 8 between arms.
4. To explore potential relationships between subject-reported outcomes (e.g. anxiety, withdrawal symptoms, depression, tobacco craving, alcohol use) with the reduction in cigarette smoking during the study Treatment Period, as well as smoking cessation outcomes at Week 4 (End of Treatment) and from Week 5 to Week 8 post-randomization.
5. To explore a potential correlation for subject's nicotine metabolite ratio (NMR) with the reduction in cigarette smoking and smoking cessation outcomes.

6.3. Safety Objectives

1. To evaluate overall safety profiles of cytisine when administered at 1.5 mg or 3.0 mg, using the 25-day commercial titration or simplified tid schedules, compared to placebo.

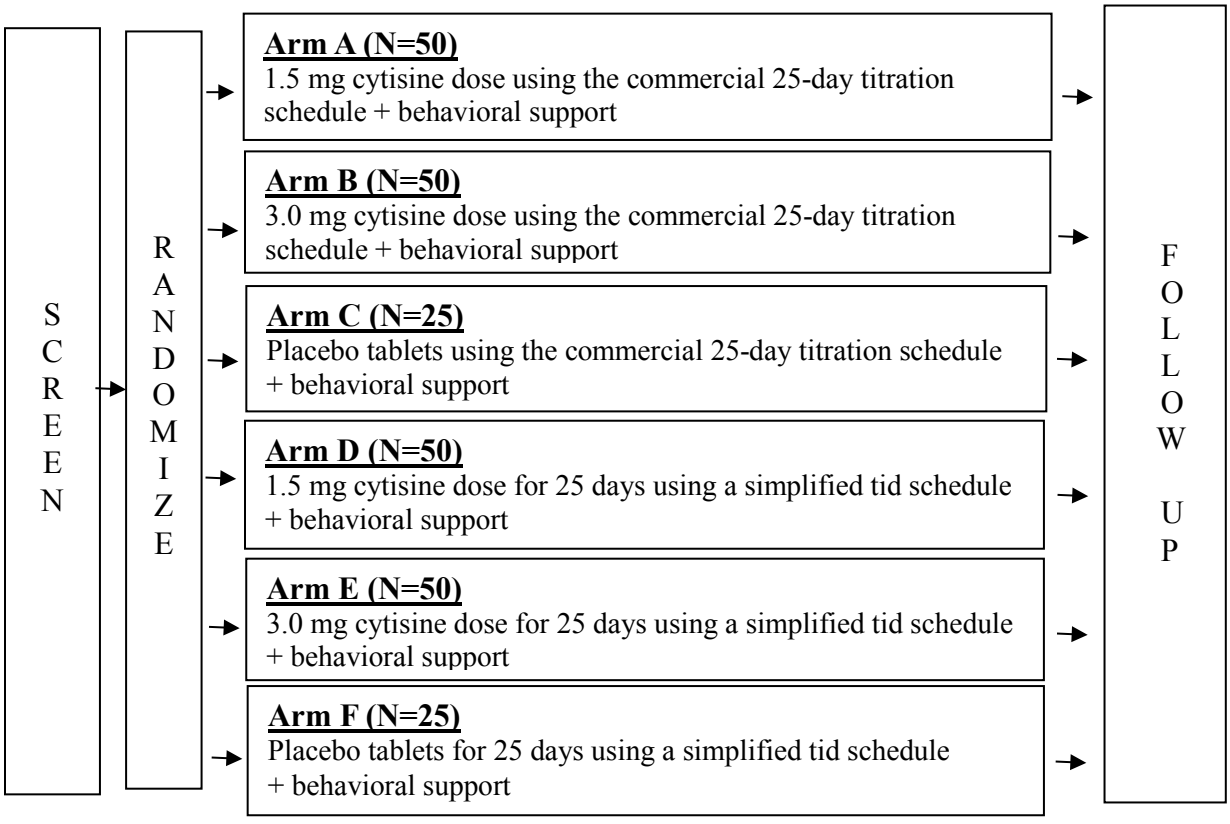
7. STUDY DESIGN OVERVIEW

7.1. Study Design

This will be a six-arm, multi-center, double-blind, randomized, placebo-controlled, Phase 2b study conducted in male or female adults ≥18 years of age, smoking 10+ cigarettes daily, and willing to set a quit date that is 5-7 days after being randomized on the study. The study will be double-blinded to dose but not to the administration schedule. Study treatment must start the day after randomization such that study treatment is initiated prior to the quit date.

Subjects must meet all inclusion and exclusion criteria. Subjects will be stratified at randomization by BMI class (18.5 to <25 kg/m^2; 25 to <30 kg/m^2; 30 to <35 kg/m^2). A total of approximately 250 subjects will be randomized 2:1 in a blinded manner to either Arm A or Arm B, vs Arm C (2:1 randomization) or Arm D or Arm E vs Arm F (2:1 randomization) as shown in Figure 2.

Figure 2: Study Design Overview



The study will be comprised of a pre-study screen, followed by twenty-five (25) days of study treatment, and post-treatment follow up visits to Week 8 post-randomization.

Each subject will receive twenty-five (25) days treatment either using the commercial titration schedule (i.e. decreasing daily tablets over the 25 days) or a simplified (tid) schedule during the Treatment Period. Smoking assessments will occur daily during the Treatment Period via self-reported cigarette count (number cigarettes smoked in the past 24 hours). Smoking abstinence

will be further assessed during the Follow-up Period starting after the Day 27±2 (Week 4) visit and documented through Week 5 (±3 days), Week 6 (±3 days), Week 7 (±3 days) and Week 8 (±3 days) post-randomization. Safety reporting will begin at randomization and continue through the Week 8 visit. The end of the study is defined as the last Week 8 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 Schema

In order to blind the study treatment dose, all subjects will take 2 tablets at every scheduled dosing. Subjects randomly assigned to Arm A or Arm D will take one 1.5 mg cytisine tablet and one placebo tablet at each dosing. Arm B or Arm E subjects will take two 1.5 mg cytisine tablets at each dosing. Arm C and Arm F subjects will receive two placebo tablets at each daily scheduled dosing to correspond to cytisine dosing. Scheduled dosing and total daily cytisine dosing are outlined in (Table 8 and Table 9).

Table 8: Scheduled Dosing and Total Daily Cytisine Dosing for Arm A and Arm B (Commercial Titration Schedule)

Treatment Days	Daily Scheduled Dosing	Total Daily Cytisine Dose			Approximate Interval
		Placebo	1.5 mg Dose (Arm A)	3.0 mg Dose (Arm B)	
1[a] -3	6 times daily	-	9.0 mg	18.0 mg	2 hours
4-12[b]	5 times daily	-	7.5 mg	15.0 mg	2.5 hours
13-16	4 times daily	-	6.0 mg	12.0 mg	3 hours
17-20	3 times daily	-	4.5 mg	9.0 mg	4-5 hours
21-24	2 times daily	-	3.0 mg	6.0 mg	6 hours
25	1 time only	-	1.5 mg	3.0 mg	-

[a]Initial treatment Day 1 for the 25-day Treatment Period must begin on the day after randomization.
[b]Quit Date to be on Day 5, 6 or 7.

Table 9: Scheduled Dosing and Total Daily Cytisine Dosing for Arm D and Arm E (Simplified TID Schedule)

Treatment Days	Daily Scheduled Dosing	Total Daily Cytisine Dose			Approximate Interval
		Placebo	1.5 mg Dose (Arm D)	3.0 mg Dose (Arm E)	
1[a,b] -20	3 times daily	-	4.5 mg	9.0 mg	4-5 hours
21[c] -24	2 times daily	-	3.0 mg	6.0 mg	6 hours
25	1 time only	-	1.5 mg	3.0 mg	-

[a]Initial treatment day 1 for the 25-day Treatment Period must begin on the day after randomization.
[b]Quit Date to be on Day 5, 6 or 7.
[c]The reduction in the frequency of administrations starting on Day 21 is intended to match the corresponding reduction in the commercial titration schedule.

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, safety and compliance outcomes. 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. The treatment manipulations of interest will be study drug and the administration schedule. This Phase 2b study evaluates the effectiveness of the 1.5 mg and the 3.0 mg dose versus placebo using the commercial titration versus a simplified tid schedule. As the commercial and tid schedules will have different tablet administrations, a corresponding placebo layout is incorporated so that placebo-bias, compliance and adverse event reporting can be accurately evaluated. The use of placebo groups is therefore considered justified.

7.3.2. Efficacy Objectives

Cytisine was developed and is being marketed using a 25-day titration treatment schedule for smoking cessation using a 1.5 mg dose. The primary efficacy objective of this Phase 2b trial is to assess the overall reduction in daily cigarette smoking during the study treatment dosing/schedules compared to the respective placebo arms (i.e. the marketed titration schedule or a simplified tid schedule). Reduction in daily cigarette smoking was chosen as the primary efficacy outcome in order to better define the effects of the different dosing and schedules during the study treatment when such factors might have different daily effects on smoking behavior. A more simplified tid schedule was selected based on the pharmacokinetic profile for cytisine. In a recent pharmacokinetic trial (ACH-CYT-01), the geometric mean elimination half-life of cytisine (in the presence of food following administration of a 3 mg dose) was 4.63 h, but with a coefficient of variation of 24.3%. Given this variability, a tid administration schedule was chosen in order to ensure that subjects with a half-life at the lower end of the expected range will have adequate plasma concentrations of cytisine throughout the day.

Other efficacy results from this study will be used for defining Phase 3 sample size calculations when using the planned behavioral support and timing of study evaluations for the Phase 3 primary endpoint of abstinence from Week 5 to Week 8 post-randomization.

7.3.3. Blinding

Although subjects and site staff will be unblinded to the treatment schedule (commercial titration vs. tid) due to packaging and dose timing requirements, this remains a double-blinded study with regard to cytisine versus placebo dosing and the design therefore protects against subjective bias in reporting both efficacy and safety. Blinding will occur by coding the individual study drug packaging 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 unblind study treatment for individual subjects. However, during the study, emergency unblinding for adverse events might need to be performed. This option may be used only if subject well-being requires knowledge of treatment assignment. The investigator must first contact the Achieve Medical Monitor, or representative, who will coordinate access to the treatment assignment code via the independent vendor. All unblinding must be documented by the site and the Sponsor.

Examples of 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.

7.4. Number of Subjects

A total of 250 subjects will be randomized, with approximately 50 subjects in each of the 4 treatment arms and 25 subjects in each of the two placebo arms. The maximum number of subjects that a single site is allowed to enroll, without consent of the Sponsor, is 50 (approximately 20% of the study total).

7.5. Randomization and Stratification

Sites will utilize an Interactive Response Technology (IRT) system for treatment arm assignment at randomization (Day 0). The IRT will stratify at randomization by BMI class (18.5 to <25 kg/m^2; 25 to <30 kg/m^2; 30 to <35 kg/m^2). Detailed instructions are provided in the Study Reference Manual.

7.6. Number of Clinical Sites

This will be a multicenter clinical trial. Approximately 7-9 clinical sites in the US will participate.

7.7. Estimated Duration/Completion of Study

Duration of this study is estimated to be approximately 2 months (8 weeks) for each subject (from randomization to the Week 8 follow-up visit). Completion of the study is estimated at 6 months with ~1 months accrual ramp-up, an additional 3 months to complete accrual and 2 months from the last randomized subject to complete study follow-up evaluations.

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, and risks. 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. These eligibility criteria are the same criteria planned for the subsequent Phase 3 trials. 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 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 that is 5-7 days after 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, comply with dosing schedule, and 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. Known hypersensitivity to cytisine or any of the excipients.
2. Positive urinary drugs of abuse screen, determined within 28 days before the first dose of cytisine.
3. Clinically significant abnormal serum chemistry or hematology values within 28 days of randomization (i.e. requiring treatment).
4. Clinically significant abnormalities in 12-lead ECG determined after minimum of 5 minutes in supine position within 28 days of randomization (i.e. requiring treatment or further assessment).

5. BMI classification for being underweight (<18.5 kg/m^2) or having ≥Class 2 obesity (≥35 kg/m^2).
6. Recent history (within 3 months) of acute myocardial infarction, unstable angina, stroke, cerebrovascular incident or hospitalization for congestive heart failure.
7. Current uncontrolled hypertension (blood pressure ≥160/100 mmHg).
8. Documented diagnosis of schizophrenia or bipolar psychiatric illness; currently psychotic; having suicidal ideation (SBQ-R score ≥7); or current symptoms of moderate to severe depression (HAD score ≥11).
9. Renal impairment defined as a creatinine clearance (CrCl) <60 mL/min (estimated with the Cockroft-Gault equation) or hepatic impairment defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.0 x the upper limit of normal (ULN).
10. Women who are pregnant or breast-feeding.
11. Male or Female subjects of child bearing potential who do not agree to use acceptable methods of birth control during the study treatment period.
12. Participation in a clinical study with an investigational drug within 4 weeks of randomization.
13. Treatment with other smoking cessation medications (bupropion, varenicline, nortriptyline, or any nicotine replacement therapy [NRT]) within 4 weeks of randomization or planned use of these other smoking cessation medications during the study.
14. Use within 2 weeks of randomization or planned use during the study of non-cigarette nicotine products (e-cigarettes, pipe tobacco, cigars, snuff, chewing tobacco, hookah) or marijuana vaping or smoking.
15. 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. Discontinuation of Study Drug or Study Withdrawal Prior to Week 8 Assessment

8.3.1. Discontinuation of Study Drug

Subjects can be discontinued from study drug for the reasons below. However, subjects who discontinue study drug will continue all remaining study evaluations as outlined in the protocol to obtain safety and efficacy outcomes, as if they were still taking study drug.

1. If a subject experiences a serious or intolerable adverse event that prevents them from continuing study drug.
2. At the Investigator's request (e.g. if the Investigator considers that the subject's health might be compromised by continuing study drug).

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

8.3.2. Withdrawal from Study

All subjects will be informed of their right to withdraw from the study at any time and for any reason. Subjects who withdraw from the study (i.e. withdraw from further study evaluations) will be asked to complete the Day 27/EOT assessments, if still receiving study drug, and willingness to attend the Week 8 assessment visit. The date and reason for study withdrawal will be recorded on the study completion form of the CRF.

If a subject is discontinued and there is an 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**.

9. INVESTIGATIONAL MEDICINAL PRODUCT (IMP)INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

9.1. Cytisine 1.5 mg Film-Coated Tablets

Cytisine (cytisinicline) will be supplied by the Sponsor. The cytisine drug product is formulated as a compressed film-coated tablet containing 1.5 mg cytisine in a single tablet. Each tablet is composed of cytisine active substance (as the base) supplied by [redacted]

9.2. Placebo Tablets

Placebo tablets will contain the same excipients as in the cytisine tablet formulation plus an additional [redacted] to match final weight of the cytisine tablet. Placebo tablets will be identical in size, shape, color, and packaging to preserve the double-blind study design.

9.3. Receipt and Storage

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 folded blister packs. The folded blister packaging will be designed for specific days of treatment and for the two different dosing schedules. Thus, the commercial titration schedule will have different blister packaging compared to the tid schedule. At specific clinic visits, a series of blister packets will be given to subjects for dosing over a few days and are to be returned at subsequent clinic visits with the last blister packets returned upon completion of treatment.

Tablets should be swallowed whole with water.

9.5. Return/Destruction

All unused study drug should be destroyed by the sites unless a prearranged return to depot or Sponsor is necessary.

9.6. Method of Assigning Subjects to Arms

Subjects will be allocated to arms according to a predetermined randomization schedule and randomly assigned (2:1) to active vs. placebo once all screening procedures are completed and verified. Randomization will be stratified by BMI class (18.5 to <25 kg/m^2; 25 to <30 kg/m^2; 30 to <35 kg/m^2).

Subjects will be assigned a unique study identification (I.D.) number upon signing the informed consent form, prior to conducting any protocol-specified procedures by the site. The study I.D. number will consist of 2 parts. The first part identifies the site (3 digits) and the second part identifies the subject (3 digits). Subject numbers will be assigned sequentially from 101 (i.e. 101, 102, etc.). Study drug assignment will occur via IRT. The IRT system will identify what study drug packet should be used via a randomly-assigned number printed on the packet so that treatment assignment blind can be maintained. The site will label the assigned packet with the subject's study I.D. number and include both in the applicable source documents (i.e. drug accountability log).

For treatment compliance, study drug will be packaged into folded packets covering treatment segments that will align with clinic visits. Treatment segment packets will be distributed, returned and reviewed at each scheduled site visit for ongoing accountability (see Section 9.8).

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 2 tablets for each dose. According to randomization, subjects will receive study drug as follows:

Specified Tablets	**Arm A or Arm D (1.5 mg Dose)**	**Arm B or Arm E (3.0 mg Dose)**	**Arm C or Arm F (Placebo)**
Cytisine 1.5 mg tablets	1 tablet	2 tablets	-
Placebo tablets	1 tablet	-	2 tablets

For 25-day titration schedule, study drug will be administered according to the following treatment day schedule:

Treatment Day	Daily Administration
1[a]-3	6 times daily
4-12	5 times daily
13-16	4 times daily
17-20	3 times daily
21-24	2 times daily
25	1 time only

[a]Initial treatment day 1 for the 25-day Treatment Period must start on the day after randomization.

For the tid schedule, study drug will be administered according to the following treatment schedule:

Treatment Day	Daily Administration
1[a]-20	3 times daily
21-24	2 times daily
25	1 time only

[a]Initial treatment day 1 for the 25-day 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.

To facilitate accurate compliance and accountability, study drug for each subject will be configured into 9 medication packs, regardless of the 25-day treatment scheduled assignment (commercial titration schedule or simplified tid schedule). Each of the 9 packs will contain the correct number of tablets for the days of treatment as follows:

Pack Number	Days of Treatment
1	1-2
2	3-4
3	5-7
4	8-10
5	11-13
6	14-15
7	16-17
8	18-21
9	22-25

Clinic staff will distribute and collect 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 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 and final accountability monitoring, all the investigational 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. This must include any use of non-cigarette nicotine products.

11. TREATMENT COMPLIANCE

Treatment compliance will be monitored during the 25 day Treatment Period via review of dosing timing and drug accountability. Subjects will have a daily 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 diary, recording the number of tablets taken and the number of missed tablets. In addition, a 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 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 2, 3, 6, 12, 16, 20 (during treatment), Day 27 (End-of-Treatment [EOT] visit), and again at the Week 5, 6, 7 and 8 visits.

12.1. Procedure Schedule

Table 10 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. Day 1 will be defined as the first day of treatment. Subjects must initiate study treatment the day after randomization, such that study treatment is initiated prior to the quit date, which must be planned within 5-7 days after start of treatment. Both the planned treatment start date and the agreed-upon quit date must be documented at the time of randomization within the source documents and CRF.

Table 10: Schedule of Study Procedures

Study Assessment	Screening Period (Day-28 to Rand)		Randomization	Treatment Period Day 1 through Day 25								Follow-up Assessment Period[1] (± 3 Days)			
Visit	SV 1	SV 2[2]	Day 0	Day 1[3]	Day 2	Day 3	Day 6 (±1 Day)	Day 12 (±1 Day)	Day 16 (±1 Day)	Day 20 (±1 Day)	Day 27 EOT (±2 Days)	Week 5	Week 6	Week 7	Week 8
Informed Consent	•														
Inclusion/Exclusion	•														
Demographics	•														
Medical and Psychiatric History	•														
SBQ-R questionnaire	•										•				•
Physical Exam	•[4]														
Smoking History	•[5]	•[5]													
Urine Pregnancy Test for all Females[6]	•														
Drugs of Abuse Screen[6,7]	•														
Vital Signs including Weight	•[8]		•		•	•	•	•	•	•	•	•	•	•	•
Hematology and Chemistry[6]	•				•	•	•	•	•	•	•				•
12-lead ECG	•							•			•				
Concomitant Medications	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Quit Date Set and Treatment Day 1 Scheduled		•													
Review Diary Completion Instructions	•[5]		•												
Review Diary for Number of Cigarettes Smoked		•[5]			•	•	•	•	•	•	•				
Adverse Event Reporting	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Study Drug Distribution, Accountability and Collection			•		•	•	•	•	•	•	•				

Study Assessment	**Screening Period (Day-28 to Rand)**		**Randomization**	**Treatment Period Day 1 through Day 25**								**Follow-up Assessment Period[1] (± 3 Days)**			
Visit	SV 1	SV 2[2]	Day 0	Day 1[3]	Day 2	Day 3	Day 6 (±1 Day)	Day 12 (±1 Day)	Day 16 (±1 Day)	Day 20 (±1 Day)	Day 27 EOT (±2 Days)	Week 5	Week 6	Week 7	Week 8
Behavioral Support		•[9]	•		•	•	•	•	•	•	•	•	•	•	•
Fagerström Test of Nicotine Dependence			•												
Self-Efficacy Questionnaire			•												
Craving Questionnaire			•		•	•	•	•	•	•	•	•	•	•	•
HADS Questionnaire	•							•			•				•
Alcohol Use Questionnaire			•												•
Smoking Cessation Status												•	•	•	•
Expired CO	•		•								•	•	•	•	•
Plasma Cotinine[6]	•[10]										•				•

[1]Once study drug dosing has been completed and the End-of-Treatment visit has occurred at Week 4 (Day 25-27 post-randomization), smoking cessation status will be performed weekly during the Follow-up Assessment Period at Week 5 through to Week 8 post-randomization. Smoking cessation status at each visit from Week 5 through Week 8 will be defined by self-report of no cigarette smoking and CO levels. Cigarette smoking for the past 7 days as well as from the last clinic visit will be recorded.

[2]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.

[3]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 and confirm the Day 2 clinic appointment.

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

[5]Number of cigarettes smoked daily will be recorded in a 7-day 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.

[6]Urine pregnancy test kits supplied to site by central laboratory. All other testing performed by a central laboratory.

[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 calculations (required for stratification).

[9]Setting the quit date and plan is to be considered the first behavioral support counseling session.

[10] Plasma sample will be collected at SV1 and stored on all subjects. Only samples from randomized subjects will be tested for 3-OH cotinine and cotinine levels to determine the nicotine metabolite ratio (NMR) at baseline.

12.2. Detailed Description of Study Visits

12.2.1. Screening Phase

Screening assessments used to evaluate inclusion and exclusion criteria will occur over a 28 day period prior to randomization and must include a minimum of 2 clinic visits.

Screening (Day 28 to Randomization Day 1)

Study procedures include:

Screening Visit #1

1. Written informed consent obtained.
2. Demographic data.
3. Medical and psychiatric history. Suicidal ideation is to be determined and documented via administration and assessment of the SBQ-R questionnaire (Appendix 1). Depression is to be assessed via administration of the HADS questionnaire (Appendix 5).
4. Physical examination.
5. Document any existing adverse events.
6. Concomitant medications.
7. Review of smoking history, to include year started smoking, information about previous quit attempts, and average number of cigarettes smoked per day over the past 30 days. Provide 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).
8. Expired CO.
9. Vital signs, including weight and height.
10. Urine pregnancy for all female subjects.
11. Drugs of abuse screen.
12. Hematology and serum chemistry testing. An additional plasma sample will be stored for all subjects. Only samples from randomized subjects will be tested for 3-OH cotinine and cotinine levels to determine the nicotine metabolite ratio (NMR).
13. 12-lead ECG.
14. Review all inclusion and exclusion criteria and if satisfied, schedule Screening Visit #2.

Screening Visit #2

1. During the Screening Visit #2 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 #2 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 occur 5-7 days prior to the agreed upon quit date so that the actual quit date falls on Treatment Day 5, 6 or 7. All other screening evaluations must be completed within 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 event(s).
3. Vital signs, including weight.
4. Expired CO.

Upon completion of all procedures and final confirmation of eligibility, 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. Short Form of the Tobacco Craving questionnaire (Appendix 4).
   d. HADS questionnaire (Appendix 5).
   e. Alcohol Use questionnaire (Appendix 6).
2. Provide subject with behavioral support information that includes counseling (Appendix 7). NOTE: it should be stressed to subjects that even if they are smoking less during the study treatment, they must maintain their dosing schedule throughout the Treatment Period.
3. Randomize according to a pre-determined, blinded, randomization schedule (see Section 7.5).
4. Provide study treatment medication packs #1 and #2, which contain tablets required for Days 1-2 and Days 3-4. Enter actual treatment dates on the packs next to the dosing day designation in the space provided. Review the layout and dosing instructions printed on the medication packs which cover dosing requirements, timing of study drug administration and how to remove individual tablets from the blister pack. Instruct subject that any/all packs must be brought back to the clinic and should never be thrown away.
5. Develop an appointment schedule that includes dates and times for each required clinic visit during the trial, providing copy to the subject.
6. Provide diary instructions.

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.
8. Remind subject of appointment time for Day 2 clinic visit.

12.2.3. Treatment Period

Treatment Day 1

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

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

1. Verify subject is taking treatment according to their assigned dose schedule, review compliance requirements and answer any questions.
2. Verify subject is recording number of cigarettes smoked in past 24 hours in the diary (to be recorded at the same time each day).
3. Ask subject if any adverse events have occurred and/or any changes in concomitant medications.
4. Remind subject of their appointment time for the following day and that they must bring with them all study medication packs.

Treatment Day 2

1. Subject to complete the short form of the Tobacco Craving questionnaire (Appendix 4).
2. Review diary to verify dosing up to time of visit. Review number of cigarettes smoked in past 24 hours from subject's diary (e.g. Day 1).
3. Assess for AEs at time of visit and record.
4. Vital signs, including weight.
5. Review medication packs for compliance.
6. Provide subject with behavioral support information that includes counseling (Appendix 7). NOTE: it should be stressed to subjects that even if they are smoking less, they must maintain their dosing schedule throughout the Treatment Period.
7. Blood for hematology and serum chemistry testing.
8. Remind subject of their appointment time for the following day and that they must bring with them all study medication packs.

Treatment Day 3

1. Subject to complete the short form of the Tobacco Craving questionnaire (Appendix 4).
2. Review diary to verify dosing up to time of visit. Review number of cigarettes smoked in past 24 hours from subject's diary (e.g. Day 2).
3. Assess for AEs and any changes to concomitant medications at the clinic visit.
4. Vital signs, including weight.

5. Review medication packs #1 and #2 for compliance and collect pack #1 (which should be empty, as it contained medication for days 1-2). Distribute pack #3 (for Days 5-7).
6. Provide subject with behavioral support information that includes counseling (Appendix 7). NOTE: it should be stressed to subjects that even if they are smoking less during the study treatment, they must maintain their dosing schedule throughout the Treatment Period.
7. Blood for hematology and serum chemistry testing.
8. Remind subject of their Day 6 appointment date and time and that they must bring with them all study medication packs.

Treatment Day 6 (±1 day)

1. Reconfirm quit date on planned Treatment Day 5, 6, or 7
2. Subject to complete the short form of the Tobacco Craving questionnaire (Appendix 4).
3. Review diary to verify dosing up to time of visit. Review number of cigarettes smoked in past 24 hours from subject's diary for each daily input (e.g. Days 3, 4 and 5).
4. Assess for AEs and any changes to concomitant medications at the clinic visit.
5. Vital signs, including weight.
6. Review medication packs #2 and #3 for compliance and collect pack #2 (which should be empty, as it contained medication for Days 3-4). Distribute packs #4 and #5 (for Days 8-10 and 11-13).
7. Provide subject with behavioral support information that includes counseling (Appendix 7). NOTE: it should again be stressed to subjects that even if they are smoking less, they must maintain their dosing schedule throughout the Treatment Period.
8. Blood for hematology and serum chemistry testing.
9. Remind subject of their Day 12 appointment date and time and that they must bring with them all study medication packs.

Treatment Day 12 (±1 day)

1. Subject to complete the short form of the Tobacco Craving questionnaire (Appendix 4) and the HADS questionnaire (Appendix 5).
2. Review diary to verify dosing up to time of visit. Review number of cigarettes smoked in past 24 hours from subject's diary for each daily input (e.g. Days 6, 7, 8, 9, 10, and 11).
3. Assess for AEs and any changes to concomitant medications at the clinic visit.
4. Vital signs, including weight.
5. 12-lead ECG.
6. Review medication packs #3, #4 and #5 for compliance and collect packs #3 and #4 (which should be empty, as they contained medication for Days 5-7 and 8-10). Distribute packs #6 and #7 (for days 14-15 and 16-17).

7. Provide subject with behavioral support information that includes counseling (Appendix 7). NOTE: it should be stressed to subjects that even if they are smoking less, they must maintain their dosing schedule throughout the Treatment Period.
8. Blood for hematology and serum chemistry testing.
9. Remind subject of their Day 16 appointment date and time and that they must bring with them all study medication packs.

Treatment Day 16 (±1 day)

1. Subject to complete the short form of the Tobacco Craving questionnaire (Appendix 4).
2. Review diary to verify dosing up to time of visit. Review number of cigarettes smoked in past 24 hours from subject's diary for each daily input (e.g. Days 12, 13, 14, and 15).
3. Assess for AEs and any changes to concomitant medications at the clinic visit.
4. Vital signs, including weight.
5. Review medication packs #5, #6 and #7 for compliance and collect packs #5 and #6 (which should be empty, as they contained medication for Days 11-13 and 14-15). Distribute pack #8 (for days 18-21).
6. Provide subject with behavioral support information that includes counseling (Appendix 7). NOTE: it should be stressed to subjects that even if they are smoking less, they must maintain their dosing schedule throughout the Treatment Period.
7. Blood for hematology and serum chemistry testing.
8. Remind subject of their Day 20 appointment date and time and that they must bring with them all study medication packs.

Treatment Day 20 (±1 day)

1. Subject to complete the short form of the Tobacco Craving questionnaire (Appendix 4).
2. Review diary to verify dosing up to time of visit. Review number of cigarettes smoked in past 24 hours from subject's diary for each daily input (e.g. Days 16, 17, 18, and 19).
3. Assess for AEs and any changes to concomitant medications at the clinic visit.
4. Vital signs, including weight.
5. Review medication packs #7 and #8 for compliance and collect pack #7 (which should be empty, as it contained medication for Days 16-17). Distribute final pack #9 (for Days 22-25).
6. Provide subject with behavioral support information that includes counseling (Appendix 7). NOTE: it should be stressed to subjects that even if they are smoking less, they must maintain their dosing schedule throughout the Treatment Period.
7. Blood for hematology and serum chemistry testing.
8. Remind subject of their End of Treatment (Day 27 ±2 days) appointment date and time and that they must bring with them all study medication packs.

Day 27 End of Treatment Visit (±2 day)

1. Subject to complete the SBQ-R questionnaire (Appendix 1), the short form of the Tobacco Craving questionnaire (Appendix 4) and the HADS questionnaire (Appendix 5).
2. Collect the completed diary from subject. Review diary to verify dosing up to time of visit. Review number of cigarettes smoked in past 24 hours from subject's diary for each daily input (e.g. Days 20, 21, 22, 23, 24, and 25).
3. Assess for AEs and any changes to concomitant medications at the clinic visit.
4. Vital signs, including weight.
5. 12-lead ECG.
6. Review medication packs for compliance and collect packs #7, #8 and #9 (which should be empty, as it contained medication for Days 16-17, 18-21 and 22-25). All used packs must be collected and available for final accountability by the study monitor.
7. Provide subject with behavioral support information that includes counseling (Appendix 7).
8. Blood for hematology, serum chemistry and cotinine testing.
9. Expired CO.
10. Remind subject that although their treatment is now complete, it is critical to provide the required weekly visits during the follow-up assessment period (Weeks 5, 6, 7 and 8). Schedule date and time for their Week 5 visit.

12.2.4. Follow-up Assessment Period

All subjects are required to complete 4 clinic visits during the Follow-up Period to assess smoking cessation status, starting at Week 5 and continuing weekly through Week 8 (i.e. Weeks 5, 6, 7 and 8).

Week 5 (±3 days)

1. Subject to complete the short form of the Tobacco Craving questionnaire (Appendix 4).
2. Vital signs, including body weight.
3. Record the following:
    a. Has the subject smoked any cigarettes since the last clinic (Day 27/Week 4) visit?
    b. Has the subject smoked any cigarettes over the past 7 days?
    c. If subject has smoked, subject should report the average daily number of cigarettes smoked.
4. Expired CO.
5. Record any adverse events and concomitant medication updates.
6. Provide subject with behavioral support information and counseling (Appendix 7).
7. Schedule Week 6 (±3 days) assessment visit.

Week 6 (±3 days)

1. Subject to complete the short form of the Tobacco Craving questionnaire (Appendix 4).
2. Vital signs, including body weight.
3. Record the following:
   a. Has the subject smoked any cigarettes since the last clinic (Week 5) visit?
   b. Has the subject smoked any cigarettes over the past 7 days?
   c. If subject has smoked, subject should report the average daily number of cigarettes smoked.
4. Expired CO.
5. Record any adverse events and concomitant medication updates.
6. Provide subject with behavioral support information and counseling (Appendix 7).
7. Schedule Week 7 (±3 days) assessment visit.

Week 7 (±3 days)

1. Subject to complete the short form of the Tobacco Craving questionnaire (Appendix 4).
2. Vital signs, including body weight.
3. Record the following:
   a. Has the subject smoked any cigarettes since the last clinic (Week 6) visit?
   b. Has the subject smoked any cigarettes over the past 7 days?
   c. If subject has smoked, subject should report the average daily number of cigarettes smoked.
4. Expired CO.
5. Record any adverse events and concomitant medication updates.
6. Provide subject with behavioral support information and counseling (Appendix 7).
7. Schedule Week 8 (±3 days) assessment visit.

Week 8 (±3 days)

1. Subject to complete the following questionnaires:
   a. SBQ-R questionnaire (Appendix 1) and assessment for any changes in suicidal ideation.
   b. Short form of the Tobacco Craving questionnaire (Appendix 4).
   c. HADS questionnaire (Appendix 5).
   d. Alcohol Use questionnaire (Appendix 6).
2. Vital signs, including body weight.
3. Blood for hematology, serum chemistry and cotinine testing.
4. Record the following:
   a. Has the subject smoked any cigarettes since the last clinic (Week 7) visit?
   b. Has the subject smoked any cigarettes over the past 7 days?

c. If subject has smoked, subject should report the average daily number of cigarettes smoked.

5. Expired CO.
6. Record any adverse events and concomitant medication updates.
7. Provide subject with behavioral support information and counseling (Appendix 7).
8. Discharge subject from study.

12.2.5. Subject Diary

A 7-day diary will be provided and 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 diary must be maintained by each subject to record daily cigarettes smoked 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 during the 25-day dosing schedule. Staff must review entries with the subject at each clinic visit and document on CRF. Data from the diary will be reviewed at all clinic visits and collected as a source document at the Day 27 End-of-Treatment visit.

12.2.6. Behavioral Support

Each participating site must have at least two or more staff members experienced and qualified to provide smoking cessation counseling. For this study, site counselors are required to have either a master's level or higher degree in a counseling profession (e.g. health educator, chemical dependence counselor) or completed a tobacco treatment training course of at least 4 hours. Evidence of the above qualification(s) must be provided during the site qualification process. The site counselors will be provided additional study-specific training prior to or during site initiation.

All subjects will receive up to 12 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 8 visit as outlined in (Table 10). Site counselor(s) are to encourage subjects to continue study drug as scheduled even if they lapse and have a cigarette after their quit date. It is important during this "grace" period for the subjects to keep trying to quit as planned.

Each behavioral session will be subject-driven and must include direct engagement with the subject about their efforts to quit smoking. Each session should last up to 10 minutes (Refer to Appendix 7).

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.[16]

This Phase 2b study will evaluate the timing and daily reduction in cigarette smoking during the various study treatment dosing/schedules compared to the respective placebo arms (i.e. the commercial titration schedule or a simplified tid schedule) as the primary efficacy analyses. The

four primary comparisons will be based on analysis of variance with main treatment effects, BMI class (3 level stratification as previously specified), and with covariate of baseline cigarettes smoked. These analyses for reduction in cigarette smoking based on cytisine dose (1.5 mg and 3.0 mg relative to placebo) and administration schedule (titration vs tid) for differences in timing or level of reduction in cigarette smoking during the treatment period.

Secondary efficacy analyses for smoking cessation (4 weeks abstinence documented at Week 5, 6, 7 and 8 post randomization) will also be determined and include the following standard criteria which are also planned for the Phase 3 studies:

1. Self-report of smoking abstinence since the last clinic visit (continued abstinence) and over the prior 7 days at each clinic assessment (7-day point prevalence abstinence);
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 8 or lost to follow up will be classified as failed to quit; and
5. Continually blinded to treatment allocation during collection of follow-up data.

14. SAFETY ASSESSMENTS

All subjects will be monitored for adverse events starting at screening (pre-existing), periodically during the Treatment Period (1 assessment via telephone on Day 1 and clinic evaluations on Days 2, 3, 6, 12, 16, and 20), at the End-of-Treatment (Day 27) visit and then weekly to the Week 8 visit (see Table 10). Laboratory (hematology and chemistry) evaluations will be performed at the Day 2, 3, 6, 12, 16, 20, and 27 visit and again at Week 8 using a central laboratory.

Safety will be assessed by consideration of all adverse events reported by or elicited from the subject, vital signs, 12-lead ECG, and abnormalities detected on 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, any safety procedures can be performed at any time 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 8 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, i.e. 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 (e.g., 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 hospitalization.
- Results in persistent or significant disability or incapacity.
- Results in a congenital abnormality or birth defect.
- Is an important medical event that requires medical intervention to prevent any of the above outcomes.

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

- Serious.
- Unexpected (i.e., is not consistent with the applicable product information e.g. 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 that 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 that 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 8 visit must be followed until final resolution or until it is medically justifiable to stop further follow up (e.g. 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 11. Only 1 severity grade will be used for each AE (e.g. mild - moderate is not acceptable).

Table 11: 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 12.

Table 12: 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 8) must be recorded and reported immediately. All SAEs including those that are ongoing at the end of the Week 8 visit will be followed until each event resolves or is assessed as chronic.

In order to satisfy regulatory requirements, any SAE, 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 or fax.

[redacted]

[redacted]

A [redacted] Pharmacovigilance Associate will notify the Sponsor and Sponsor's Responsible Physician of the SAE via email within 24 h of receipt of the initial SAE report.

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 to Week 8 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.

14.3. Laboratory

14.3.1. Routine Laboratory Assessments

Routine laboratory safety samples will be analysed at screening and at each clinic visit as identified in (Table 10) 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 page. The reference ranges for laboratory parameters will also be entered in the database and filed in 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.

14.3.2. Expired Air Carbon Monoxide (CO) and Cotinine

Expired CO will be obtained using a calibrated instrument (e.g. the Bedfont Micro+Smokerlyzer®) provided and maintained by the clinical site. Each clinical site must have documentation of instrument used and current calibration. CO values are to be reported in parts per million (ppm). Cotinine will be determined by central laboratory.

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. 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 Monitor

Safety monitoring will be performed by an independent Data Safety Monitor (DSM) who will be appointed for this study. The DSM will be an M.D. experienced in the treatment of adult smokers. The primary responsibility of the DSM will be to monitor for any unexpected safety risk for subjects on the protocol. The DSM will:

- Review all SUSARs and SAEs reported to the Sponsor. The Sponsor will provide the DSM 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 DSM with copies of all expedited SAE reports submitted to regulatory agencies.
- Perform periodic reviews of specific safety data for the study (e.g. moderate and higher adverse events).

The DSM 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. The Sponsor and sites will not be unblinded unless the DSM requests that individual or other unblinding occurs due to a safety concern.

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 (i.e., when unblinding cannot induce bias in collection of data and interpretation of results).

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

16.1. Statistical Design

This study will be analyzed without specific statistical criteria. The overall study intent is to obtain effect outcomes and conduct estimates to further inform the design and plans for Phase 3 studies.

16.2. Efficacy Outcomes

The primary comparisons will be: Arm A versus Arm C, Arm B versus Arm C, Arm D versus Arm F, and Arm E versus Arm F (comparison of active arms to the associated placebo arm).

The primary outcome Y is the percent of expected cigarettes smoked computed for each subject as follows:

Let N=total of number of cigarettes smoked each day over the treatment period from 1 to 25 days.

Let R=representation of the average number of cigarettes smoked daily over the 7-day screening period as baseline.

Let T=number of post-randomization days where number of cigarettes smoked is recorded.

Compute Y = $\frac{100 \times N}{T \times R}$

The denominator is the expected number of cigarettes that would have been smoked without intervention over the days where the number of cigarettes smoked is recorded, and the numerator is 100 times the actual number of cigarettes smoked (the purpose of the 100 factor is to convert to a percent).

The primary analyses will include all randomized subjects by randomized arm (intent-to-treat analysis). The four primary comparisons will be based on analysis of variance with main effects arm (2 levels for the arms to be compared) and BMI class (3 level stratification as previously specified), and with covariate of baseline cigarettes smoked. Sensitivity analyses will include the assessment of the contribution of interaction terms and effect modification analyses. Analyses of data associated with other objectives will be specified in a statistical analysis plan (SAP).

16.3. Study Size

The trial size is based on projected realization of the effect size estimate for the primary outcome based on data from a Phase 1/2 study in adult smokers. The primary outcome standard deviation from this study was found to be approximately 17. Based on this standard deviation, the estimated between-arm differences in the primary comparisons can be estimated with a 95% confidence interval that is ±8.3.

The trial size will not have sensitivity for a dichotomous outcome (e.g. smoking cessation as the secondary efficacy outcome), other than for possibly large differences. For example, if the control

arm outcome is 12% (3/25 defined as successes), then the experimental arm will have a two-sided 95% confidence interval for the probability difference that excludes zero when the success probability is 36% (8/50) or more (computation based on exact confidence interval).

16.4. Safety Objective

Safety assessments include reported adverse events, laboratory tests results, and vital signs.

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 adverse event data will primarily be assessed for clinical safety. Data will be listed and summarized for each treatment according to measurement time.

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, 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 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 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 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 to the Sponsor 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.

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, who must be a physician, 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 (i.e. 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 subject's 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.
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). 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 schedule, 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-09

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	Sponsor's Representative's name
Signature	Signature
Date **(ddmmYYYY)**	Date **(ddmmYYYY)**
Institution	

21. REFERENCES

1. Etter J. Cytisine for smoking cessation: A literature review and a meta-analysis. Archives of Internal Medicine 2006;166:1553-9.
2. Papke RL, Heinemann SF. Partial agonist properties of cytisine on neuronal nicotinic receptors containing the beta 2 subunit. Molecular pharmacology 1994;45:142-9.
3. Parker MJ, Beck A, Luetje CW. Neuronal nicotinic receptor beta2 and beta4 subunits confer large differences in agonist binding affinity. Molecular pharmacology 1998;54:1132-9.
4. Coe JW, Brooks PR, Vetelino MG, et al. Varenicline: an alpha4beta2 nicotinic receptor partial agonist for smoking cessation. Journal of medicinal chemistry 2005;48:3474-7.
5. West R, Zatonski W, Cedzynska M, et al. Placebo-Controlled Trial of Cytisine for Smoking Cessation. New England Journal of Medicine 2011;365:1193-200.
6. Walker N, Howe C, Glover M, et al. Cytisine versus nicotine for smoking cessation. The New England journal of medicine 2014;371:2353-62.
7. World Health Organization. WHO report on the global tobacoo epidemic, 2017: monitoring tobacco use and prevention policies. Geneva 2017.
8. Hughes JR, Keely J, Naud S. Shape of the relapse curve and long-term abstinence among untreated smokers. Addiction (Abingdon, England) 2004;99:29-38.
9. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. BMJ (Clinical research ed) 2004;328:1519.
10. Foulds J, Burke M, Steinberg M, Williams JM, Ziedonis DM. Advances in pharmacotherapy for tobacco dependence. Expert opinion on emerging drugs 2004;9:39-53.
11. Hughes JR, Stead LF, Hartmann-Boyce J, Cahill K, Lancaster T. Antidepressants for smoking cessation. The Cochrane database of systematic reviews 2014:Cd000031.
12. Stead LF, Perera R, Bullen C, et al. Nicotine replacement therapy for smoking cessation. The Cochrane database of systematic reviews 2012;11:Cd000146.
13. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. The Cochrane database of systematic reviews 2013:Cd009329.
14. Cahill K, Lindson-Hawley N, Thomas KH, Fanshawe TR, Lancaster T. Nicotine receptor partial agonists for smoking cessation. The Cochrane database of systematic reviews 2016:Cd006103.
15. Anthenelli RM, Benowitz NL, West R, et al. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. The Lancet 2016;387:2507-20.
16. West R, Hajek P, Stead L, Stapleton J. Outcome criteria in smoking cessation trials: proposal for a common standard. Addiction (Abingdon, England) 2005;100:299-303.
17. Osman A, Bagge CL, Gutierrez PM, Konick LC, Kopper BA, Barrios FX. The Suicidal Behaviors Questionnaire-Revised (SBQ-R): validation with clinical and nonclinical samples. Assessment 2001;8:443-54.
18. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. British journal of addiction 1991;86:1119-27.
19. Etter JF, Bergman MM, Humair JP, Perneger TV. Development and validation of a scale measuring self-efficacy of current and former smokers. Addiction (Abingdon, England) 2000;95:901-13.

20. Heishman SJ, Singleton EG, Pickworth WB. Reliability and validity of a Short Form of the Tobacco Craving Questionnaire. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco 2008;10:643-51.
21. Stern AF. The hospital anxiety and depression scale. Occupational medicine (Oxford, England) 2014;64:393-4.

APPENDIX 1. SUICIDAL BEHAVIORS QUESTIONNAIRE-REVISED (SBQ-R)

The Suicidal Behaviors Questionnaire-Revised (SBQ-R)[17] provides a broad range of information in a brief administration. Responses can be used to identify at-risk individuals and specific risk behaviors. This questionnaire must be completed by all potential study subjects during screening. A score ≥7 indicates potential for suicidal ideation and would confirm study exclusion criteria #8.

This questionnaire must also be completed by all study subjects at the Day 27 (End of Treatment) and Week 8 clinic visits to monitor for any potential suicidal ideation or behaviour during the study as a safety parameter. An SBQ-R score ≥7 will be used to identify at-risk individuals who will need immediate evaluation by site personnel for any potential suicidal ideation. Any potential suicidal ideation or behavior will be considered an SAE.

Copies of this questionnaire and details for interpretation and scoring will be provided in the study Procedure Manual and completed questionnaires must be present as source documents. Any subject meeting this exclusion must be followed by the clinical site according to site policies.

1. **Have you ever thought about or attempted to kill yourself?** (check one only)
   - □ 1. Never
   - □ 2. It was just a brief passing thought
   - □ 3a. I have had a plan at least once to kill myself but did not try to do it
   - □ 3b. I have had a plan at least once to kill myself and really wanted to die
   - □ 4a. I have attempted to kill myself, but did not want to die
   - □ 4b. I have attempted to kill myself, and really hoped to die
2. **How often have you thought about killing yourself in the past year?** (check one only)
   - □ 1. Never
   - □ 2. Rarely (1 time)
   - □ 3. Sometimes (2 times)
   - □ 4. Often (3-4 times)
   - □ 5. Very Often (5 or more times)
3. **Have you ever told someone that you were going to commit suicide, or that you might do it**? (check one only)
   - □ 1. No
   - □ 2a. Yes, at one time, but did not really want to die
   - □ 2b. Yes, at one time, and really wanted to die
   - □ 3a. Yes, more than once, but did not want to do it
   - □ 3b. Yes, more than once, and really wanted to do it
4. **How likely is it that you will attempt suicide someday?** (check one only)
   - □ 0. Never
   - □ 1. No chance at all
   - □ 2. Rather unlikely
   - □ 3. Unlikely
   - □ 4. Likely
   - □ 5. Rather likely
   - □ 6. Very likely

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[18] and will be administered at the randomization visit only. Copies of this FTND will be provided in the study Procedure Manual. 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)[19] 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. Copies of this questionnaire will be provided in the study Procedure Manual. 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. SHORT FORM OF THE TOBACCO CRAVING QUESTIONNAIRE

The short form of the Tobacco Craving Questionnaire has been validated as a self-report instrument to measure tobacco craving[20] and will be administered to study subjects at randomization and each clinic visit (Days 2, 3, 6, 12, 16, 20, 27, and Weeks 5, 6, 7, and 8). Copies of this questionnaire will be provided in the study Procedure Manual. Analysis of results is outlined in the study Statistical Analysis Plan.

Question	**Response**						
	Strongly Disagree....Strongly Agree						
Factor 1 (emotionality)							
I would be less irritable now if I could smoke.	☐	☐	☐	☐	☐	☐	☐
If I were smoking now I could think more clearly.	☐	☐	☐	☐	☐	☐	☐
I could control things better right now if I could smoke.	☐	☐	☐	☐	☐	☐	☐
Factor 2 (expectancy)							
I would enjoy a cigarette right now.	☐	☐	☐	☐	☐	☐	☐
A cigarette would taste good right now.	☐	☐	☐	☐	☐	☐	☐
Smoking a cigarette would be pleasant.	☐	☐	☐	☐	☐	☐	☐
Factor 3 (compulsivity)							
If I smoked right now, I would not be able to stop.	☐	☐	☐	☐	☐	☐	☐
I could not stop myself from smoking if I had some cigarettes here.	☐	☐	☐	☐	☐	☐	☐
I would not be able to control how much I smoked if I had some cigarettes here.	☐	☐	☐	☐	☐	☐	☐
Factor 4 (purposefulness)							
If I had a lit cigarette in my hand, I probably would smoke it.	☐	☐	☐	☐	☐	☐	☐
It would be hard to pass up the chance to smoke.	☐	☐	☐	☐	☐	☐	☐
I could not easily limit how much I smoked right now.	☐	☐	☐	☐	☐	☐	☐

APPENDIX 5. HOSPITAL ANXIETY AND DEPRESSION SCALE (HADS)

The HADS questionnaire[21] has been validated as a self-report instrument to measure levels of anxiety and depression and will be administered to study subjects at Screening Visit #1, at the Day 12, Day 27 (End-of-Treatment visit) and again at Week 8. Copies of this questionnaire will be provided in the study Procedure Manual. 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
A	**I can sit at ease and feel relaxed:**
0	Definitely
1	Usually
2	Not Often
3	Not at all

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
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 6. ALCOHOL USE QUESTIONNAIRE

The following questions will be administered to study subjects at randomization and again at Week 8 upon completing the Follow-up Assessment Period. Copies of this questionnaire will be provided in the study Procedure Manual. Analysis of results is exploratory and outlined in the study Statistical Analysis Plan.

1. Over the past 7 days, how often did you have a drink containing alcohol? Consider a "drink" to be a can or a bottle of beer, a glass of wine, a wine cooler, or one cocktail or a shot of hard liquor (like scotch, gin, or vodka).
    - Never
    - 2 to 3 times
    - 4 to 5 times
    - 6 or more times
    - Don't know
2. If you did drink in the past 7 days, how many drinks did you have on a typical day when you drank alcohol?
    - 1 to 2 drinks
    - 3 to 4 drinks
    - 5 to 6 drinks
    - 7 to 9 drinks
    - 10 or more drinks
    - Don't know
3. If you did drink in the past 7 days, how often did you have 6 or more drinks on one occasion?
    - Never
    - Daily or almost daily
    - Don't know

APPENDIX 7. BEHAVIORAL SUPPORT

Each participating site must have at least two or more staff members experienced and qualified to provide smoking cessation counseling. Study site counselors who provide behavioral support during this study are required to have either a) a master's level or higher degree in some sort of counseling profession (e.g. health educator, chemical dependence counselor) or b) completed a tobacco treatment training course of at least 4 hours.

At the Screening Visit #2 visit, subjects will be provided behavioral support and assistance in developing a quit plan. Most importantly this ensures the subject's quit date is chosen prior to randomization and that they are planning on trying to quit smoking. Site counselor(s) are to encourage subjects to continue study drug as scheduled even if they lapse and have a cigarette after their quit date. It is important during this "grace" period for the subjects to keep trying to quit as planned. It is also important to reiterate to each subject that the purpose of this study is to evaluate the potential benefits of cytisine in achieving abstinence even after a lapse or "slip" during study treatment because cytisine is thought to block the effects of nicotine.

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 (e.g. 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 will receive up to 12 behavioral support sessions by a qualified staff member, starting at the Screening Visit #2, again at randomization and then continuing through each clinic visit up to the Week 8 visit.

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 cytisine 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 up to 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 (e.g., 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 (i.e. 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 (i.e. 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?
- How will I handle withdrawal symptoms?
- What are my stress triggers for cravings?
- How will I deal with these stressors instead of smoking?
- What are my biggest concerns/fears about quitting smoking?
- How will I remember to take my medication as directed?

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.