Statistical Analysis Plan:
PROTOCOL ACH-CYT-04 (ORCA-3 Trial)

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

April 27, 2023

Version 1.0

CONFIDENTIAL

Achieve Life Sciences Technologies Inc. [redacted]

Achieve Life Sciences, Inc. [redacted]

APPROVAL SIGNATURES

Protocol	**ACH-CYT-04**
Document Title	Statistical Analysis Plan: Protocol ACH-CYT-04 (ORCA-3 Trial)
Document Version	Version 1.0
Document Date	April 27, 2023

By signing this section, the individuals below agree that they have reviewed the scope of the effort described in this Statistical Analysis Plan for the ACH-CYT-04 (ORCA-3) study. The signatures below represent the approval and acceptance of this document by [redacted] and Achieve Life Sciences, Inc.

Approved By:	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
ADaM	Analysis Data Model
ADaM IG	Analysis Data Model Implementation Guide
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CDISC	Clinical Data Interchange Standards Consortium
CO	Carbon Monoxide
CRF	Case Report Form
C-SSRS	Columbia - Suicide Severity Rating Scale
DEG	Data Entry Guidelines
ECG	Electrocardiogram
EMA	Effect Modification Analyses
eCRF	Electronic Case Report Form
EOT	End of Treatment
FTND	Fagerstrom Test of Nicotine Dependence
HADS	Hospital Anxiety and Depression Scale
ICH	International Conference on Harmonization
IRT	Interactive Response Technology
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MNWS	Minnesota Nicotine Withdrawal Scale
NMR	Nicotine Metabolite Ratio
NRT	Nicotine Replacement Therapy
PCS	Potentially Clinically Significant
OR	Odds Ratio
PT	Preferred Term
QSU-Brief	Brief Questionnaire of Smoking Urges
RTF	Rich Text Format
SAP	Statistical Analysis Plan
SDTM	Study Data Tabulation Model
SDTM IG	Study Data Tabulation Model Implementation Guide
SEQ-12	Smoking Self-Efficacy Questionnaire
SI	Système International
SOC	MedDRA System Organ Class
SV1	Screening Visit #1
TEAE	Treatment Emergent Adverse Event
TID	Three Times Daily
WHODrug	World Health Organization Drug Dictionary

TABLE OF CONTENTS

LIST OF FIGURES

1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a thorough description of statistical methods and presentation of the study data to be used for the analysis of data generated from the clinical trial described in protocol ACH-CYT-04 (ORCA-3 Trial): "A Multicenter, Double-blind, Randomized, Placebo-controlled Phase 3 Trial Evaluating the Efficacy and Safety of Cytisinicline in Adult Smokers", Version 3.0 (September 10, 2020).

This SAP was prepared by Achieve Life Sciences Inc. (Achieve) and reviewed by [redacted] ([redacted]). It includes details of data handling procedures and statistical methodology. The final statistical analyses will proceed in accordance with this SAP. Any deviation from this SAP will be documented in the final CSR.

For this study, [redacted] is responsible for programming of datasets. [redacted] will provide to Achieve the Study Data Tabulation Model (SDTM) as well as Analysis Data Model (ADaM) dataset specifications based on:

- SDTM Model 1.7 and SDTM Implementation Guide (SDTM IG) Version 3.3.
- ADaM Model 2.1 and ADaM Implementation Guide (ADaM IG) Version 1.1.

It is essential that the user of this document also be familiar with the contents of the protocol. The protocol is the designated place where background, operational, and procedural details necessary for the understanding of this trial can be found to supplement this SAP. In addition to the protocol, the following study documents were reviewed in preparation of this SAP:

- Electronic Case Report Form (eCRF): Version 5.0, 27-Jul-2022
- Data Entry Guidelines (DEG): Version 4.0, 03-Aug-2022
- Data Management Plan: Version 3.0, 12-Jan-2023
- Data Transfer Specification (DTS) for Achieve ACH-CYT-04 IRT to eCRF: Version 2.0, 17-Jan-2022

2. STUDY DESCRIPTION

2.1. Study Design

Study ACH-CYT-04 will be a multi-center, double-blind, randomized, placebo-controlled, Phase 3 study conducted in male or female adults who are ≥18 years age, current daily cigarette smokers, intending to quit smoking, and willing to set a quit date within 5-7 days of being randomized on the study. Study treatment must start the day after randomization such that study treatment is initiated prior to the quit date.

Subjects must meet all requirements outlined in the inclusion and exclusion criteria. A total of approximately 750 subjects will be randomly assigned with equal probability (1:1:1) to one of three arms as summarized below and shown in more detail in the study design figure:

- Arm A (N=250; placebo three times daily (TID) for 12 weeks plus behavioral support)

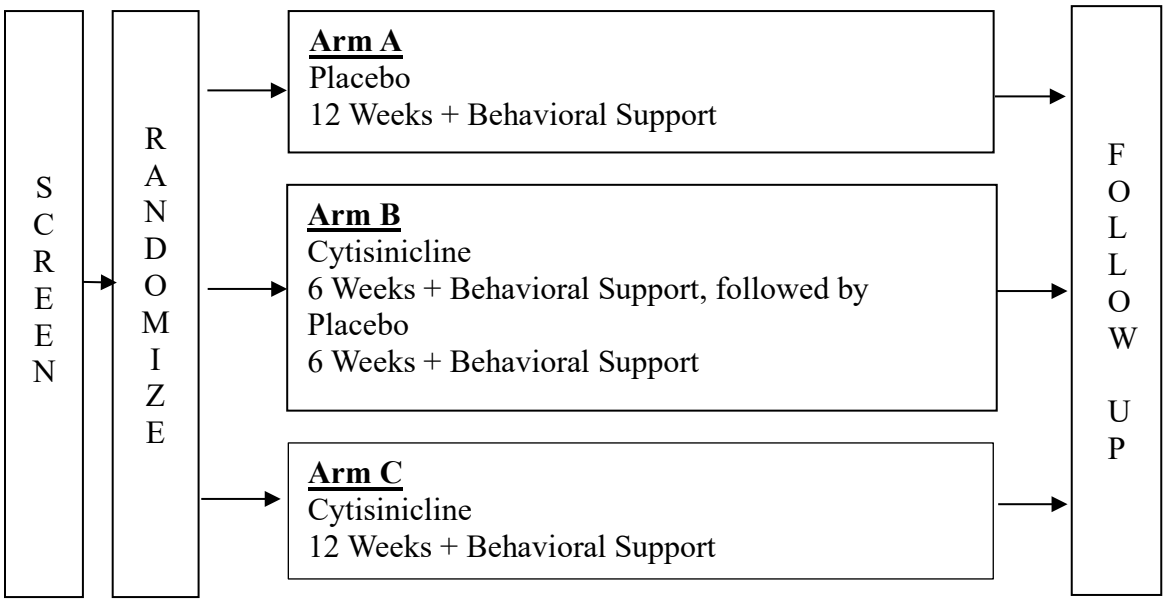
- Arm B (N=250; 3 mg cytisinicline TID for 6 weeks followed by placebo TID for 6 weeks plus behavioral support)
- Arm C (N=250; 3 mg cytisinicline TID for 12 weeks plus behavioral support)

For brevity, the arms may be described as follows:

- Arm A (placebo)
- Arm B (cytisinicline 6 weeks)
- Arm C (cytisinicline 12 weeks)

All subjects are to receive behavioral support during the 12-week treatment period with additional behavioral support during the follow-up period.

Figure 1: Study Design Overview



This study will be conducted at approximately 15-19 clinical sites across the US. Subjects will be randomized within site (see Randomization Plan, Appendix 1), with the goal of balancing between arm allocation within clinical sites in order to minimize imbalance for the assessment of evidence of heterogeneity of effect estimates across sites. Clinical site will be used as a stratification factor in primary analyses.

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

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

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

Safety will be assessed by consideration of all adverse events reported by or elicited from the subject. Subjects will be monitored for adverse events starting at screening (pre-existing), by telephone contact on Day 1, and at weekly clinic visits from Week 1 through Week 12. Adverse events will be monitored through the follow-up period. Any ongoing adverse events at Week 16 will be followed until resolved or determined to be chronic.

Safety assessments performed at clinic visits will include hematology and chemistry, vital signs, weight, ECG, subject questionnaires (HADS, C-SSRS), and urine pregnancy testing (if applicable). Post-treatment assessments will be done for all subjects approximately 1 – 3 days after the last dose of study drug (Week 12). If a subject discontinues treatment early, safety assessments outlined for the Week 12 visit should be completed at the time of discontinuation.

The end of study will be defined as the last follow-up visit (up to the Week 24 visit) for the last subject.

2.2. Determination of Sample Size

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

Data from the international EAGLES trial (N=8,120) were used to assess predictors for continuous smoking abstinence outcomes from Weeks 9-24. These analyses provided evidence that subjects treated in the US had lower success rates of quitting, regardless of treatment (varenicline, bupropion, or NRT). The continuous abstinence rates from 9-24 weeks in the US were 16.1%, 11.4% and 10.6% for varenicline, bupropion, or NRT, respectively, compared to 6.7% for placebo treatment. The odds ratios (OR) for these treatments in the US were 2.66, 1.78, and 1.64, respectively. The lower success rate in US smokers supports the view that smokers in the US may have particular characteristics that make it more difficult for them to stop smoking.

The trial size for this study is specified as 250 subjects per arm. The assumed control arm probability of success (continued abstinence to Week 24) is 0.07 (7%). The hypothesized experimental arm minus control arm probability difference is specified as 0.12 (12 points), corresponding to a hypothesized odds ratio of 3.116 (eg, 7% for placebo vs 19% for cytisinicline treatment). The significance level to be used is adjusted from the overall type I error probability of one-sided 0.025 to one-sided 0.0125 using the Bonferroni method to control for multiplicity. The statistical operating characteristics for each comparison are illustrated using simulation of Fisher's exact test with 10,000 replicates. These specifications are consistent with 95.7% power for each comparison with, conditional on 0.07 control arm probability outcome, an odds ratio critical region of ≥1.83, corresponding to a critical difference of ≥0.051 (7% for placebo vs 12% for cytisinicline treatment). The trial sizing simulations were not done using the Hochberg method for controlling inferential multiplicity for the two primary comparisons. (The use of the

Hochberg methods is described subsequently.) The statistical power estimated from simulation therefore should be regarded as an underestimate of power because the Hochberg method is slightly less conservative relative to the Bonferroni method.

2.3. Treatment Assignment

A total of approximately 750 subjects will be randomized with equal probability (1:1:1) to three arms (Arm A, Arm B, Arm C). Refer to Section 2.1.

2.4. Administration of Study Medication

Tablets with identical appearance containing 3 mg cytisinicline or matched placebo will be administered orally. During the 12-week treatment period, subjects will take one tablet three times daily.

3. STUDY OBJECTIVES

3.1. Multiple Primary Efficacy Objectives

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

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

3.2. Secondary Efficacy Objectives

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

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

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

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

3.3. Other Objectives

1. To compare arms (Arm B vs Arm A, Arm C vs Arm A) on 7-day point prevalence abstinence weekly at Week 2 through Week 12, then at Weeks 16, 20, and 24.
2. To compare arms (Arm B vs Arm A; Arm C vs Arm A) on serum cotinine levels every other week at Week 2 through Week 12, then at Weeks 16, 20, and 24.
3. To compare arms (Arm B vs Arm A; Arm C vs Arm A) on expired CO levels every week at Week 2 through Week 12, then at Weeks 16, 20, and 24.
4. To compare arms (Arm B vs Arm A; Arm C vs Arm A) on use of any non-cigarette nicotine products, including vaping, during study treatment (Week 2 through Week 12) and study follow-up (Week 16 through Week 24).
5. Assess whether subjects randomized to Arm B have a higher probability of abstinence from Week 9 to Week 12 as compared to subjects randomized to Arm A (placebo).
6. Assess among the subset of subjects who achieve abstinence from Week 3 to Week 6, whether subjects randomized to Arm B have a higher probability of continuous abstinence from Week 3 to Week 24 post-randomization as compared to homologous subjects randomized to Arm A.
7. Assess among the subset of subjects who achieve abstinence from Week 3 to Week 6, whether subjects randomized to Arm C have a higher probability of continuous abstinence at Week 24 post-randomization as compared to subjects randomized to Arm B.
8. Assess among the subset of subjects who achieve abstinence from Week 9 to Week 12, whether subjects randomized to Arm C have a higher probability of continuous abstinence from Week 9 to Week 24 post-randomization as compared to homologous subjects randomized to Arm A.
9. Among subjects who achieve abstinence from Week 3 to Week 6, compare time to failure to maintain abstinence between arms (Arm B vs Arm A, Arm C vs Arm A) to Week 24.
10. To explore the magnitude of treatment effect between arms across various subgroups defined by demographic and baseline characteristics for the primary and secondary outcomes.
11. To explore potential relationships between subject-reported outcomes (eg, anxiety, depression, tobacco craving) and the primary and secondary outcomes.

12. To assess possible withdrawal symptoms at Week 7 in Arm B subjects who will have discontinued cytisinicline at Week 6, analyzing separately for nicotine status (eg, either smoking, abstinent, or if using other nicotine products including vaping or nicotine replacement therapy [NRT]) compared to Arms A and C.
13. To explore the relationship of expired CO and cotinine by primary endpoint abstinence status.

3.4. Safety Objectives

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

4. EFFICACY AND SAFETY ENDPOINTS

4.1. Efficacy Endpoints

Efficacy endpoints will be based on a subject's self-reported cigarette smoking data with biochemical verification at each assessment. Biochemical verification of smoking abstinence will be defined by a CO concentration in exhaled breath of less than 10 ppm.

4.1.1. Primary Efficacy Endpoints

The comparisons for the primary efficacy objectives will be between experimental arms and the placebo arm, for the following endpoints:

- Abstinence from Week 3 to Week 6: Arm B (cytisinicline 6 weeks) vs Arm A (placebo)
- Abstinence from Week 9 to Week 12: Arm C (cytisinicline 12 weeks) vs Arm A (placebo)

The smoking abstinence endpoint for each subject is binary: success versus failure. Success is biochemically verified smoking abstinence documented at Weeks 3, 4, 5, and 6 (Arm B) or Weeks 9, 10, 11, and 12 (Arm C), compared to the corresponding weekly assessments in the placebo arm (Arm A). At each visit, success will be defined for an individual subject as having reported smoking abstinence (no cigarettes since the last clinic visit) and having CO concentration in exhaled breath of less than 10 ppm. For subjects that say no to the question 'Has the subject smoked any cigarettes since the last clinical visit' and number of cigarettes smoked is missing this will be imputed to 0. Subjects will be allowed only 1 missed visit (smoking status unknown) for analysis of the primary endpoint (ie, one of Week 4 or Week 5 for the comparison of Arm B vs Arm A; one of Week 10 or Week 11 for the comparison of Arm C vs Arm A).

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

success for smoking abstinence. Examples of subjects with insufficient data include the following:

- Smoking status unknown at more than 1 of the interim visits listed above. A smoking status is unknown when data are missing for either the number of cigarettes smoked since the last clinic visit or CO reading or both.
- Smoking status unknown at key visits for the endpoint. For the Week 3 to Week 6 endpoint, subjects with smoking status unknown at either Week 3 or Week 6 will be regarded as failures. Likewise, for the Week 9 to Week 12 endpoint, subjects with smoking status unknown at either Week 9 or Week 12 will be regarded as failures.

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

Statistical methods for the primary efficacy endpoints are described in Section 10.1.

4.1.2. Secondary Efficacy Endpoints

There are 3 secondary efficacy objectives, 2 objectives for continuous abstinence through to Week 24 and 1 objective for assessing reduction in risk of relapse for Arm C compared to Arm B (eg, once achieving successful abstinence at Weeks 3-6, whether there is a greater chance of being relapse-free, if the subject continues on treatment for an additional 6 weeks compared to being switched to placebo).

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

The following operational details are applicable to these secondary efficacy comparisons:

- Being abstinent requires meeting both a self-reported criterion and a biochemical verification. The beginning of self-reported abstinence is Week 3 to Week 6 for comparisons of Arm A and Arm B and Week 9 to Week 12 for comparison of Arm A and Arm C. For comparison of Arm C to Arm B, the failure of self-reported abstinence starts at Weeks 3-6 for both Arms B and C.
- Self-reported abstinence over the Week 16 to Week 24 Follow-up period will be assessed using the Russell Standard[1] which allows up to a total of 5 cigarettes to be smoked in order to be regarded as abstinent or without relapse.
- Biochemical verification of non-smoking status is defined by a carbon monoxide concentration in exhaled breath of less than 10 ppm.

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

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

4.1.2.1. Continuous Abstinence

The comparisons for the 2 continuous abstinence efficacy objectives will be between experimental arms and the placebo arm, as follows:

- Continuous abstinence from Week 6 to Week 24: Arm B (cytisinicline 6 weeks) vs Arm A (placebo)
- Continuous abstinence from Week 12 to Week 24: Arm C (cytisinicline 12 weeks) vs Arm A (placebo).

For the comparison of Arm A to Arm B (secondary objective 1), success for the continuous abstinence from Week 6 to Week 24 endpoint will be defined as having all of the following observed:

- Abstinence determined at the primary evaluation (Weeks 3-6), and
- At the Week 7 to Week 11 visits, subject self-report of abstinence since the last clinic visit together with biochemical verification of abstinence, and
- At the Week 12 visit, subject self-report of abstinence since the last clinic visit together with biochemical verification of abstinence, and
- Self-reported abstinence during the Week 16 to Week 24 Follow-up period, defined as smoking up to a total of 5 cigarettes at the attended Week 16, Week 20, and Week 24 visits together with biochemical verification of abstinence at each attended visit. (Only one visit, either Week 16 or Week 20, is allowed to be missing.)

For the comparison of Arm A to Arm C (secondary objective 2), success for the continuous abstinence from Week 12 to Week 24 endpoint will be defined as having all of the following observed:

- Abstinence determined at the primary evaluation (Weeks 9-12), and
- Self-reported abstinence during the Week 16 to Week 24 Follow-up period, defined as smoking up to a total of 5 cigarettes at the attended Week 16, Week 20, and Week 24 visits together with biochemical verification of abstinence at each attended visit. (Only one visit, either Week 16 or Week 20, is allowed to be missing.)

Any other outcome will be regarded as a failure. There are therefore two types of failure for the subject: (1) subjects with adequate data that they are not abstinent at any time (either by the subject's self-report or CO ≥10 ppm) and (2) subjects having insufficient data to be determined as a success for continuous abstinence.

Statistical methods for the continuous abstinence endpoints are described in Section 10.1.3.

4.1.2.2. Reduction in Risk of Relapse (Relapse-Free)

For the comparison of Arm C to Arm B (secondary objective 3), relapse free (success of not having relapsed) from Weeks 3-6 through to Week 24 will be defined as having the following observed after initial abstinence (ie, primary success criteria) is determined from Weeks 3-6:

- At the Week 12 visit, subject self-report of abstinence (relapse-free) since the last clinic visit together with biochemical verification of abstinence, and
- Self-reported abstinence (relapse-free) during the Week 16 to Week 24 Follow-up period, defined as smoking up to a total of 5 cigarettes at the attended Week 16, Week 20, and Week 24 visits together with biochemical verification of abstinence at each attended visit. (Only one visit, either Week 16 or Week 20, is allowed to be missing.)

Subjects not observed to meet the above success criteria will be regarded as having relapsed to the secondary efficacy 3 outcome. Non-success or relapse will have two types: (1) subjects with adequate data that fail to meet the above criteria, and (2) subjects having insufficient data to be assessed as a success. Note: subjects not abstinent at Week 6 (eg, Weeks 3-6) will be regarded as having already relapsed.

Statistical methods for the reduction in risk of relapse (relapse free) endpoint are described in Section 10.1.3.

4.1.3. Other Efficacy Endpoints

In general, the other efficacy endpoints defined in this section are associated with tertiary efficacy objectives. The other efficacy endpoints are:

7-day point prevalence abstinence is a binary endpoint (success, failure) at each visit from Week 2 through Week 24. At each visit, success will be defined for a subject as having reported smoking abstinence with biochemical verification (CO<10 ppm). 7-day point prevalence for smoking abstinence will be defined as reporting no smoking since the last clinic visit at each weekly clinic visit from Week 2 through Week 12 and over the past 7 days during Follow-up visits at Weeks 16, 20 and 24. Any other outcome will be regarded as a failure. All subjects will have a realization of this endpoint, thereby enabling analyses that follow the ITT principle without imputation.

Serum cotinine levels (ng/mL) are a continuous endpoint measured every other week from Week 2 to Week 12, then at Week 16, Week 20, and Week 24.

Expired CO levels (ppm) are a continuous endpoint measured at each visit from Week 2 through Week 24.

Use of non-cigarette nicotine products, including vaping, will be assessed at each visit from Week 2 to Week 24. Subjects report whether they have used any non-cigarette nicotine products since the last visit (yes, no) and report all products used during the interval (eg, pipe tobacco, e-cigarettes/vaping, marijuana smoking/vaping).

Continuous abstinence from Week 3 to Week 24 (subset analysis): Assess among the subset of subjects who achieve abstinence from Week 3 to Week 6 in Arm A and Arm B (ie, are a

success on the primary efficacy endpoint for primary objective 1). Success will be defined for a subject following the same rules as the continuous abstinence endpoint (see Section 4.1.2.1).

Continuous abstinence from Week 9 to Week 24 (subset analysis): Assess among the subset of subjects who achieve abstinence from Week 9 to Week 12 in Arm A and Arm C (ie, are a success on the primary efficacy endpoint for primary objective 2). Success will be defined for a subject following the same rules as the continuous abstinence endpoint (see Section 4.1.2.1).

Time to failure to maintain abstinence will be evaluated for the subset of subjects who were classified as a success for abstinence at Weeks 3-6. Time to failure to maintain abstinence (days) will be calculated as end date of abstinence minus start date of abstinence +1. The start date of abstinence will be defined as the date of the Week 6 visit. The end date of abstinence will be defined as the earliest date that the subject was known to have resumed smoking, or will be censored, as described below:

- At a visit during the treatment period, if a subject reported smoking since the last visit (either by the subject's self-report or CO ≥10 ppm), the end date of abstinence will be the earliest of the following dates: the date the subject reported resuming smoking, or the date of CO ≥10 ppm.
- During the follow-up period, if a subject reported smoking a total of more than 5 cigarettes at the attended Week 16, Week 20, and Week 24 visits, or CO≥10 ppm at a visit, the end date of abstinence will be the earliest of the following dates: the date the subject reported smoking the 6th cigarette, or the date of CO≥10 ppm.
- Subjects who have not resumed smoking at their final visit will have end date of abstinence censored at the date of that final visit. (The final visit is expected to be the Week 24 visit.)

4.2. Safety Endpoints

The safety endpoints are:

- adverse events, including serious adverse events and other significant adverse events
- laboratory assessment
  - hematology
  - chemistry
- vital signs
- 12-lead ECG results
- concomitant medications

4.2.1. Definitions

4.2.1.1. Treatment-emergent Adverse Event

A TEAE is any AE that is new in onset or was aggravated in severity or frequency following the first dose of study drug, up to and including the last visit of the study. Treatment emergence will be determined by comparing the AE start date/time with the actual date/time of first dose of

study drug. TEAEs are defined as events with start date/time on or after the date/time of first dose of study drug. If either the AE start date or start time is unknown on the date of first dose, treatment-emergent events will be defined based on a "Yes" response to the CRF item "Did the AE start after the first dosing?"

4.2.1.2. Serious Adverse Event (SAE)

An SAE is defined as an AE that:

- 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.

4.2.1.3. Other Adverse Events of Special Interest

The following events will be reported as "other adverse events of special interest":

- Treatment-emergent suicidal ideation or risk, as measured by responses on the C-SSRS on or after first dose of study drug. Suicidal ideation or risk will be defined as a response of "Yes" to either question 4 or question 5 or "Yes" to any suicidal behavior question on the C-SSRS.

  Note: Suicidal ideation or risk for suicide prior to randomization ("Yes" to either question 4 or question 5 OR "Yes" to any suicidal behavior question on the C-SSRS) is an exclusion criterion.

- Treatment-emergent moderate to severe depression, as measured by a HADS depression score ≥11 on or after first dose of study drug.

  Note: Current symptoms of moderate to severe depression prior to randomization (HADS depression score ≥11) is an exclusion criterion.

- New pregnancy documented by a positive pregnancy test on or after first dose of study drug.

  Note: Pregnancy is an exclusion criterion.

- Treatment-emergent coronavirus disease 2019 (COVID-19) will be selected using the Medical Dictionary for Regulatory Activities (MedDRA) standardized MedDRA query (SMQ) for COVID-19.

4.2.1.4. End of Treatment (EOT) Visit

As specified in the protocol, post-treatment assessments will be done for all subjects approximately 1 – 3 days after the last dose of study drug (the EOT assessments).

The timing of EOT assessments will be different for subjects who complete treatment and subjects who discontinue treatment early. Subjects that complete treatment will have EOT assessments done at the Week 12 (Day 86/EOT) visit. Subjects who discontinue treatment early, will have EOT assessments done at an earlier visit that coincides with their date of treatment discontinuation. The visit at which EOT safety assessments were done will be documented in study datasets.

Subjects who discontinue treatment early are expected to continue in the study through Week 24. Therefore, it is expected that the procedures outlined under the Week 12 (Day 86/EOT) visit will be repeated at that time.

In order to accurately summarize changes from baseline to EOT in safety endpoints, the EOT safety assessments for all subjects will be combined into a derived visit named “EOT”. That visit will be included in summary tables of safety endpoints.

4.3. Pharmacokinetic and Pharmacodynamic Evaluations

None planned.

5. TRIAL CONDUCT CONSIDERATIONS

5.1. Changes in Inclusion and Exclusion Criteria

No changes are planned.

5.2. Interim Analysis and Early Stopping

None planned.

5.3. Sample Size Adjustment

If higher than expected early treatment discontinuations (>5%) occur before completion of 6 weeks study treatment due to reasons other than adverse events, additional enrollment may be allowed up to 10% or 75 subjects.

6. DATA ANALYSIS CONSIDERATIONS

6.1. Clinical Databases

There will be two clinical data sources for this study: a web-based interactive response technology (IRT) application and an eCRF database.

IRT will be used to collect subject diary data, randomize subjects, and allocate study drug. In general, data collected in the IRT application will be transferred to the eCRF database. The

following data will not be transferred to the eCRFs but will be extracted from the IRT application after the eCRF database is locked:

- Subject randomization data: date randomized, value of stratification factor at randomization, treatment arm assignment.
- Subject treatment-diary data: date and time of each dose (or indication if dose was missed) as recorded by subjects each day during the treatment period.

All other subject data will be entered into the eCRF database and will be extracted from that application after the eCRF database is locked.

6.2. General Considerations

Statistical analyses will be performed at the end of the study after the last subject has completed the Week 24 visit, all data have been reported, cleaned, and the eCRF database has been locked.

Medical history events and adverse events will be coded to standard “preferred terms” and “system organ classifications (SOC)” using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1 or higher. Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug) Version Mar-2021 B2 or higher.

All statistical programming will be done using SAS® Version 9.4 or higher (SAS® Institute, Cary, North Carolina). All tables, figures and listings will be produced in landscape format.

In general, all data will be listed by treatment arm, subject and visit/time point where appropriate. The summary tables will have columns corresponding to, or be stratified by, treatment arm. In listings and summary tables the treatment arms will be ordered and labelled as follows: Placebo, Cytisinicline 6 Weeks, Cytisinicline 12 Weeks.

The total number of subjects under the stated analysis set in each treatment arm (N) will be displayed in the header of summary tables.

Data will be summarized using descriptive statistics for continuous variables. Unless otherwise specified, descriptive statistics will include number of subjects (n), mean, standard deviation, minimum, median and maximum. In case of $n<2$, where n indicates the number of subjects with evaluable data at the particular time point, the standard deviation will be empty. The statistic “Missing” will also be presented as the number of missing entries/subjects, if any at that visit/timepoint, and presented as a summary statistic only when non-zero. The minimum and maximum statistics will be presented to the same number of decimal places as the original data. The mean and median will be presented to one more decimal place than the original data, whereas the standard deviation will be presented to two more decimal places than the original data.

In summary tables of categorical variables, counts and percentages will be used. The count [n] indicates the actual number of subjects with a particular value of a variable or event, which should always be less than or equal to the total number of subjects with non-missing value of the variable or event [M]. Percentage will be obtained by: $\%=(n/M) \times 100$. Unless otherwise stated, all percentages will be expressed to one decimal place.

In by-visit summary tables only scheduled visits/timepoints will be summarized. In listings all visits and timepoints with any data collected, including both scheduled and unscheduled ones, will be included.

All dates in tables, figures and listings will be displayed in YYYY-MM-DD format.

All outputs will be sent to Achieve as electronic files in RTF format documents. In addition, RTFs for similar outputs (eg, tables, figures, listings) will be concatenated, output to bookmarked PDF files, and sent to Achieve.

6.3. Definition of Analysis Timepoints

- **Baseline:** The last non-missing observation (including unscheduled visits) prior to the first dose of study drug (cytisinicline and/or placebo), unless otherwise specified. The last non-missing observation prior to the first dose of study drug (cytisinicline and/or placebo), unless for randomized subjects who do not receive study drug then baseline is defined prior to date of randomization. If both a planned assessment and repeat assessment (eg, retest) meet the above criteria and were collected on the same date and time, the repeat assessment will be used as baseline.
- **Change from Baseline:** The change from baseline values will be derived for each subject as the post-baseline value minus the baseline value.
- **End of Treatment (EOT) Visit:** The last clinic visit during the treatment period. Expected to occur at Week 12 (Day 86/EOT visit) for subjects who complete the 12-week treatment period. Subjects who discontinue treatment prior to 12 weeks will have the EOT visit when treatment is discontinued. (See Section 4.2.1.4.)
- **Pre-treatment Period:** Prior to first dose of study drug on Day 1.
- **Treatment Period:** The treatment period is expected to be 84 days (12 weeks) in duration. For an individual subject, the treatment period starts on the date of the first dose of study drug (Day 1), continues through the date of the last dose of study drug, and ends on the date of the Week 12 (Day 86/EOT) visit.
- **Follow-up Period:** The follow-up period is expected to be 12 weeks in duration, and includes the monthly visits at Week 16, Week 20, and Week 24.
- **Study Day:** Study day will be calculated for all assessment dates relative to the first dose of study drug (cytisinicline and/or placebo). The first dose of study drug will be Day 1, and the date preceding Day 1 will be Day –1 which is consistent with the Submission Data Standards (Version 3.1) from Clinical Data Interchange Standards Consortium (CDISC).

6.4. Data Handling Rules

Dropouts (ICH E3/11.4.2.2) will not be replaced during the study, but will be included in the data analysis to the extent that evaluable data are present.

For qualitative parameters, a category with the number of subjects with missing values will be presented where applicable.

6.4.1. Missing Dates

Partial or missing dates will be imputed only if a date is required to derive a study endpoint (eg, time to failure, duration of AE) or a variable used in study analyses. Otherwise no date imputation will be done. Date imputation will follow the rules below.

Efficacy Related Dates

Partial or missing dates required to compute efficacy endpoints will be imputed as follows:

- Missing day only: For partial dates with only the day of the month missing, the day will be imputed as the 15th day of the month, provided that a preceding date of interest does not occur in the same month. If the preceding date does occur in the same month, then the missing day will be imputed as half the distance between the preceding date and the end of the month. For example, if the Week 2 visit occurs on the 15th day and Week 3 day was missing, Week 3 day could not be day 15, it would be day 22.
- Missing month and day: For partial dates with the month and day missing, the month and day will be imputed as July 1st, provided that a preceding date of interest does not occur in the same year. If the preceding date occurs in the same year, then the month and day will be imputed as half the distance from the preceding date to the end of the known year.
- Missing month, day, and year: Missing dates will be imputed as the date of first dose.
- In situations where the above rules result in an illogical time (eg, negative study day, negative time to failure, etc) the date will be imputed as the date half the distance between the preceding date of interest and the partial date.

Safety Related Dates

For medications occurring prior to first dose of study drug. Missing or partial date will not be imputed. For safety data besides medications where the date of onset is during or after administration of the first dose of study drug, missing or partial start dates will be imputed as the earliest possible date that is on or after the date of the first dose of study drug. For events occurring prior to first dose of study drug, missing or partial dates will not be imputed.

- Missing day only: If the start date and date of first dose share the same month and year, the missing start day will be imputed as the day of first dose. If the start date month is after the month of first dose, day will be imputed as the 1st (ie, 01-Jan-2019).
- Missing month only: If the start date and date of first dose share the same year, month will be imputed as the month of the first dose. If the start date year is after the year of the first dose, the month will be imputed as Jan.
- Missing month and day: If the start date and date of first dose share the same year, day and month will be imputed as the day and month of first dose. If the start date year is after the year of first dose, the month and day will be imputed as January 1st (ie, 01-Jan-2019).

- Missing month, day, and year: Missing start dates will be imputed as the date of first dose.
- For partial end dates: Missing month and day: if year matches the year of the last date of study (date of last contact if subject lost to follow-up; date of completion or early termination), then impute as the month and day of the last date of the study, otherwise assign 31-December.
- Missing month only: if year matches the year of the last date in the study (date of last contact if subject lost to follow-up; date of completion or early termination), then impute as the month of the last date of the study, otherwise assigned December.
- Missing day only: if the month and year match the month and year of the last date of study, then impute as the day of the last date of the study; otherwise assign the last day of the month.

6.4.2. Questionnaire Scoring

This section describes scoring for the questionnaires that will be used in the study. No imputation will be done for missing item responses on the questionnaires. Total scores will only be computed if there are no missing item scores.

Fagerstrom Test of Nicotine Dependence (FTND)

The FTND is a 6-item multiple-choice questionnaire (see Appendix 2 of the study protocol). It will be administered at SV1. An FTND total score will be derived for each subject providing all questions have been answered, using the scoring key that follows:

Item #	Item Text	Item Response	Item Score
1	How soon after you wake up do you smoke your first cigarette?	Within 5 minutes	3
		6–30 minutes	2
		31–60 minutes	1
		After 60 minutes	0
2	Do you find it difficult to refrain from smoking in places where it is forbidden (eg, in church, at the library, in the cinema, etc.)?	Yes	1
		No	0
3	Which cigarette would you hate most to give up?	The first one in the morning	1
		All others	0
4	How many cigarettes/day do you smoke?	10 or less	0
		11 – 20	1
		21 – 30	2
		31 or more	3
5	Do you smoke more frequently during the first hours after waking than during the rest of the day?	Yes	1
		No	0
6	Do you smoke if you are so ill that you are in bed most of the day?	Yes	1
		No	0

Smoking Self-efficacy Questionnaire (SEQ-12)

The SEQ-12 is a 12-item questionnaire that will be administered at the Day 0 visit. Item scores will be assigned using the scoring key pre-printed on the questionnaire (see Appendix 3 of the study protocol). Three scores will be derived for each subject providing there are no missing questions: SEQ-12 internal stimuli score (items 1-6), external stimuli score (items 7-12) and a total score (items 1-12).

Hospital Anxiety and Depression (HADS)

The HADS questionnaire will be administered at SV1, Week 6 and Week 12. Item scores will be assigned using the scoring key pre-printed on the questionnaire (see Appendix 6 of the study protocol). Providing there are no missing questions, total scores for depression and anxiety and overall will be derived for each subject.

Brief Questionnaire of Smoking Urges (QSU-Brief)

The QSU-Brief is a 10-item questionnaire that will be administered Day 0, and at various visits during the treatment period (Day 2, Week 1 through Week 6). Item scores will be assigned using the scoring key pre-printed on the questionnaire (see Appendix 4 of the study protocol). A total QSU-Brief score will be derived for each subject, providing all questions have been answered.

Minnesota Withdrawal Scale (MNWS)

The MNWS is a 9-item questionnaire that will be administered at Day 0, and at various visits during the treatment period (Week 1 through Week 7). Item scores will be assigned using the scoring key pre-printed on the questionnaire (see Appendix 5 of the study protocol). A total MNWS score will be derived for each subject, providing all questions have been answered.

Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS (see Appendix 1 of the study protocol) is an assessment of both suicidal ideation and behavior. Suicidal ideation or risk for suicide ("Yes" to either question 4 or question 5 OR "Yes" to any suicidal behavior question on the C-SSRS) is an exclusion criterion.

The "Screening" version of the C-SSRS assesses suicidal ideation over the past 3 months, and suicidal behavior over the subject's lifetime. The "Screening" version of the C-SSRS will be administered at SV1. The "Since Last Visit" version of the C-SSRS evaluates both suicidal ideation and behavior since the last assessment. This version of the C-SSRS will be administered at Week 6 and Week 12.

C-SSRS Suicidal Ideation: In both the "Screening" and "Since Last Visit" forms, there are 5 items that assess suicidal ideation. Subjects indicate (Yes/No) whether each of the following applies:

1. Wish to be dead
2. Non-specific active suicidal thoughts
3. Active suicidal ideation with any methods, without intent to act
4. Active suicidal ideation with some intent to act, without specific plan

5. Active suicidal ideation with specific plan and intent.

Each item will be assigned a numeric score (0=No, 1=Yes).

C-SSRS Suicidal Behavior: In both the "Screening" and "Since Last Visit" forms, there are 5 items that assess suicidal behavior. Subjects indicate (Yes/No) whether each of the following applies:

1. Actual attempt (non-fatal)
2. Interrupted attempt
3. Aborted attempt
4. Preparatory acts or behavior
5. Suicidal behavior

Each item will be assigned a numeric score (0=No, 1=Yes).

6.5. Analysis Sets

Three analysis sets will be used.

Screening Set: all subjects who give written informed consent and enter screening. The Screening Set consists of two mutually exclusive subgroups:

- subjects who were not randomized at completion of screening, generally due to failure of one or more of the study entry criteria (ie, the inclusion/exclusion criteria) and
- subjects who were randomized at completion of screening

All Randomized Set: all randomized subjects. Subjects will be evaluated by their randomized treatment arm ('intent-to-treat' analysis) unless otherwise specified. The All Randomized Set will be the primary set for efficacy analyses.

Safety Set: all randomized subjects who take at least one dose of study drug. Subjects will be evaluated by their randomized treatment arm ('intent-to-treat' analysis) unless otherwise specified. The Safety Set will be the primary set for safety summaries. Safety summaries may also be provided based on the treatment actually received.

Achieve will approve the list of subjects to be excluded from the Safety Set after database lock. Achieve must approve this list before any analysis is to be performed.

7. SUBJECT DISPOSITION

The number of subjects who were screened, screen failures, randomized and treated will be summarized overall for the Screening Set. The reason for failing screening will also be summarized.

The number of subjects who were screened, randomized, treated, completed or withdrew from study, as well as the number of subjects in each analysis set will be summarized for each treatment arm. In addition, the number of subjects randomized and treated will be summarized by investigational site for each treatment arm.

For subjects who did not complete the study, the reasons for withdrawal (eg, adverse event, withdrawal by subject, lost to follow-up) will be summarized for each treatment arm. The list of subjects who withdrew from the study will be reported, along with the reason for withdrawal.

For the Safety Set the number of subject randomized, treated, completed, or withdrew from the study as well as the number of subject tin each analysis set will be summarized for each treatment arm. For subjects who did not complete the study, the reasons for withdrawal (eg, adverse event, withdrawal by subject, lost to follow-up) will be summarized for each treatment arm. The list of subjects who withdrew from the study will be reported, along with the reason for withdrawal. In addition, the number of subjects randomized and treated will be summarized by investigational site for each treatment arm.

A listing will be provided of subjects who were excluded from either the All Randomized Set or the Safety Set. The listing will include the reason for exclusion.

Attendance at each study visit will be reported with the number and percentage of subjects who attended each visit (ie, Screening #1, Screening #2, Day 0 (randomization), Day 1 (treatment start), etc). Similarly, the last study visit attended will be reported with the number and percentage of subjects having their last study visit at Week 24, Week 20, etc.

The number and percentage of subjects who completed the treatment period, and enter the follow-up period (ie, attended the Week 16 or Week 20 or Week 24 visit) will be reported.

A Kaplan-Meier figure will be produced by treatment arm of time to last recorded data related to the abstinence endpoints (ie, time from date of randomization to date of last smoking cessation data recorded at or prior to the Week 24 visit). If a subject is randomized and not treated (no visits after Day 0) then time from randomization to last recorded data would be 0 days. The date of the last smoking assessment data will be the date of the last self-report of cigarette smoking since the last clinic visit (yes, no), self-report of cigarette smoking over the past 7 days (yes, no) or expired CO levels.

7.1. Protocol Deviations

Protocol deviations will be reported as outlined in the ACH-CYT-04 Monitoring Plan and documented in the CRF. Each deviation will be classified as either “major” or “minor”. Major deviations are defined in the monitoring plan as those requiring direct/immediate escalation to the Sponsor/Medical Monitor in order to determine if the deviation could affect study results or the subject’s study participation. These include deviations in the following categories:

- Inadequate informed consent procedures,
- Violations of inclusion/exclusion criteria,
- Errors in randomization/stratification,
- Errors in study drug administration such that the planned and actual treatment are discrepant (eg, subject assigned to Arm A [placebo] receiving treatment prescribed for Arm B [cytisinicline 6 weeks]),
- Missing results from screening assessments used for determining subject eligibility.

The number and percentage of subjects with at least one deviation (major or minor) and with at least one major deviation will be summarized by treatment arm. For major deviations, the number and percentage of subjects with each type of deviation (eg, informed consent, inclusion/exclusion violation, etc) will be summarized by treatment arm.

8. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic and other baseline characteristics will be listed and summarized.

8.1. Demographics

Demographic data (gender, age informed consent, race, ethnicity, body weight, height, and BMI) will be summarized for each of the subgroups (Randomized, Not Randomized) in the Screening Set, and overall.

Demographic data will also be summarized by treatment arm and overall for both the All Randomized Set and the Safety Set.

8.2. Medical and Psychiatric History

A medical and psychiatric history summary will be provided for both the All Randomized Set and the Safety Set. The number and percentage of subjects with events will be summarized for each treatment arm by MedDRA SOC and preferred term. Multiple occurrences of the same event within a subject will be counted only once.

Medical and psychiatric history conditions will be coded using MedDRA version 23.1.

8.3. Prior Medications

Concomitant medications will be recorded beginning at the Screening #1 (SV1) visit. Prior medications will be defined as medications with a stop date prior to the first dose of study drug. For medications with partial dates, these will be imputed as specified in Section 6.4.1; safety related dates. Prior medications will be summarized for both the All Randomized Set and the Safety Set. The number and percentage of subjects with each prior medication will be summarized for each treatment arm by highest available Anatomical Therapeutic Chemical (ATC) class and preferred name. Multiple occurrences of the same medication within a subject will be counted only once.

Prior medications will be coded using WHO Drug Dictionary March 2021.

8.4. Smoking History

Smoking history will be summarized for both the All Randomized Set and the Safety Set.

At SV1 the following subject-reported smoking history variables will be summarized by treatment arm.

- Duration of smoking (years) – started smoking date minus the screening 1 visit date.
- Average number of cigarettes the subject reported smoking per day over the past 30 days

- Type of cigarettes typically smoked (regular vs menthol)
- Number (%) of subjects who attempted to quit in the past
- Number of previous quit attempts
- Time from last quit attempt to date of SV1 visit (months) – screening 1 visit date minus date of last quit attempt. If month of last quit attempt date is unknown use December of that year, unless the quit date year is the same year as the screening 1 visit date then December of the previous year would be used.

In addition, the number (%) of subjects reporting past use of various smoking cessation treatments will be summarized separately for the most recent quit attempt and all quit attempts. For each of these summaries, multiple occurrences of the same treatment within a subject will be counted only once.

8.5. Baseline Smoking and Nicotine Testing

The following baseline data related to smoking will be summarized by treatment arm for both the All Randomized Set and the Safety Set:

- Average number of cigarettes smoked per day over 7 consecutive days, as reported in the subject diary
- Expired CO (ppm) at SV1
- Expired CO (ppm) at Day 0
- Cotinine result (ng/mL) at SV1.

If nicotine metabolism ratio (NMR) testing is done at SV1 then NMR will be derived as the ratio of the results for 3-hydroxycotinine (3-OH cotinine) and cotinine (ie, 3-OH cotinine / cotinine) and summarized by treatment arm.

8.6. Baseline Questionnaires

Questionnaire scores will be derived as described in Section 6.4.2.

The following will be summarized at baseline by treatment arm for both the All Randomized Set and the Safety Set:

- FTND: total score
- HADS: total score, anxiety score, depression score
- SEQ-12: internal stimuli score, external stimuli score, and total score.
- QSU-Brief: total score
- MNWS: total score.

8.7. Other Baseline Characteristics

Vital signs (body temperature, heart rate, and systolic and diastolic blood pressure) will be assessed at two timepoints prior to randomization: SV1 and Day 0. Baseline vital signs will be summarized by treatment arm for both the All Randomized Set and the Safety Set.

Serum chemistry and hematology testing will be performed at SV1. Baseline laboratory test results will be summarized by treatment arm for both the All Randomized Set and the Safety Set. Separate summaries will be provided for hematology tests (hemoglobin, red blood cells, white blood cells, neutrophils, lymphocytes, monocytes, eosinophils, basophils and platelets), serum chemistry tests (total protein, albumin, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, glucose, sodium, potassium, calcium, creatinine and urea) and creatinine-clearance.

Urine pregnancy testing will be performed for all female subjects at SV1 and Day 0. Test results will be summarized by treatment arm and visit for all females in both the All Randomized Set and the Safety Set.

A 12-lead ECG will be performed at SV1. Baseline ECG findings (normal, abnormal – not clinically significant, abnormal – clinically significant) will be summarized by treatment arm for both the All Randomized Set and the Safety Set.

9. EXPOSURE TO STUDY TREATMENT

Study treatment consists of administration of study drug in combination with behavioral support.

9.1. Duration of Study Drug Treatment

The time (days) from randomization to first dose of study drug will be derived and summarized by treatment arm for the Safety Set.

Duration of study drug treatment (days) will be calculated as date of last dose of study drug minus date of first dose of study drug +1. Duration of study drug treatment will be summarized by treatment arm for the Safety Set. The number (%) of subjects who had duration of 84 days will also be summarized by treatment arm.

9.2. Study Drug Compliance

All subjects are planned to receive 3 doses of study drug each day for 84 days, for a total of 252 prescribed doses. If there are subjects that inadvertently enter in their patient diary taking more than the 252 prescribed doses, for the analysis 252 doses will be used. Per protocol, on a case-by-case basis, the study treatment may be reduced to twice a day. These dose reductions will only be allowed for subjects who experience moderate or severe adverse events that might be attributed to study drug and who would otherwise discontinue study treatment due to the adverse event. For subjects with a dose reduction, # doses prescribed is based on the number of days with 3 doses prescribed as well as the number days with 2 doses prescribed.

Each dose contains study drug (3 mg cytisinicline or placebo) in a single tablet.

For each dosing day (Day 1 to Day 84) subjects will record a diary entry for each dose: whether the dose was taken by the subject or missed and, for doses taken, the date and time of each dose.

The following variables will be calculated for each subject from the diary data and summarized by treatment arm for the Safety Set:

- total number of doses taken by the subject,
- total number of doses that were not taken (ie, missed)
- percentage of doses missed: (#doses missed / # doses prescribed) × 100
- study drug compliance: [(# doses taken) / # doses prescribed] × 100
- total dose of cytisinicline, calculated as number of cytisinicline taken × 3 mg per dose
- Number and percentage of subjects with a dose reduction

Compliance with study drug will be summarized both as a continuous variable and as a categorical variable (<80%, 80-<90%, 90-<100%, 100%).

In addition to summary tables, details of study drug compliance will be listed. The listing will include the total dose of study drug (mg), total number of doses taken by the subject, total number of doses missed, percentage of doses missed, and percentage of doses taken (ie, compliance with study drug).

9.3. Behavioral Support Compliance

Twelve (12) behavioral support sessions are planned during the treatment period, Week 1 to Week 12 visits. Additional behavioral support will be provided during the follow-up period based on issues/concerns/questions raised by the subject.

The total number of behavioral support sessions received during the treatment period will be calculated for each subject and summarized by treatment arm for the Safety Set. Summaries will also be provided for compliance with behavioral support, derived as:

- [(# behavioral support sessions received) / (12)] × 100.

10. EFFICACY ANALYSIS

The efficacy analyses will be conducted using subjects in the All Randomized Set. Unless otherwise specified, all randomized subjects will be included in efficacy analyses. Subjects will be evaluated by their randomized treatment arm (‘intent-to-treat’ analysis).

For qualitative endpoints, summary tables will present the number and percentage of subjects for each class of the endpoint. Quantitative endpoints will be summarized by presenting the mean, SD, minimum, median and maximum values. All summary statistics will be presented by treatment arm.

10.1. Analyses of Primary and Secondary Efficacy Endpoints

10.1.1. General Considerations

In general, the implementation of familywise error protection for a family of comparisons is most logically implemented using one-sided hypothesis testing because the tests must be interchangeable with respect to the goal of the research. The P values reported by statistical programs, unless otherwise indicated, will always be two-sided. A two-sided P value associated with a one-sided hypothesis is converted to a one-sided P-value for that hypothesis as follows: Let P be the two-sided P value. If the estimate associated with the hypothesis is consistent with the one-sided alternative hypothesis the one-sided P value is P/2, otherwise the one-sided P value is 1 – P/2. Unless otherwise stipulated, one-sided P values will be used only to execute the Hochberg procedures for passing statistical criterion.

The overall Type I error probability for the trial is specified to be one-sided 0.025 (overall one-sided alpha). The primary objective has two endpoints therefore the interpretation of these analyses must protect the overall one-sided alpha of 0.025. The primary objective analyses will provide two one-sided P values. Assessing whether the primary objective meets statistical criterion will be implemented using the Hochberg procedure as follows. If neither one-sided P values are ≤0.025 then the primary objective will have failed to meet statistical criterion, whereas if both one-sided P values are ≤0.025 then both null hypotheses can be rejected and the primary objective will have met statistical criterion. If one of the one-sided P values is >0.025 then in order for the primary objective to meet statistical criterion the other one-sided P value must be ≤0.0125 (=0.025/2).

Secondary objectives will be analyzed only if a statistical criterion for the primary objective is met. Specifically, the amount of alpha passed to the secondary objectives will depend on the one-sided P values associated with the primary analyses (See FDA Guidance: Multiple Endpoints in Clinical Trials). There are three possibilities: (1) If the primary objective statistical criterion is not met then no alpha is left for the secondary analysis and the associated analyses of those endpoints cannot be associated with specified significance testing. (2) If both one-sided P values are ≤0.025 the amount of alpha passed to the secondary analyses is 0.025. (3) If one of the one-sided P values is >0.025 and the other is ≤0.0125 then the amount of alpha is based on the Hochberg procedures having been truncated and the amount of alpha that can be passed to the secondary analyses is 0.0125. (Note on truncated Hochberg when there are two hypotheses, the alpha to be passed is invariant to the fraction specification to be used in the computing of the alpha passed per FDA Guidance).

If case (2) happens (both primary comparisons are successful) then the Hochberg procedure based on one-sided 0.025 as described above can be used for secondary endpoints 1 and 2. Secondary endpoint 3 can be analyzed with multiplicity protection only if both secondary endpoints 1 and 2 are successful, and can be analyzed using one-sided significance level 0.025.

If case (3) happens (only one of the primary comparisons is successful) then the corresponding secondary endpoint can be analyzed using significance level one-sided 0.0125, and secondary endpoint 3 cannot be analyzed with multiplicity protection.

10.1.2. Primary Efficacy Analysis

The primary efficacy endpoint (abstinence) is described in Section 4.1.1. Two primary objectives are described in Section 3.1. Two between-arm comparisons are planned, corresponding to the two objectives:

- Abstinence from Week 3 to Week 6: Arm B (cytisinicline 6 weeks) vs Arm A (placebo)
- Abstinence from Week 9 to Week 12: Arm C (cytisinicline 12 weeks) vs Arm A (placebo)

The abstinence endpoint is binary (success, failure). For each of the comparisons listed above, the two treatment arms will be compared in terms of the proportion of subjects classified as a success. All randomized subjects will be included in the comparisons according to their randomized arm (ITT analysis).

The statistical significance of each comparisons will be based on the odds ratio using exact computations for stratified 2×2 frequency tables and using Monte Carlo estimation if necessary. The stratifier will be clinical site, with the possibility of pooling clinical sites having a small contribution, as described below. If cytisinicline is not favored by the effect size point estimate, then the comparison will be designated as not statistically significant.

The estimated common odds ratio and its exact confidence interval (CI) will be reported. Also, the estimated odds ratio and exact (midp) confidence interval for the marginal 2x2 table across sites (unadjusted odds ratio), and the estimated difference in proportions and the associated derived exact confidence interval using the exact confidence interval on the odds ratio will be reported. The exact difference in proportion confidence interval will be derived using the method of Thomas (1971 and 1977).[2, 3]

Following is template SAS code for performing each of the statistical comparisons using SAS PROC FREQ:

```
proc freq data=data;
  exact fisher or comor eqor;
  table s*x*y / nopercent nocol;
run;
```

Where
s: site designator (with the possibility of pooling)
x: Two-level arm designator with x=0 for control arm and x=1 for experimental arm.
y: Indicator of success(y=1) or nonsuccess (y=0).
The coding of x and y assures that an estimated odd ratio >1 indicates favorable outcome for experimental arm.

The output from SAS PROC FREQ for the above template will have three tables of interest for assessing success of the comparison, with the following steps to be used to extract relevant items and assess whether the statistical criterion has been met:

1. Table “Tests for Homogeneity of the Odds Ratios”: The P value preferred for the test of homogeneity is “Exact Pr <=P” (Zelen exact test). If the Zelen exact test is not computable (it is known to be susceptible to memory exhaustion), then use the Breslow-Day P value indicated as "Pr > Chisq".
2. Table “Common Odds Ratio”: Extract from this table the “Mantel-Haenszel Estimate” of the odds ratio and the “Exact Conf Limits” of this odds ratio estimate.
3. Table “Exact Test of H0: Common Odds Ratio=1”: Extract “One-Sided Pr>=S” as the one-sided P value for the between-arm comparison. If this one-sided P value is less than or equal to the applicable one-sided favorable direction significance level specified above then statistical criterion for the between-arm comparison will have been met, and not met otherwise. Report whether significance has been met and the two-sided P value “Sum<=Point.” The two-sided P value is to be reported because it is conventional (and less confusing). Reporting the one-sided P value is optional but not recommended; if reported it requires an explicit labeling as one-sided.

If the number of subjects within a stratum (clinical site) is small, then clinical sites stratification may require pooling to create a pseudo-site. The criterion for pooling will be to pool clinical sites with fewer than 2 subjects in any treatment arm. The pseudo site will represent the effect of sites with relatively small contribution. For purposes of statistical analysis, a unique site identification number will be assigned to the pseudo-site; the original clinical site identification number will be used for the remaining sites (ie, sites that did not meet the criterion for pooling). If no clinical sites meet the criterion for pooling, the original clinical site identification number will be used in the statistical analysis.

10.1.2.1. Sensitivity Analyses

The sensitivity analyses described in this section will be performed separately for each of the primary efficacy endpoints (abstinence from Week 3 to Week 6, abstinence from Week 9 to Week 12). Sensitivity analyses for each endpoint will include the treatment arms of interest for that endpoint. That is, the sensitivity analyses for the abstinence from Week 3 to Week 6 endpoint will include the cytisinicline 6 weeks (Arm B) and placebo (Arm A) treatment arms and the analyses for the abstinence from Week 9 to Week 12 endpoint will include the cytisinicline 12 weeks (Arm C) and placebo (Arm A) treatment arms.

When there is evidence of material non-homogeneity of odds ratio across clinical sites then the interpretation of the results will be evaluated for each clinical site. The results of each clinical site can be assessed using Fisher’s exact test for the 2x2 table specific to that site, including the site specific odds ratio estimate and its confidence interval. The above code template for Fisher’s exact test and odds ratio confidence interval is modified as follows: delete “comor eqor” in the exact statement. This modification will produce a separate 2x2 table analysis for each site. Extract odds ratio confidence interval for each table from the “Confidence Limits for the Odds Ratio” table. Note: The assessment of the degree of variability of the site-specific odds ratio

estimates is also specified as a planned sensitivity analysis and is somewhat informative even if the interaction is not material.

The analyses described below as Effect Modification Analyses and Tipping Point Analyses will be conducted by an independent statistician (Brent A. Blumenstein, PhD; TriArc Consulting) who will document the results of these analyses in a statistical report that will be included as an appendix to the clinical study report.

Effect Modification Analyses (EMA)

The goal of the EMA will be to evaluate the degree to which arm effects estimated for discrete values of a baseline attribute differ. For example, an EMA of sex estimates sex-specific arm effects and evaluates whether these estimates differ. If a baseline attribute to be evaluated using EMA is not discrete, the attribute is made discrete by specifying cutpoints based on external criteria or using percentiles computed from the pooled data (median, tertiles, or quartiles), for example, baseline CO split at below 10 or not, or using pooled quartile values.

For each of the primary efficacy endpoints, the relationship between treatment arm and the proportion of subjects with abstinence will be evaluated within stratum defined by the effect modifier. Evidence of effect modification will be indicated by a material interaction between the baseline attribute and arm, with the criterion for a material interaction set at ≤0.10. The interaction P value is a measure of the contribution to the statistical model of the interaction, and will be reported. For each stratum, the number (%) of subjects within each stratum with abstinence will be reported for each treatment arm. Odds ratios and their 95% CIs will also be reported. Forest plots will be used to display the stratum-specific 95% CIs.

Tipping Point Analyses

A tipping point analysis[4] will be performed for each of the primary efficacy endpoints, including sensitivity analyses if applicable.

The goal of each tipping point analysis will be to assess the degree to which the assignment of cases defined as failure due to inability to assess for success would influence results. The tipping point evaluation will re-analyze the data for all possible reversals of the failure assignment to a success, and present the results in a graph.

10.1.3. Secondary Efficacy Analysis

The three secondary efficacy objectives are stated in Section 3.2. The secondary efficacy endpoints (continuous abstinence, risk of relapse [relapse free]) are described in Section 4.1.2.

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

Two between-arm comparisons are planned for secondary objectives 1 and 2:

- Continuous abstinence from Week 6 to Week 24: Arm B (cytisinicline 6 weeks) vs Arm A (placebo)
- Continuous abstinence from Week 12 to Week 24: Arm C (cytisinicline 12 weeks) vs Arm A (placebo)

Each continuous abstinence endpoint is binary (success, failure). Note: For the secondary analyses, smoking abstinence during the follow up period only (Week 16 to Week 24) followed the Russell Standard of allowing up to 5 cigarettes and still be regarded as abstinent/success. Each analysis will then compare the treatment arms in terms of the proportion of subjects classified as a success using the same statistical methods as described above for the primary endpoint.

The analysis for secondary objective 3 will be conditional and performed only if both primary comparisons 1 and 2 pass statistical criterion. One between-arm comparison is planned for secondary objective 3.

- Reduction in Relapse from Week 6 to Week 24: Arm C (cytisinicline 12 weeks) vs Arm B (cytisinicline 6 weeks)

This endpoint is binary (relapsed, without relapse). The treatment arms will be compared in terms of the proportion of subjects without relapse (relapse-free) using the same statistical methods as described above for the primary endpoint.

10.2. Analyses of Other Efficacy Endpoints

The other efficacy objectives are stated in Section 3.3. The other efficacy endpoints are defined in Section 4.1.3. Analyses of the other efficacy endpoints will be exploratory. There will be no multiplicity protection scheme for these analyses, and the results of these analyses will be labeled as exploratory.

The results for each endpoint will be displayed graphically by treatment arm. Side-by-side bar charts may be used to display categorical endpoints, Kaplan-Meier figures will be used for time-to-event endpoints. For binary endpoints, forest plots may be used to display 95% CIs for the odds ratio.

For each of the other efficacy endpoints identified below, 3 between arm comparisons will be performed, where appropriate:

- Arm B (cytisinicline 6 weeks) vs Arm A (placebo)
- Arm C (cytisinicline 12 weeks) vs Arm A (placebo)
- Arm C (cytisinicline 12 weeks) vs Arm B (cytisinicline 6 weeks) (this comparison will be two-sided)

The statistical analyses that will be performed for binary endpoints will follow the specification as described for the secondary objectives according to whether the comparison is one-or two-sided. For other than binary endpoints, the analysis methodologies are described below.

10.2.1. 7-day Point Prevalence Abstinence

The 7-day point prevalence abstinence endpoints are binary (success, failure) endpoints defined at each of the following visits: Weeks 2 to Week 12, Week 16, Week 20, and Week 24. The analyses of point prevalence abstinence endpoints will be conducted using all subjects in the All Randomized Set. The analysis methodology for binary endpoints was described in secondary objectives.

10.2.2. Serum Cotinine Levels

Serum cotinine levels will be measured every other week from Week 2 to Week 12, then at Week 16, Week 20, and Week 24.

Serum cotinine levels may be reported by the central laboratory as less than the lower limit of quantitation (eg, result reported as "<10 ng/mL") or greater than the upper limit of quantitation (eg, result reported as ">2000 ng/mL"). Results reported as "<X" will be converted to a numeric result of "X – 1" prior to statistical analysis (eg, <10 ng/mL will be converted to 9 ng/mL). Results reported as ">X" will be converted to a numeric result of "X+1" prior to statistical analysis (eg, >2000 ng/mL will be converted to 2001 ng/mL).

Summary tables and figures of serum cotinine levels by treatment arm and visit will be provided for the All Randomized Set.

The treatment arms will be compared (cytisinicline 6 weeks vs placebo, cytisinicline 12 weeks vs placebo) using repeated-measures analysis of variance models with fixed effect term for treatment arm, visit and visit * treatment arm interaction. A compound symmetry covariance matrix will be used. The between-arm difference in means, their respective 95% CIs and Bonferroni-adjusted p-values will be reported. Forest plots may be used to display 95% CIs for the differences of the means.

10.2.3. Expired CO Levels

Expired CO levels (ppm) will be measured every week from Week 2 to Week 12, then at Week 16, Week 20, and Week 24.

Summary tables and figures of expired CO levels by treatment arm and visit will be provided for the All Randomized Set.

The treatment arms will be compared (cytisinicline 6 weeks vs placebo, cytisinicline 12 weeks vs placebo) using repeated-measures analysis of variance models with fixed effect term for treatment arm, visit and visit * treatment arm interaction. A compound symmetry covariance matrix will be used. The between-arm difference in means, their respective 95% CIs and Bonferroni-adjusted p-values will be reported. Forest plots may be used to display 95% CIs for the differences of the means.

An additional analyses will be performed by abstinence status for the primary endpoint (Weeks 3 – 6 and Weeks 9 -12).

10.2.4. Use of Non-cigarette Nicotine Products

At each study visit from Week 2 through Week 24, subjects will be asked whether they have used (yes, no) any non-cigarette nicotine products since the previous clinic visit. The name of any product used during the interval will be recorded in the CRF (eg, pipe tobacco, smokeless tobacco, e-cigarettes/vaping).

The number (%) of subjects reporting use of non-cigarette nicotine product will be summarized by treatment arm and visit for the All Randomized Set. The summary table will report both the number (%) of subjects using any non-cigarette nicotine product and the number (%) of subjects using each specific product. The summary table will include visits from Week 2 to Week 24, as well as the following study periods: Week 2 to Week 24 (Entire Study Period), Week 2 to

Week 12 (Treatment Period), and Week 16 to Week 24 (Follow-up Period). For the summary by study periods, multiple occurrences of the same nicotine product within a subject will be counted only once.

Statistical comparisons between treatment arms (Arm B vs Arm A; Arm C vs Arm A) will be performed for the Treatment Period and the Follow-up Period. For each period, Fisher's Exact Tests will be used to compare treatment arms in terms of the incidence of using any non-cigarette nicotine products.

10.2.5. Abstinence from Week 9 to Week 12: Arm B vs. Arm A

The statistical methods for this binary endpoint will follow the specifications as described for the secondary objectives.

10.2.6. Continuous Abstinence from Week 3 to Week 24 (Subset Analysis)

The summaries and statistical analyses of the continuous abstinence from Week 3 to Week 24 binary endpoint will include the subset of subjects who achieve abstinence from Week 3 to Week 6 (ie, subset of subjects who are a success on the primary efficacy endpoint for primary objective 1) and have continuous abstinence to Week 24. The statistical methods for binary endpoints will follow the specifications as described for the secondary objectives.

10.2.7. Continuous Abstinence from Week 9 to Week 24 (Subset Analysis)

The summaries and statistical analyses of the continuous abstinence from Week 9 to Week 24 binary endpoint will include the subset of subjects who achieve abstinence from Week 9 to Week 12 (ie, subset of subjects who are a success on the primary efficacy endpoint for primary objective 2) and have continuous abstinence to Week 24. The statistical methods for binary endpoints will follow the specifications as described for the secondary objectives.

10.2.8. Time to Failure to Maintain Abstinence

Time to failure to maintain abstinence will be evaluated for the subset of subjects who were classified as a success for abstinence from Week 3 to Week 6. Time to failure (days) will be calculated for individual subjects as described in Section 4.1.3. Subjects who are still abstinent at Week 24 will have time to failure censored at the date of the Week 24 visit.

Time to failure will be summarized by treatment arm; the minimum, maximum, median and 95% confidence interval for the median time to failure reported by the LIFETEST procedure will be reported. A Kaplan-Meier figure of treatment arm by time to failure will be produced.

10.2.9. Relationship Between Treatment Effect and Demographic and Baseline Characteristics

The analyses described below will only be performed for the primary efficacy endpoint (biochemically verified abstinence). The objective of these analyses is to assess the homogeneity of treatment effect within strata (subgroups) defined by potential effect-modifying variables. If both primary comparisons (Arm B vs Arm A, Arm C vs Arm A) performed for the primary efficacy endpoint do not meet statistical criterion (ie, are not statistically significant) then the statistical analyses described below will not be performed. If only one of the comparisons meets

statistical criterion then the analyses described below will be performed using data from only two of the treatment arms.

Strata for continuous effect modifiers will be defined by either logical considerations (eg, age >65 years) or statistical criteria (eg, quantile (median, tertile or quartile) split). The variables (factors) that will be evaluated as effect modifiers include, but are not limited to:

- demographic characteristics (eg, sex, age, race, BMI),
- smoking history variables (eg, duration of smoking, average number of cigarettes the subject reported smoking per day over the past 30 days, number of previous quit attempts, type of cigarettes typically smoked: regular vs menthol, prior smoking cessation treatment with varenicline, bupropion, nicotine patch),
- baseline smoking variables (eg, average number of cigarettes smoked per day over 7 consecutive days as reported in the subject diary, baseline CO (ppm), baseline cotinine (ng/mL)),

For each stratum, the number (%) of subjects within each stratum with biochemically verified abstinence will be reported for each treatment arm. Odds ratios (Arm B vs Arm A, Arm C vs Arm A) and their 95% CIs will also be reported. Forest plots will be used to display the stratum-specific 95% CIs.

10.2.10. Relationship Between Subject-Reported Outcomes and Primary and Secondary Efficacy Endpoints

The correlation of subject-reported outcomes (eg, anxiety, withdrawal symptoms, tobacco craving) with the primary and secondary efficacy endpoints (abstinence, continuous abstinence) will be explored. Descriptive statistics for each of the subject-reported outcome variables will be produced for subgroups defined by success/failure on those endpoints.

10.2.11. Questionnaires

The HADS, QSU-Brief, and MNWS questionnaires will be administered at baseline and after the start of treatment. Scores for each questionnaire will be derived as described in Section 8.6.

Questionnaire scores will be summarized using descriptive statistics. For each score, the actual value, change from baseline and percent change from baseline will be summarized by treatment arm and visit. Only subjects with non-missing results at both the baseline and post-baseline visit will be summarized at each time point.

10.2.12. Number of Cigarettes Smoked Over Time

The number of cigarettes smoked will be collected every week from Week 2 to Week 12, then at Week 16, Week 20, and Week 24.

The treatment arms will be compared (cytisinicline 6 weeks vs placebo, cytisinicline 12 weeks vs placebo) using repeated-measures analysis of variance models with fixed effect terms for treatment arm, visit and visit * treatment arm interaction. The between-arm difference in means, their respective 95% CIs and Bonferroni-adjusted p-values will be reported. A figure for the number of cigarettes smoked by treatment arm and visit will be provided for the All Randomized Set.

An additional analyses will be performed by abstinence status for the primary endpoint (Weeks 3 – 6 and Weeks 9 -12).

10.3. Other Analyses Not Specified

Other analyses not detailed in this SAP are anticipated and will be conducted by an independent statistician (Brent A. Blumenstein, PhD; TriArc Consulting). These analyses fall into the class of being "data-directed" and will be labeled as such. Explanations of objectives, details of methodology, identification of limitations, any known/anticipated biases, and known/anticipated threats to validity will accompany each analysis. Here are examples:

- Additional sensitivity analyses that have the potential to provide alternative explanations for observed between-arm differences or lack thereof.
- Analyses of observed trial conduct anomalies and the relationship of these to understanding the observed results.
- Fitting of multiple explanatory variable models of outcomes including and especially including interactions.
- Analyses designed to explore the associations between outcomes.
- Analyses designed to explore the relationship between safety and efficacy.
- Analyses illustrating consistency across multiple outcomes measures.

11. SAFETY ANALYSIS

Safety objectives are described in Section 3.4. All safety analyses described below will be presented for each treatment arm using the Safety Set (see Section 6.5).

Safety analyses that are presented "by visit" will include a derived visit named EOT (see Section 4.2.1.4). This includes summaries of hematology and serum chemistry test results, vital signs, weight, and 12-lead ECG results.

No statistical comparisons between treatment arms are planned for safety endpoints; thus, no statistical test results will be reported.

11.1. Adverse Events

Per the study protocol all adverse events (AE) occurring during the study, whether or not attributable to study drug, will be recorded in the subject's source documents and CRF. The adverse event reporting period will start at the date of informed consent and continue through the end of the study (Week 24 visit). Treatment emergent adverse events (TEAE) are defined in Section 4.2.1.

AE severity will be assessed by the Investigator as mild, moderate or severe. The Investigator will also assess the relationship of each AE to study drug (none, unlikely, possible, probable, definite). Treatment-related AEs are defined as events the Investigator considers to be possibly, probably, or definitely related to study drug, as well as events with "unknown" relationship.

Adverse event summaries will present data for the 3 treatment arms. An overall summary of adverse events will be provided that reports, for each treatment arm, both the number (%) of events meeting a specific criterion and the number (%) of subjects with at least one event meeting that criterion during the AE reporting period. Events meeting the following specific criteria will be presented in this table:

- Any reported adverse event (ie, both pre-existing and treatment-emergent events)
- For treatment-emergent AEs:
  - Any TEAE
  - Any serious TEAE
  - Any related serious TEAE
  - TEAEs by severity (mild, moderate, severe)
  - TEAEs by relationship (none, unlikely, possible, probable, definite)
  - TEAEs by relationship (not related, related)
  - TEAEs by action taken with study drug (dose not changed, dose reduced, dose interrupted, drug withdrawn, not applicable, unknown)
  - TEAEs by outcome (Fatal, Not recovered/Not resolved, Recovered/Resolved, Recovered/Resolved with sequelae, Recovering/Resolving)

Three overall summary tables will be provided, as follows:

- all AEs during the study
- all AEs occurring after Week 6 on the study, defined as AEs with start date after the date of the Week 7 Day 1 dose.
- All AEs occurring after Week 6 of the study defined as AEs with start date after the date of the Week 7 Day 1 dose, or AEs that are ongoing (ie, not resolved) on the date of the Week 7 Day 1 dose.

Dosing dates will be obtained from subject treatment diaries.

In addition to the overall summaries described above, the following summaries of TEAEs occurring anytime during the study will be produced:

- Incidence by SOC and preferred term (PT), in alphabetical order of SOC and PT, for both all TEAE and related TEAE
- Incidence by PT, in decreasing frequency of PT, for both all TEAE and related TEAE
- Incidence of TEAEs that resulted in dose reduction or discontinuation of study drug (ie, action taken with study drug reported as dose reduced, dose interrupted, or drug withdrawn), in decreasing frequency of PT
- Incidence of TEAE by PT and severity (mild, moderate, severe), in alphabetical order of PT

- Incidence of TEAE by PT and relationship (related, not related), in alphabetical order of PT
- Incidence of TEAE by PT for events of special interest: COVID-19

The following summaries will also be produced of TEAEs occurring after Week 6 (occurring after Week 6 or ongoing after Week 6) on the study (see definitions above):

- Incidence by SOC and PT, in alphabetical order of SOC and PT
- Incidence by PT, in decreasing frequency of PT
- Incidence of TEAEs that resulted in dose reduction or discontinuation of study drug (ie, action taken with study drug reported as dose reduced, dose interrupted, or drug withdrawn), in decreasing frequency of PT

The following will also be summarized:

- Incidence of TEAEs that occurred from Week 6 (approximately Study Day 42) visit + 1 day through Week 7 visit (approximately Study Day 49) will be assessed for any possible withdrawal effects when switching to placebo during the first Week 7 timeframe for the cytisinicline 6 weeks arm.
- Incidence of TEAEs by time of onset (Up to Week 6 [approximately Study Day 42]visit and after Week 6 visit through Last Dose)
- Incidence of TEAEs by primary endpoint status

In summaries of AE incidence, if a subject experiences the same AE (preferred term) multiple times that subject will be counted only once for that preferred term. Similarly, if a subject experiences multiple AEs (preferred terms) within the same SOC then that subject will be counted only once for that SOC. When summarizing by severity and relationship, only the AE with the highest severity or relationship will be counted.

A Kaplan-Meier figure of time to first TEAE (ie, time from date of randomization to earliest TEAE start date) will be provided by treatment arm. Subjects with no Adverse events will be censored at their last visit.

In addition to summary tables, the following listings will be produced.

- All AEs
- AEs which resulted in dose reduction or discontinuation of study drug (ie, action taken with study drug reported as dose reduced, dose interrupted, or drug withdrawn)

11.1.1. Serious Adverse Events

Serious adverse events (SAEs) will be summarized by SOC and PT for each treatment arm using counts and percentages. The followings summaries of SAEs will be produced.

- Incidence by SOC and PT, in alphabetical order of SOC and PT
- Incidence by PT, in decreasing frequency of PT

In addition to summary tables, a listing of SAEs will be produced.

11.1.2. Other Adverse Events of Special Interest

Other adverse events of special interest were defined in Section 4.2.1.3 as the following events:

- treatment-emergent suicidal ideation or behavior
- treatment-emergent moderate to severe depression
- new pregnancy
- COVID-19

The number (%) of subjects with each event will be summarized by treatment arm.

11.2. Hematology and Chemistry Data

Hematology and chemistry samples will be collected at SV1, Week 1, Week 6, and at Week 12 (Day 86/EOT).

The protocol-specified hematology tests are hemoglobin, red blood cells (erythrocytes), platelets, white blood cells (leukocytes), and absolute counts for neutrophils, lymphocytes, monocytes, eosinophils and basophils. The protocol-specified serum chemistry tests are total protein, albumin, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, glucose, sodium, potassium, calcium, creatinine, creatinine clearance/glomerular filtration rate and blood urea nitrogen (BUN). Samples will be analyzed by a central laboratory. If the central laboratory does not provide results in Système International (SI) units then the designated Clinical Research Organization (CRO) will convert all laboratory results to SI units prior to analysis. The SI unit values will be derived from CDISC controlled terminology.

Hematology and serum chemistry values may be reported by the central laboratory as less than the lower limit of quantitation (eg, result reported as "<10 ng/mL") or greater than the upper limit of quantitation (eg, result reported as ">2000 ng/mL"). Results reported as "<X" will be converted to a numeric result of "X" prior to statistical analysis (eg, <10 ng/mL will be converted to 10 ng/mL). Results reported as ">X" will be converted to a numeric result of "X" prior to statistical analysis (eg, >2000 ng/mL will be converted to 2000 ng/mL). Values outside the upper and lower limits of quantitation will be presented as collected (eg "<10 ng/mL") in the corresponding listings.

The following laboratory summaries will be provided for the protocol-specified tests by treatment arm and visit:

- Actual value and change from baseline will be summarized using descriptive statistics, by laboratory test and visit.
- Shift tables will be used to summarize the number (%) of subjects with changes from baseline in normal range flag (L=low, N=within normal limits, H=high), by laboratory test and visit.

Separate summary tables will be produced for serum chemistry tests and hematology tests. In addition to summary tables, separate listings of protocol-specified laboratory test results will be produced.

11.3. Vital Signs and Weight

Vital signs, including weight, will be assessed at SV1, Day 0 (Randomization), and at each clinic visit during the treatment period.

For each test (oral temperature, pulse rate, systolic and diastolic blood pressure, weight), the actual value and change from baseline will be summarized by treatment arm and visit using descriptive statistics. For change from baseline, only subjects with non-missing results at both the baseline and post-baseline visit will be summarized at each time point.

Shift table by treatment group will summarize the number (%) of subjects who gain or loss ≥5% of their baseline body weight at each visit, as well as subjects who gain or loss ≥10% of their baseline body weight at each visit.

The number and percentages of subjects reporting potentially clinically significant (PCS) vital signs at any time post-baseline will be summarized by treatment arm, where PCS will be defined as follows:

	PCS – Low if:			**PCS – High if:**		
	Observed Value is:	**AND**	**Decrease from Baseline is:**	**Observed Value is:**	**AND**	**Increase from Baseline is:**
Systolic Blood Pressure	<85 mmHg		≥20 mmHg	>160 mmHg		≥20 mmHg
Diastolic Blood Pressure	<40 mmHg		≥10 mmHg	>90 mmHg		≥10 mmHg
Heart Rate	<35 bpm		≥15 bpm	>100 bpm		≥15 bpm

11.4. 12-Lead ECG Interpretation

A 12-lead ECG will be done at the SV1, Week 6 and Week 12 (Day 86/EOT) visits.

An overall interpretation (normal, abnormal – not clinically significant, abnormal – clinically significant) will be recorded in the CRF for each assessment.

The number (%) of subjects with shifts in overall interpretation (eg, normal to abnormal – NCS, normal to abnormal - CS) will be summarized by visit and treatment arm. The number (%) of subjects with at least one shift from a baseline result of "normal" or "abnormal – not clinically significant" to a post-treatment result of "abnormal – clinically significant" will also be reported.

In addition, an ECG listing will be provided.

11.5. Concomitant Medications

All medications taken during the trial will be recorded in the CRF. Concomitant medications will be defined as any medication (other than study drug) taken during the course of treatment (ie, with medication start date on or after the date of the first dose of study drug). Additionally, medications will be considered concomitant if the medication started prior to the first dose of study drug and the stop date is either on or after the first dose of study drug, missing (not available) or reported as ongoing. For medication start and end dates with unknown month or day, month will be imputed as specified in Section 6.4.1; safety related dates. The number and percentage of subjects with each concomitant medication will be summarized for each treatment arm by highest available ATC class and preferred name. Multiple occurrences of the same medication within a subject will be counted only once.

Concomitant medications will be coded using WHO Drug Dictionary March 2021.

12. PHARMACOKINETIC ANALYSES

None planned.

13. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

There are no changes in the planned analyses described in this SAP from the planned analyses outlined in the study protocol.

Any changes that might need to be made to this document after database lock will be documented in the Clinical Study Report.

14. REFERENCES

1. 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.
2. Thomas, D. G. Algorithm AS 36: Exact confidence limits for the odds ratio in a 2 × 2 table, *Journal of the Royal Statistical Society Series C (Applied Statistics)*. **1971, *20,*** 105-110.
3. Thomas, D. G.; Gart, J. J. A table of exact confidence limits for differences and ratios of two proportions and their odds ratios, *Journal of the American Statistical Association*. **1977, *72,*** 73-76.
4. Yan, X.; Lee, S.; Li, N. Missing data handling methods in medical device clinical trials, *Journal of biopharmaceutical statistics*. **2009, *19,*** 1085-1098.

APPENDIX 1. RANDOMIZATION PLAN

[redacted]RTSM

RANDOMIZATION SPECIFICATION

Sponsor:	Achieve Life Sciences
Protocol Number:	ACH-CYT-04
Protocol Version and Date:	V 2.0, 15 November 2021
Specification Version:	V 1.0
Specification Date:	14 Jan 2022
Prepared by:	[redacted]

APPROVAL SIGNATURES:

By signing this section, the individuals below agree that they have reviewed and accepted the [redacted] Randomization Specification document for the **Achieve ACH-CYT-04** study. The signatures below represent the approval and acceptance of this document by [redacted] and **Achieve.**

Prepared By [redacted]	
Approval [redacted]	
Approval [redacted]	
Approval (Achieve Life Sciences)	

Approval (Achieve Life Sciences)	[redacted]

Table of Contents

Revision History

Version	Date	Prepared by	Brief Description of Change
0.1	20 Dec 2021	[redacted]	Initial Version
0.2	11 Jan 2022	[redacted]	Responded to comments
0.3	14 Jan 2022	[redacted]	Added to list of key personnel

1 INTRODUCTION

1.1 Protocol Number:

- ACH-CYT-04

1.2 Study Title:

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

1.3 Development Phase:

- Phase 3

1.4 Purpose

The purpose of this document is to define the subject randomization lists (dummy and live) used within the RTSM system for the study.

1.5 Scope

This document is the final specification for the randomization list to be generated by [redacted] for the study.

2 STUDY SPECIFIC KEY PERSONNEL

The list of key study personnel that are responsible for the generation and validation of the randomization lists are listed below and will be maintained by the [redacted] Project Manager.

Company	Role	Name	Blinded /Unblinded	Email
[redacted]	Director, RTSM Professional Services	[redacted]	Unblinded	[redacted]
[redacted]	RTSM Development Team Lead	[redacted]	Unblinded	[redacted]
[redacted]	RTSM, Subject Matter Expert	[redacted]	Unblinded	[redacted]
[redacted]	Project Manager	[redacted]	BLINDED	[redacted]
Achieve Life Sciences	Biometrics	[redacted]	BLINDED	[redacted]

3 DISTRIBUTION OF RANDOMIZATION LIST

The list of key study personnel that have received the randomization lists will be maintained by the [redacted] Project Manager.

To request the LIVE randomization, an email must be sent to [redacted] from one of the sponsor nominated contacts below. The live list will be extracted and sent to the named recipients below within 3 days.

Company	Reason	Type	Name	Email	Delivery method
[redacted]	RTSM Load	**Dummy** and LIVE	[redacted]	[redacted]	Secure file transfer
Achieve Life Sciences	Verification	Dummy ONLY	[redacted]	[redacted]	Email of password protected zip file
Achieve Life Sciences	Verification	Dummy ONLY	[redacted]	[redacted]	Email of password protected zip file
[redacted]	Verification	Dummy ONLY	[redacted]	[redacted]	Email of password protected zip file
[redacted]	Verification	Dummy ONLY	[redacted]	[redacted]	Email of password protected zip file

[redacted]	DSMB	Dummy and **LIVE**	[redacted]	[redacted]	Email of password protected zip file

4 [redacted] GENERATED RANDOMIZATION LISTS

[redacted] will produce a dummy randomization list for Achieve's approval, system validation and user acceptance testing (UAT).

[redacted] will generate the live Subject Randomization list as specified below.

The [redacted] Project Manager verifies that the appropriate tests will be performed and that the correct schedules will be loaded into the Test and Live environments.

5 SUBJECT RANDOMIZATION LIST

5.1 Subject List Details

Blinding	Double blinded
Number of cohorts	N/A
List cohorts (if applicable)	N/A
Number of subjects	750
Number of sites	up to 19
Number of treatment arms	3
Treatment arms description	1. Placebo 12 weeks 2. Cytisinicline 6 weeks followed by Placebo 6 weeks 3. Cytisinicline 12 weeks
Allocation ratio	1:1:1
Blocking	Permuted blocks
Block size (if applicable)	mixed blocks: 6 and 9
Number of blocks	200 blocks of 6 and 200 blocks of 9
Total records	3000
Stratification factors?	Site
How is the list stratified?	Site stratification dynamically allocated per block
Additional comments	The maximum number of subjects that a single site may be allowed to enroll, is 10% (75 subjects) of the study total.

5.2 Subject List File Attributes

File type	CSV
Dummy list filename	Achieve_ACH-CYT-04_Subjects_DUMMY_DDMMMYYYY.csv
Live list filename	Achieve_ACH-CYT-04_Subjects_LIVE_DDMMMYYYY.csv
Additional comments	

5.3 Subject List File Contents

Seq	Name	Description	Type	Format	Valid values
1	R_ID	Rand ID	Number	4 digits	1001-3000
2	BLOCK_ID	Block ID	Number	3 digits	1-400
3	RG_ID	Treatment Group ID	Number	1 digit	1-3
4	RG_DESC	Treatment Group Description	Text		- Placebo 12 weeks - Cytisinicline 6 weeks followed by Placebo 6 weeks - Cytisinicline 12 weeks

Treatment group mapping

1 = Placebo 12 weeks
2 = Cytisinicline 6 weeks followed by Placebo 6 weeks
3 = Cytisinicline 12 weeks

5.4 Subject sample file

R_ID, BLOCK_ID, RG_ID, RG_DESC
1001,1,1,Placebo 12 weeks
1002,1,3,Cytisinicline 12 weeks
1003,1,2,Cytisinicline 6 weeks followed by Placebo 6 weeks