Statistical Analysis Plan:
PROTOCOL ACH-CYT-10 (ORCA-V1 Trial)

A Multicenter, Double-blind, Randomized, Placebo-controlled Phase 2 Trial Evaluating the Efficacy and Safety of Cytisinicline in Adults Using Nicotine-containing E-cigarettes

29 March 2023

Version 1.0

CONFIDENTIAL

Achieve Life Sciences Technologies Inc.

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Achieve Life Sciences, Inc.

[redacted]

APPROVAL SIGNATURES

Protocol	**ACH-CYT-10**
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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-10 (ORCA-V1) trial. The signatures below represent the approval and acceptance of this document by [redacted] and Achieve Life Sciences, Inc.

Approved By:	
[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
CI	Confidence Interval
CDISC	Clinical Data Interchange Standards Consortium
CO	Carbon Monoxide
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
C-SSRS	Columbia - Suicide Severity Rating Scale
ECG	Electrocardiogram
EMA	Effect Modification Analyses
eCRF	Electronic Case Report Form
EOT	End of Treatment
ePRO	electronic Patient Reported Outcome
ET	Early Termination
HADS	Hospital Anxiety and Depression Scale
ITT	Intent-to-Treat
MCQ	Marijuana Craving Questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
MNWS	Minnesota Nicotine Withdrawal Scale
PCS	Potentially Clinically Significant
PSECD	Penn State Electronic Cigarette Dependence Index
PT	Preferred Term
RTF	Rich Text Format
RTSM	Random and Trial Supply Management
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SDTM IG	Study Data Tabulation Model Implementation Guide
SI	Système International
SMQ	standardized MedDRA query
SOC	MedDRA System Organ Class
SV1, SV2	Screening Visit #1, Screening Visit #2
TEAE	Treatment Emergent Adverse Event
TID	Three Times Daily
WHODrug	World Health Organization Drug Dictionary

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1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a more detailed 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-10 (ORCA-V1 Trial): "A Multicenter, Double-blind, Randomized, Placebo-controlled Phase 2 Trial Evaluating the Efficacy and Safety of Cytisinicline in Adults Using Nicotine-containing E-cigarettes", Version 3.0 (May 4, 2022).

This SAP was prepared by Achieve Life Sciences Inc. (Achieve) and reviewed by [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 clinical study report.

For this study, [redacted]s 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 3.0, 27 July 2022
- Data Entry Guidelines: Version 4.0, 03-Jan-2023
- Data Management Plan: Version 2.0, 06-Jan-2023
- Data Validation Plan: Version 4.0, 01 September 2022

2. STUDY DESCRIPTION

2.1. Study Design

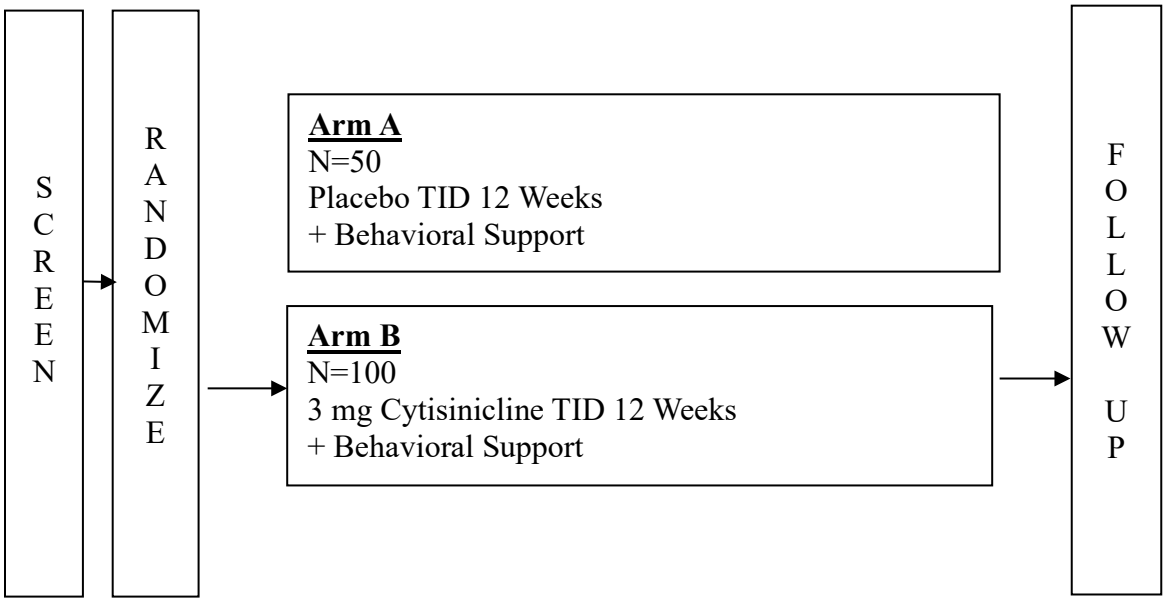
Study ACH-CYT-10 is a multi-center, double-blind, randomized, placebo-controlled, Phase 2 study conducted in male and female subjects ≥18 years who vape nicotine e-cigarettes daily and intend to make a quit attempt during the study.

Study ACH-CYT-10 evaluates the potential benefit of cytisinicline in treating nicotine addiction among users whose only source of nicotine is via the use of e-cigarettes. The study population of e-cigarette users only (not dual users who are also smoking combustible cigarettes) is intentional for this study in order to monitor expired CO levels for any reverting to combustible cigarette smoking, which would be viewed as increasing harm while reducing nicotine e-cigarette usage.

Study treatment must start the day after randomization, such that study treatment is initiated on Day 1 prior to the quit date. The quit date must be within 7-14 days of starting treatment.

Subjects must meet all requirements outlined in the inclusion and exclusion criteria. A total of approximately 150 subjects will be randomly assigned (2:1) to 1 of 2 arms: (Arm B, 12 weeks cytisinicline + behavioral support: N=100 or Arm A, 12 weeks of placebo+ behavioral support: N=50) as shown in the study design figure below.

Figure 1: Study Design Overview



TID = 3 times daily

This study will be conducted at approximately 5-8 clinical sites across the United States. Randomization will be stratified on whether subjects have smoked >100 cigarettes in their lifetime (yes vs no). This will be used as a stratification factor in the primary analysis.

The study will be comprised of a pre-study screen, followed by 12 weeks of treatment, and a post-treatment follow-up visit at 16 weeks post-randomization.

Each randomized subject will receive 12 weeks of treatment using a 3 times daily (TID) dosing schedule. Determination of vaping cessation will be made from the subject's self-report of vaping abstinence accompanied by biochemical verification at each assessment. Biochemical verification will be defined by saliva cotinine levels of less than 10 ng/mL. Assessments for vaping abstinence will begin on Week 2 (Day 14 ±1 post-randomization) and will continue weekly during the treatment period to Week 12, then at the Week 16 follow-up visit.

All subjects will receive concurrent nicotine cessation behavioral support during the treatment period (Weeks 1–12).

Safety will be assessed by consideration of all adverse events (AEs) reported by or elicited from the subject. Subjects will be monitored for AEs starting at screening (pre-existing), by telephone contact on Day 1, and at weekly clinic visits from Week 1 through Week 12. AEs 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 designated clinic visits will include hematology and chemistry, vital signs, weight, electrocardiogram (ECG), completion of the Hospital Anxiety and

Depression (HADS) and Columbia – Suicide Severity Rating Scale (C-SSRS) questionnaires, and urine pregnancy testing (if applicable).[a] 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, at an Early Termination (ET) visit.

The end of study is defined as the last visit for the last subject.

2.2. Determination of Sample Size

The target accrual is for approximately 150 subjects (100 subjects treated with cytisinicline and 50 subjects treated with placebo) which should be adequate to obtain additional safety assessments as well as for measuring cytisinicline effect outcomes compared to placebo. A statistical sensitivity assessment of the planned 150 subject trial size was evaluated using Fisher's exact test (no stratification included) by assuming a placebo arm success proportion of 6% (historical estimate). When the cytisinicline arm success proportion is 18% or higher, the exact odds ratio 95% confidence intervals will exclude one; with an odds ratio of 3.44. In addition, the sample size will have 95% power to detect a 57 ng/mL reduction in cotinine levels at baseline levels of 300 ng/mL (eg, approx. 19% reduction from baseline).

2.3. Treatment Assignment

A total of approximately 150 subjects will be randomly assigned (2:1) to 1 of 2 arms: (Arm B = cytisinicline treatment + behavioral support, Arm A = placebo treatment + behavioral support). Randomization will be stratified on whether subjects have smoked >100 cigarettes in their lifetime (yes vs no).

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 1 tablet TID.

3. STUDY OBJECTIVES

3.1. Primary Efficacy Objective

Assess whether subjects randomized to Arm B (3 mg cytisinicline TID for 12 weeks plus behavioral support) have a higher probability of nicotine vaping cessation from Week 9 to Week 12 post-randomization as compared to subjects randomized to Arm A (placebo TID for 12 weeks plus behavioral support).

3.2. Secondary Efficacy Objectives

1. Assess whether subjects randomized to Arm B (cytisinicline TID) can achieve vaping abstinence/cessation at any time during treatment or reduce their daily vaping as objectively measured with biomarkers of nicotine exposure compared to subjects

[a] For female subjects, pregnancy test not required only if surgically sterile (hysterectomy or tubal ligation) or > 2 years post-menopausal.

randomized to Arm A (placebo TID). Specific Secondary Efficacy Objectives related to this are described below:

- Assess whether subjects randomized to Arm B have a higher probability of achieving vaping cessation between Week 3 and Week 9 post-randomization (eg, Weeks 3-6 or Weeks 6-9) as compared to subjects randomized to Arm A.
- To compare arms (Arm B vs Arm A) on 7-day point prevalence rates for vaping abstinence on a weekly basis from Week 2 to Week 12.
- To compare arms (Arm B vs Arm A) for a reduction in nicotine vaping using weekly quantitative cotinine levels from Week 2 to Week 12.

2. Assess whether subjects randomized to Arm B have a higher probability for continuous vaping abstinence between Week 9 and Week 16 post-randomization (ie, subjects achieving primary endpoint abstinence with continued abstinence through follow-up).

3.3. Other Objectives

Explore the magnitude of treatment effect between arms across various subgroups defined by demographic and baseline characteristics for the primary and secondary outcomes.

Evaluate for nicotine withdrawal symptoms at Weeks 1-4 and again for any possible withdrawal symptoms due to study drug discontinuation pre- and post-Week 12.

3.4. Safety Objectives

To evaluate the safety profile of 3 mg cytisinicline TID when administered for 12 weeks.

4. EFFICACY AND SAFETY ENDPOINTS

4.1. Efficacy Endpoints

Weekly nicotine vaping assessments will start at Week 2 and continue weekly through Week 12. An assessment will also be done at follow-up (Week 16). Each assessment will include asking the subject whether they have vaped (yes, no) since the last clinic visit (ie, in the past 7 days for weekly visits) and collecting a saliva sample for cotinine testing at a central laboratory.

Vaping abstinence is a binary efficacy endpoint (success, failure) with success defined at each visit as a self-report of no nicotine-containing vaping since the last clinic visit and biochemical verification (saliva cotinine <10 ng/mL). Any outcome other than success will be regarded as a failure.

4.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint of nicotine vaping cessation from Week 9 to Week 12 post-randomization is a binary endpoint (success, failure). Success is defined for a subject as having reported no nicotine-containing vaping since the last clinic visit at each clinic assessment from Week 9 to Week 12 with biochemical verification (saliva cotinine <10 ng/mL) at each assessment.

Any outcome other than success will be regarded as a failure. There are two types of failure for a subject: (1) subjects with adequate data that they are vaping (either by the subject's self-report or saliva cotinine ≥10 ng/mL) and (2) subjects having insufficient data to be determined as a success for vaping cessation. Examples of subjects with insufficient data include the following:

- Vaping status unknown at key visits for the endpoint. Subjects with vaping status unknown at either Week 9 or Week 12 will be regarded as failures.
- Vaping status unknown at more than 1 of the interim visits. (Week 10 and Week 11 are interim visits.) A vaping status is unknown when data are missing for either the subject's self-report of nicotine-containing vaping since the last clinic visit (yes, no) or saliva cotinine or both.

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 10.2.

4.1.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Vaping cessation between Week 3 and Week 9 post-randomization (eg, Weeks 3-6 or Weeks 6-9)
- 7-day point prevalence vaping abstinence rates from Week 2 to Week 12
- Reduction from baseline in quantitative saliva cotinine levels from Week 2 to Week 12
- Continuous vaping abstinence between Week 9 and Week 16 post-randomization.

Vaping cessation between Week 3 and Week 9 post-randomization endpoints are binary (success, failure), defined for 2 intervals of time: Week 3 to Week 6 and Week 6 to Week 9. Success will be defined for a subject as having reported no nicotine-containing vaping since the last clinic visit at each visit within a time interval with biochemical verification (saliva cotinine <10 ng/mL) at each visit.

Any outcome other than success will be regarded as a failure. There are two types of failure for a subject: (1) subjects with adequate data that they are vaping (either by the subject's self-report or saliva cotinine ≥10 ng/mL) and (2) subjects having insufficient data to be determined as a success for vaping cessation. Examples of subjects with insufficient data include the following:

- Vaping status unknown at key visits for an interval. A vaping status is unknown when data are missing for either the subject's self-report of nicotine-containing vaping since the last clinic visit (yes, no) or saliva cotinine or both. Key visits are defined as the starting and ending visits for an interval (eg, Week 3 and Week 6 are key visits for the Week 3 to Week 6 interval).
- Vaping status unknown at more than 1 of the interim visits within an interval (eg, at both Week 4 and Week 5 for the Week 3 to Week 6 interval).

7-day point prevalence vaping abstinence is a binary endpoint (success, failure) derived at each visit during the treatment period (Week 2 to Week 12). Success will be defined for a subject

as having reported no vaping since the last clinic visit with biochemical verification (saliva cotinine <10 ng/mL). 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.

Reduction from baseline in quantitative saliva cotinine levels. Saliva cotinine levels (ng/mL) are a continuous endpoint measured at Day 0, weekly during treatment (Week 2 to Week 12), and at follow-up (Week 16).[a] Reduction from baseline saliva cotinine levels will be assessed using change from baseline.

Continuous vaping abstinence between Week 9 and Week 16 is a binary endpoint (success, failure). Success is defined for a subject as having achieved the primary efficacy endpoint (ie, coded as success for nicotine vaping cessation from Week 9 to Week 12) and having reported no nicotine-containing vaping since the last clinic visit (on Week 12) at the Week 16 follow-up visit with biochemical verification (saliva cotinine <10 ng/mL) at Week 16. Any outcome other than success will be regarded as a failure.

Statistical methods for the secondary efficacy endpoints are described in Section 10.3.

4.1.3. Other Endpoints

Other endpoints at baseline and/or during the study were assessed for all subjects, unless otherwise indicated. These included:

- Minnesota Nicotine Withdrawal Scale (MNWS) questionnaire
- Use of any other combustible or non-combustible nicotine products (yes, no) and type of nicotine product used[b]
- Questionnaires:
  - Hospital Anxiety and Depression Scale
  - Penn State Electronic Cigarette Dependence Index (PSECD)
  - Marijuana Craving Questionnaire (MCQ) – Short Form.

4.2. Safety Endpoints

The safety endpoints are:

- Adverse events, including serious adverse events
- Adverse events of special interest
  - Treatment-emergent suicidal ideation or risk, as measured by the C-SSRS
  - Treatment-emergent moderate to severe depression, as measured by the HADS
  - Treatment-emergent moderate to severe anxiety, as measured by the HADS

[a] Cotinine was also measured at SV1 but the result was reported as "positive" (≥30 ng/mL) or "negative" (<30 ng/mL).
[b] Reported on the Vaping Abstinence Status eCRF.

  - New pregnancy
  - Treatment-emergent COVID-19.
- Laboratory assessments
  - hematology
  - chemistry
- Vital signs
- 12-lead ECG results
- Concomitant medications.

4.2.1. Treatment-emergent Adverse Event (TEAE)

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 eCRF item "Did the AE start after the first dosing?"

4.2.2. 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

4.2.3. 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 prior to randomization ("Yes" to either question 4 or question 5 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 (HADS depression score ≥11) within 3 months prior to randomization is an exclusion criterion.

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

  Note: There was no exclusion criteria based on level of anxiety; however, this is of special interest since anxiety can be a symptom of nicotine withdrawal/cessation.

- 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.

4.2.4. Expired Carbon Monoxide (CO)

Expired carbon monoxide (CO) levels (ppm) will be summarized by treatment arm and, for subjects with CO >10 ppm the following will be reported:

- whether the subject smoked combustible cigarettes since the last clinic visit (yes, no) and the total number of cigarettes smoked since the last clinic visit
- whether the subject smoked any cannabis since the last clinic visit (yes, no), and total number of days cannabis was used.

4.2.5. 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 timing of EOT assessments will be different for subjects who complete treatment and subjects who discontinue treatment early. Subjects that complete treatment will have those assessments done at the Week 12 visit and recorded on Week 12 CRFs. Per protocol, subjects who discontinue treatment early will have those assessments done at an earlier visit and recorded on Early Termination eCRFs.

In order to accurately summarize changes from baseline to end of treatment in safety endpoints, the EOT safety assessments for all subjects will be combined into a derived visit named “EOT”. If a subject discontinues treatment early but did not have data recorded on Early Termination eCRFs, then data recorded at the subject’s last visit during the treatment period will be used for the EOT visit. 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.

6. DATA ANALYSIS CONSIDERATIONS

6.1. Clinical Databases

There will be 4 clinical data sources for this study: a randomization and trial supply management (RTSM) application, an electronic patient reported outcome (ePRO) application, central laboratory datasets, and an eCRF database.

The RTSM system will be used to randomize subjects and allocate study drug. Subject randomization data (date randomized, value of stratification factor at randomization, treatment arm assignment) will not be transferred to the eCRFs but will be extracted from the RTSM application after the eCRF database is locked.

The ePRO application will be used to collect subject diary data and the MNWS questionnaire data. Data collected in the ePRO application will be transferred to the eCRF database.

Laboratory data (eg, hematology, chemistry, saliva cotinine test results) will reside in vendor databases and will not be transferred to the eCRF database.

All other subject data will be entered into the eCRF database.

6.2. General Considerations

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

Medical history events and AEs will be coded to standard “preferred terms” and “system organ classifications (SOC)” using 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 arm, subject and visit/time point where appropriate. The summary tables will have columns corresponding to, or be stratified by, arm. In listings and summary tables, the arms will be ordered and labelled as follows: Placebo and Cytisinicline 12 Weeks.

The total number of subjects under the stated analysis set in each 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 (SD), 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 SD will be empty. The statistic "Missing" will also be presented as the number of missing entries/subjects, if any at that visit/time point, 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 1 more decimal place than the original data, whereas the SD 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) × 100. Unless otherwise stated, all percentages will be expressed to 1 decimal place.

In by-visit summary tables, only scheduled visits/time points will be summarized. In listings all visits and time points 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 Time Points

- **Baseline:** The last non-missing observation (including unscheduled visits) prior to the first dose of study drug (cytisinicline or placebo), unless otherwise specified. The last non-missing observation prior to the first dose of study drug (cytisinicline 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 Visit:** The last clinic visit during a subject's treatment period. Expected to occur at Week 12 for subjects who complete the 12-week treatment period. Subjects who discontinue treatment prior to 12 weeks will have end of treatment assessments done earlier, 1-3 days after treatment is discontinued. (See Section 4.2.4)
- **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 visit.

- **Follow-up Period:** The follow-up period is expected to be 4 weeks in duration, starting after the Week 12 visit and ending at the Week 16 visit.
- **Study Day:** Study day will be calculated for all assessment dates relative to the first dose of study drug (cytisinicline 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 (International Conference of Harmonization 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 or a variable used in study analyses. Otherwise no date imputation will be done. Date imputation will follow the rules below.

6.4.1.1. 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 for a post-baseline assessment, negative time to failure) the date will be imputed as the date half the distance between the preceding date of interest and the partial date.

6.4.1.2. Safety Related Dates

When tabulating AEs or concomitant medications, missing or partial date for onset or stop dates will be handled as follows:

- Reported AEs that have a missing day of onset will be considered treatment-emergent if the month and year occur on or after the month and year of the first dose of study drug.
  - 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 (eg, UNK-Jan-2019 becomes 01-Jan-2019).
- If an AE has a missing month and day of onset, the event will be considered treatment-emergent unless the year of occurrence is before the year of the first dose of study drug.
  - 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 (eg, UNK-UNK-2019 becomes 01-Jan-2019).
- If an AE is missing the month, day, and year of onset, the event will be considered treatment-emergent.
  - Missing start dates will be imputed as the date of first dose.
- If an AE is missing the month of onset only, the following imputation will be performed.
  - 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 day of onset is greater than or equal to the day of first dose. If the day of onset is prior to the day of first dose, month will be imputed as the month after the date of first dose (except when month of first dose is in December). If the start date year is after the year of the first dose, the month will be imputed as Jan (eg, 15-UNK-2019 becomes 15-Jan-2019).
- If an AE has missing month and day of end date, the following imputation will be performed:
  - 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 and day of the last date of the study, otherwise assign 31-December.
- If an AE has missing month only of end date, the following imputation will be performed
  - 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 if the end date day is less than or equal to the last date in the study. If the end date day is after the last date day in the study, month will be imputed as the month prior to last date in the study month (except when month of last date in study is in January). If end date year does not match the year of last date in the study then assign December.

- If an AE has missing day only of end date, the following imputation will be performed
  - 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.
- Medication (other than the study-specific treatment) end dates can determine prior vs concomitant medication distinction regardless of start date missingness.
- If a medication has a completely missing start date and either the stop date is after the first dose of study drug or the stop date is completely missing, the medication will be considered concomitant. If the medication has a completely missing start date and the stop date is before the first dose of study medication, the medication will be considered a prior medication.

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. Baseline scores will be derived as described in Section 6.3.

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. The questionnaire must be administered by trained study staff. Suicidal ideation ("Yes" to either question 4 or question 5 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).

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 2 of the study protocol). Providing there are no missing questions, a total HADS score as well as total scores for depression and anxiety will be derived for each subject.

Marijuana Craving Questionnaire (MCQ)-Short Form

The MCQ Short Form is a 12-item questionnaire that will be administered at SV2 and Week 12. Item scores will be assigned using the scoring key pre-printed on the questionnaire (see Appendix 4 of the study protocol). A total MCQ score will be derived for each subject, providing all questions have been answered. Total scores will also be derived for 4 factors, providing there are no missing item scores:

- Compulsivity: sum of scores for items 2, 7, and 10
- Emotionality: sum of scores for items 4, 6, and 9
- Expectancy: sum of scores for items 5, 11, and 12
- Purposefulness: sum of scores for items 1, 3, and 8.

Minnesota Nicotine Withdrawal Scale (MNWS)

The MNWS is a 9-item questionnaire that will be administered at Week 1, Week 2, Week 3, Week 4, and twice around the Week 12 visit (first to be 3 days [+/- 1 day] prior to the Week 12 visit and again 3 days [+/- 1 day] after the Week 12 visit). 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 will be derived for each subject.

Penn State Electronic Cigarette Dependence Index (PSECD)

The PSECD is a 10-item questionnaire that will be administered at Screening, Week 6 and Week 12. Item scores will be assigned using the scoring key in Appendix 2 of this document. Item 3 asks "Do you sometimes awaken at night to use your electronic cigarette?", with response options "Yes" and "No". Item 4 asks "If yes, how many nights per week do you typically

awaken to do so?". Subjects who respond "No" to item 3 will not have a response for item 4. An item 4 score of 0 (corresponding to a response of "0-1 nights") will be imputed for such subjects.

A total PSECD score will be derived for each subject, providing all questions have been answered. Based on the total score, subjects will be classified as not dependent (total score 0-3 points), low dependence (4-8 points), medium dependence (9-12 points) or high dependence (13 points or higher).

6.5. Analysis Sets

Three analysis sets will be used.

Screening Set

The Screening Set is defined as all subjects who give written informed consent and enter screening but are not randomized. Only demographic data and reasons for non-participation in the study will be summarized for this analysis set.

Efficacy Set

This is the All Randomized Set, defined as all randomized subjects. Subjects will be evaluated by their randomized treatment arm (ITT analysis) unless otherwise specified. This set is referred to as the All Randomized Set within this document.

Safety Set

The Safety Set is defined as all randomized subjects who take at least 1 dose of study drug. The Safety Set will be the primary set for safety summaries. Safety summaries will be provided based on the actual treatment received.

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

7. SUBJECT DISPOSITION

The number of subjects who were screened and the number of screen failures[a] will be summarized. The reason for failing screening (eg, inclusion or exclusion criteria not met, withdrew consent, lost to follow-up) will also be summarized.

The number of subjects who were 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.

[a] Subjects not randomized.

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 for the All Randomized Set with the number and percentage of subjects who attended each visit (ie, SV1, SV2, 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 16, Week 12, etc.

The number and percentage of subjects who completed the treatment period (ie, attended the Week 12 visit), and the number and percentage of subjects who completed the follow-up period (ie, attended the Week 16 visit) will be reported.

A Kaplan-Meier figure will be produced for the All Randomized Set by treatment arm of time to last recorded data related to the vaping abstinence endpoints (ie, time from date of randomization to date of last vaping abstinence data recorded at or prior to the Week 16 visit). If a subject is randomized and is either not treated (no visits after Day 0) or does not have any vaping abstinence assessments while on study, then time from randomization to last recorded data will be assigned as 0 days. The date of the last vaping cessation data will be the date of the last self-report of vaping since the last clinic visit (yes, no) or cotinine level.

7.1. Protocol Deviations

Protocol deviations will be reported as outlined in the ACH-CYT-10 Protocol Deviation Plan and documented in the CRF. Each deviation will be classified as either “major” or “minor”. Major deviations are defined in the deviation plan as those affecting key study results or the subject’s study participation. Potential major deviations required 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
- Non-compliance with inclusion/exclusion criteria, including not obtaining or not completing certain screening assessments that would affect a subject’s eligibility for the study
- Errors in randomization/stratification
- Non-compliance with 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 12 weeks])
- Missing results for primary efficacy endpoint.
- Missing results from screening assessments used for determining subject eligibility.

Protocol deviations will be summarized for the All Randomized Set. The number and percentage of subjects with at least 1 deviation (major or minor) and with at least 1 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, race, ethnicity, age at date of informed consent, height, body weight, and body mass index [BMI]) will be summarized by analysis set (Screening Set, All Randomized Set, Safety Set) and overall (ie, Screening Set and All Randomized Set pooled).

Demographic data will also be summarized by treatment arm and overall (ie, treatment arms pooled) 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 medical/psychiatric history events will be summarized for each treatment arm by MedDRA SOC and PT. Multiple occurrences of the same PT within a subject will be counted only once.

8.3. Prior Medications

Concomitant medications will be recorded beginning at SV1. 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 6.4.1.2. 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 and overall 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.

8.4. Smoking History, Other Nicotine Use, Vaping History

The following smoking (combustible cigarette) history and other nicotine use data will be summarized by treatment arm and overall for both the All Randomized Set and the Safety Set:

- History of tobacco cigarette smoking (yes, no)
- Age (yrs) at first cigarette
- Average number of cigarettes smoked per day
- Smoked in past 30 days (yes, no)
- Time (yrs) since last cigarette smoked
- Electronic cigarette used in most recent cigarette smoking quit attempt (yes, no)
- Methods used during most recent cigarette smoking quit attempt (eg, nicotine products, Chantix)
- Confidence in ability to continue to abstain from cigarette smoking (1=not at all confident through 5=extremely confident).
- History of other tobacco product use (yes, no)

- Other tobacco product use in past 30 days (yes, no).

The following vaping history data will be summarized by treatment arm and overall for both the All Randomized Set and the Safety Set:

- Age (yrs) at first nicotine-containing electronic cigarette
- Nicotine vaping product use in past 30 days (days used)
- All vaping devices used in past 30 days
- Vaping device used most often in past 30 days[a]
- Flavors of e-cigarette liquid used in past 30 days
- Total e-liquid (mL) from nicotine vaping products in past week[b]
- Attempted to quit nicotine-vaping in the past (yes, no)
- Number of previous nicotine-vaping quit attempts[c]
- Methods used in past to quit vaping (eg, nicotine products, Chantix)
- Reasons for current nicotine-vaping quit attempt (eg, health effects, money/cost)
- Desire to quit vaping now (1=not at all through 5=very much)
- Confidence in quitting vaping now (1=not at all confident through 5=extremely confident)
- Health risks of e-cigarettes vs cigarettes (1=e-cigarettes much more harmful through 5=e-cigarettes much less harmful).

8.5. Baseline Vaping and Nicotine Test Results

Summaries of baseline vaping and nicotine test results will be presented by treatment arm and overall, for both the All Randomized Set and the Safety Set.

During the screening period subjects will complete a vaping diary, reporting vaping (yes, no) for 7 consecutive days. The total number of days each subject vaped over 7 consecutive days will be summarized.

At SV1 and Day 0 saliva samples will be collected for cotinine determination. Site personnel will use the Alere iScreen® OFD Cotinine Oral Fluid Screening Device to measure saliva cotinine levels at SV1. The device reports saliva cotinine as “positive” or “negative”, with “positive” corresponding to a cotinine level ≥30 ng/mL.

The Day 0 (baseline) saliva sample will be collected by site personnel and tested at a central laboratory. Due to a shortage of saliva cotinine test kits some saliva samples were collected using a kit designated for an unscheduled collection rather than the actual visit kit. If the date of collection associated with an unscheduled sample is the same as the date of an actual visit, then

[a] Response to this question on the CRF was not required if subject reported using only 1 vaping device in past 30days. For those subjects, vaping device used most often in past 30 days will be assigned to that 1 device.
[b] Calculated by site based on subject report.
[c] For subjects who did not have previous nicotine-vaping quit attempts, assign 0.

the test result will be analyzed as the visit result. Saliva cotinine results (ng/mL) will be summarized at both visits as a categorical variable (<30 ng/mL, ≥30 ng/mL) and at Day 0 as a continuous variable.

Site personnel will assess CO levels in expired air samples at SV1 and Day 0. Baseline CO levels (ppm) will be derived as described in Section 6.3. The baseline result, as well as the results at each of the pre-treatment visits (SV1, Day 0), will be summarized. The number (%) of subjects with baseline CO <10 ppm and ≥10 ppm will also be reported.

8.6. Baseline Questionnaires

The C-SSRS, HADS, MCQ Short Form and PSECD questionnaires will be administered prior to randomization. Questionnaire scoring is described in Section 6.4.2.

Baseline scores will be derived as described in Section 6.3 and the following will be summarized by treatment arm and overall for both the All Randomized Set and the Safety Set:

- C-SSRS: item scores for the suicidal ideation and suicidal behavior items (see Section 6.4.2) on the screening questionnaire. In addition, the number (%) of subjects with suicidal ideation or risk at baseline will be reported. Suicidal ideation or risk at baseline will be defined as a response of "Yes" to either suicidal ideation question 4 or question 5 or "Yes" to any suicidal behavior question on the C-SSRS screening questionnaire.
- HADS: total score, anxiety score, depression score
- MCQ Short Form: total score, compulsivity score, emotionality score, expectancy score, purposefulness score.
- PSECD: total score, dependence category (not dependent, low dependence, medium dependence, high dependence).

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. 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. If there are subjects who inadvertently enter more than the 252 prescribed doses in their diary, 252 doses will be used for the analyses. Details of study drug administration will be included in a subject data listing.

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 AEs that might be attributed to study drug and who would otherwise discontinue study treatment due to the AE. For subjects with a dose reduction, the number of doses prescribed will be based on the number of days with 3 doses prescribed as well as the number of days with 2 doses prescribed.

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) will be summarized both as a continuous variable and a categorical variable (0, 1-5, 6-10, 11-15, 16-20, >20)
- 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 doses 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

All subjects will receive up to 14 behavioral support sessions by a qualified study site staff member, starting prior to randomization. Twelve (12) sessions are planned during the treatment period, at Week 1 to Week 12 visits.

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

10.1. General Considerations

The primary outcome and analysis will be based on the analysis of the stratified arm by primary outcome tables using stratification by having smoked >100 cigarettes in their lifetime (yes vs no). The intent-to-treat principle will be followed for all major analyses.

The efficacy analyses will be conducted using 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 (ITT analysis). For binary efficacy endpoints, the rate of vaping cessation/abstinence will be reported for each treatment arm.

The overall study intent is to also obtain other effect estimates for efficacy endpoints and to conduct safety assessments. There is no formal statistical hypothesis testing for these secondary or other analyses, and consequently, a level of significance (α level) is not specified. There will be statistical testing performed with p-values, and confidence intervals (CIs). The p-values will be interpreted as an assessment of consistency with the play of chance (small p-values indicating a small likelihood that the observed effect was due to chance).

For binary efficacy endpoints, the rate of vaping cessation/abstinence will also be reported for each treatment arm.

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.

10.2. Analyses of Primary Efficacy Endpoint

The primary objective is described in Section 3.1. The primary efficacy endpoint (nicotine vaping cessation from Week 9 to Week 12) is described in Section 4.1.1.

10.2.1.1. Primary Efficacy Analysis

The primary efficacy endpoint (nicotine vaping cessation from Week 9 to Week 12) is binary (success, failure). The two treatment arms will be compared in terms of the proportion of subjects classified as a success (ie, in terms of the rate of vaping cessation from Week 9 to Week 12). All randomized subjects will be included in the comparisons according to their randomized arm (ITT analysis).

The between-arm comparison will be based on the odds ratio using exact computations for stratified 2×2 frequency tables and using Monte Carlo estimation if necessary. The stratifier will be whether subjects have smoked >100 cigarettes in their lifetime (yes, no). 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 CI will be reported. Also, the estimated odds ratio and midp CI for the marginal 2x2 table across levels of the stratification factor (unadjusted odds ratio), and the estimated difference in proportions and the associated derived exact CI using

the exact CI on the odds ratio will be reported. The exact difference in proportion CI will be derived using the method of Thomas (1971 and 1977).[1,2]

Following is template SAS code for performing the statistical comparison using SAS PROC FREQ:

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

Where
s: Stratification designator (s=0 for smoked >100 cigarettes is no, s=1 for yes)
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 3 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 1-sided p-value for the between-arm comparison. Also report 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 1-sided p-value is optional but not recommended; if reported it requires an explicit labeling as 1-sided.

10.2.1.2. Sensitivity Analyses

When there is evidence of material non-homogeneity of odds ratio across levels of the stratification factor then the interpretation of the results will be evaluated for each stratum. The results for each stratum can be assessed using Fisher’s exact test for the 2x2 table specific to that stratum, including the stratum-specific odds ratio estimate and its CI. The above code template for Fisher’s exact test and odds ratio confidence interval is modified as follows: (1) Delete “comor eqor” in the exact statement. This modification will produce a separate 2x2 table analysis for each category. Extract the 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 stratum-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 the primary efficacy endpoint, the relationship between treatment arm and the proportion of subjects with nicotine vaping cessation 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 nicotine vaping cessation 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.

Specific analysis may be done for redefining success if a subject had evidence of vaping abstinence (self-report of vaping abstinence with saliva cotinine level verification) however was missing a required visit (week 9 or week 12).

Tipping Point Analysis

A tipping point analysis as presented in Yan (2009)[3] will be performed for the primary efficacy endpoint, including sensitivity analyses if applicable.

The goal of the 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, if appropriate.

10.3. Analyses of Secondary Efficacy Endpoints

The secondary efficacy objectives are described in Section 3.2. The secondary efficacy endpoints are defined Section 4.1.2 and below. The stratification factor will not be used in statistical analyses of the secondary efficacy endpoints.

10.3.1. Vaping Cessation Between Week 3 and Week 9 Post-Randomization

Vaping cessation between Week 3 and Week 9 will be assessed by vaping cessation for 2 time intervals: Week 3 to Week 6 and Week 6 to Week 9. Analyses of these endpoints will be conducted using the All Randomized Set. Analyses will follow the methodology for the primary efficacy endpoint described in Section 10.2.1.1, except that the stratification factor will not be included.

10.3.2. 7-day Point Prevalence Abstinence

The 7-day point prevalence abstinence endpoints are binary (success, failure), defined at each of the following visits: Week 2 to Week 12.

The analyses of point prevalence abstinence endpoints will be conducted using the All Randomized Set. The analyses will follow the methodology for the primary efficacy endpoint described in Section 10.2.1.1, except that the stratification factor will not be included. Abstinence rates will be summarized by treatment arm and visit. The 95% CIs for odds ratios and differences in proportions will be reported at each visit.

The 95% CIs for the odds ratio will be displayed by treatment arm and visit in a forest plot.

10.3.3. Saliva Cotinine Levels

Saliva cotinine levels (ng/mL) will be measured weekly from Week 2 to Week 12 during the treatment period, and at follow-up (Week 16). Due to a shortage of saliva cotinine test kits some saliva samples were collected using a kit designated for an unscheduled collection rather than the actual visit kit. If the date of collection associated with an unscheduled sample is the same as the date of an actual visit, then the test result will be analyzed as the visit result.

Saliva cotinine levels may be reported by the central laboratory as less than the lower limit of quantitation (eg, result reported as "$<X_L$") or greater than the upper limit of quantitation (eg, result reported as "$>X_U$"). Results reported as "$<X_L$" will be converted to a numeric result of "X-1" prior to statistical analysis (eg, <1 ng/mL will be converted to 0 ng/mL). Results reported as "$>X_U$" will be converted to a numeric result of "X+1" prior to statistical analysis (eg, >750 ng/mL will be converted to 751 ng/mL).

Summary tables and figures of actual values and change from baseline saliva cotinine levels by treatment arm and visit will be provided for the All Randomized Set. Summary tables by treatment arm and visit will also be provided for each level (success, failure) of the primary efficacy endpoint for the All Randomized Set.

The treatment arms will be compared for change from baseline using repeated-measures analysis of variance models with fixed effect term for treatment arm, visit and visit x 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.

10.3.4. Continuous Vaping Abstinence Between Week 9 and Week 16

Analyses of continuous vaping abstinence between Week 9 and Week 16 will be conducted using the All Randomized Set. The analyses will follow the methodology for the primary efficacy endpoint described in Section 10.2.1.1, except that the stratification factor will not be included. The continuous vaping abstinence rate will be summarized by treatment arm. The 95% CIs for odds ratios and differences in proportions will be reported.

10.4. 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. Summaries will be provided for the All Randomized Set, unless otherwise specified.

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

10.4.1. MNWS Questionnaire

The MNWS questionnaire will be a measure for assessing nicotine withdrawal symptoms during Weeks 1-4 as well as for assessing possible cytisinicline withdrawal symptoms at the Week 12 visit (Day 86±1). It will be completed electronically by subjects at Week 1, Week 2, Week 3, Week 4, and pre- and post-Week 12 (ie, at visits named Day 83 and Day 89, respectively). The Day 83 questionnaire is expected to be completed 3 (±1) days prior to the Week 12 clinic visit. The Day 89 questionnaire is expected to be completed 3 (±1) days after the Week 12 clinic visit.

MNWS total scores and item scores will be summarized by treatment arm and visit for the All Randomized Set. Summary tables by treatment arm and visit will also be provided for each level (success, failure) of the primary efficacy endpoint for the All Randomized Set.

A separate summary will be provided for the Day 83 and Day 89 visits. The change in total MNWS score from Day 83 to Day 89 will be derived. Questionnaire total scores and change scores will be summarized by treatment arm and visit (Day 83, Day 89). A Student's t-test will be used to compare the treatment arms for change from Day 83 to Day 89. Summary tables by treatment arm and visit will also be provided for each level (success, failure) of the primary efficacy endpoint for the All Randomized Set.

Questionnaire total scores will be displayed graphically by visit and treatment arm.

10.4.2. Use of Any Other Nicotine Products

At each visit during treatment (Week 2 to Week 12) and at follow-up (Week 16) subjects report whether they have used any other combustible or non-combustible nicotine products since the last visit (yes, no) and report all products used during the interval (eg, pipe tobacco, cigars, snuff).

A summary table will report both the number (%) of subjects using any other nicotine product and the number (%) of subjects using each specific product. The summary table will include each visit from Week 2 to Week 16, as well as the following study periods: Week 2 to Week 16 (Entire Study Period), Week 2 to Week 12 (Treatment Period), and Week 16 (Follow-up Period). The summary table will be by treatment arm and time interval (ie, visit/study period). For the summary by study periods, multiple occurrences of the same nicotine product within a subject will be counted only once for each study period. Fisher's Exact Tests will be used to compare treatment arms in terms of the incidence of using any other nicotine products during the Treatment Period and the Follow-up Period.

Summary tables of use of any other nicotine products will also be provided by treatment arm and visit for each level (success, failure) of the primary efficacy endpoint for the All Randomized Set.

10.4.3. Other Questionnaires

The HADS, MCQ Short Form and PSECD questionnaires will be administered both at baseline and after the start of treatment. The HADS and PSECD will be administered at Screening, Week 6 and Week 12. The MCQ Short Form will be administered at Screening and Week 12.

For each questionnaire, total scores will be derived as described in Section 6.4.2. Change and percent change from baseline will be derived for subjects with non-missing results at both the baseline and post-baseline visit (see Section 6.3).

Actual scores, change from baseline and percent change from baseline will be summarized for each questionnaire by treatment arm and visit. Both total scores and item scores will be presented in the summary tables. For the PSECD, the number (%) of subjects in each dependence category (ie, not dependent, low dependence, medium dependence, high dependence) will also be summarized by treatment arm and visit.

Summary tables will also be provided by treatment arm and visit for each level (success, failure) of the primary efficacy endpoint for the All Randomized Set.

No statistical comparisons between the treatment arms are planned.

10.4.4. Relationship Between Treatment Effect and Demographic and Baseline Characteristics

The analyses described below will be performed for both the primary efficacy endpoint (nicotine vaping cessation from Week 9 to Week 12) and two of the secondary efficacy endpoints (nicotine vaping cessation from Week 3 to Week 6 and from Week 6 to Week 9). The objective of these analyses is to assess the homogeneity of treatment effect within strata (subgroups) defined by potential effect-modifying variables.

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, past smoker (yes, no), age when first cigarette smoked)
- Dependence on any marijuana use by MCQ-Short Form scores
- Vaping history variables (eg, total e-liquid (mL) from nicotine vaping products in past week, number of previous nicotine vaping quit attempts)
- Baseline electronic cigarette dependence by PSECD questionnaire scoring
- Baseline vaping variables (eg, number of days vaped over 7 consecutive days as reported in the subject vaping diary, 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) and their 95% CIs will also be reported. Forest plots will be used to display the stratum-specific 95% CIs.

10.5. 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 4.2.4). 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 AEs 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 16 visit). Treatment-emergent adverse events 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" or missing relationship.

Adverse event summaries will present data for the 2 treatment arms. An overall summary of AEs 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 1 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).

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

- Incidence by SOC and PT, in alphabetical order of SOC and PT, for both all TEAEs and related TEAEs
- Incidence by PT, in decreasing frequency of PT in the Cytisinicline 12 Weeks arm, for both all TEAEs and related TEAEs
- 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 in the Cytisinicline 12 Weeks arm
- Incidence of TEAEs by PT and severity (mild, moderate, severe), in alphabetical order of PT
- Incidence of TEAEs by PT and relationship (related, not related), in alphabetical order of PT

The following will also be summarized:

- Incidence of TEAEs by primary endpoint status.

In summaries of AE incidence, if a subject experiences the same PT multiple times that subject will be counted only once for that PT. Similarly, if a subject experiences multiple PTs 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 TEAEs 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

Treatment-emergent SAEs will be summarized by SOC and PT for each treatment arm using counts and percentages. The following summaries of treatment-emergent 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 the Cytisinicline 12 Weeks arm.

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 4.2.3 as the following events:

- Treatment-emergent suicidal ideation or behavior
- Treatment-emergent moderate to severe depression
- Treatment-emergent moderate to severe anxiety
- New pregnancy
- Treatment-emergent COVID-19.

The number (%) of subjects with each event will be summarized by treatment arm. In addition, the number (%) of subjects with each PT within the COVID-19 category 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 the Week 12/ET visit.

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, ALT, AST, alkaline phosphatase, glucose, sodium, potassium, calcium, creatinine, creatinine clearance/glomerular filtration rate and urea. 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 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 "<X_L") or greater than the upper limit of quantitation (eg, result reported as ">X_U"). Results reported as "<X_L" will be converted to a numeric result of "X" prior to statistical analysis (eg, <10 mg/dL will be converted to 10 mg/dL). Results reported as ">X_U" will be converted to a numeric result of "X" prior to statistical analysis (eg, >2000 mg/dL will be converted to 2000 mg/dL). Values outside the upper and lower limits of quantitation will be presented as collected (eg, "<10 mg/dL") 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), weekly during the treatment period, and at the Week 12/ET visit.

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 tables by treatment arm will summarize the number (%) of subjects at each visit who gain or lose ≥5% of their baseline body weight, as well as subjects who gain or lose ≥10% of their baseline body weight. The number (%) of subjects with at least 1 weight gain or loss from baseline of ≥5% and ≥10% will also be summarized by treatment arm.

The number and percentage 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/ET 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 1 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. Expired CO Levels

Nonsmoking at screening in this study is confirmed by standard expired CO levels <10 ppm. Expired CO levels (ppm) will be measured at SV1, Day 0, weekly during treatment (Week 2 to Week 12), and at follow-up (Week 16) as a safety measure to assess for the potential risk of a subject to start, or relapse into, smoking combustible cigarettes while trying to reduce or stop nicotine vaping.

Expired CO will be summarized by treatment arm and visit both as a categorical endpoint (<10 ppm, ≥10 ppm) and as a continuous endpoint (ppm). If a subject's expired CO level was ≥10 ppm at a visit details of cigarette smoking and cannabis/marijuana use since the last clinic visit were recorded on the Expired CO eCRF. Thus, the number (%) of subjects with at least 1 CO level ≥10 ppm that has been reported with combustible cigarette use during the Treatment Period (Week 2 to Week 12) and at follow-up (Week 16) will also be summarized.

Summary tables of expired CO will also be provided by treatment arm and visit for each level (success, failure) of the primary efficacy endpoint for the Safety Set.

The treatment arms will be compared for change from baseline using repeated-measures analysis of variance models with fixed effect term for treatment arm, visit and visit x 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.

11.6. 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 and/or day will be imputed as specified in Section 6.4.1.2. 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.

12. PHARMACOKINETIC ANALYSES

None planned.

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

There were typographical errors in Section 4.2 (Secondary Efficacy Objectives) of the protocol. The protocol stated that secondary objectives were to assess whether subjects assigned to Arm A (placebo) had higher probability of achieving secondary endpoints than Arm B (cytisinicline). The text in Section 3.2 of this document has been corrected.

The protocol made reference to "time to vaping abstinence" in two locations, the synopsis and Section 14.8. "Time to vaping abstinence" is not a study endpoint. The phrase was used in the protocol to describe a collection of study endpoints related to the timing of vaping abstinence, including the primary efficacy endpoint (vaping cessation Week 9 to Week 12) and assorted secondary efficacy endpoints (ie, vaping cessation Week 3 to Week 6 and Week 6 to Week 9, 7-day point prevalence Week 2 through Week 12, and continuous vaping abstinence Week 9 to Week 16).

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. Thomas DG. 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(1):105-110. DOI: 10.2307/2346643.
2. Thomas DG, Gart JJ. 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(357):73-76. DOI: 10.2307/2286908.
3. Yan X, Lee S, Li N. Missing data handling methods in medical device clinical trials. Journal of biopharmaceutical statistics 2009;19(6):1085-98. (In eng). DOI: 10.1080/10543400903243009.

APPENDIX 1. RANDOMIZATION PLAN

RANDOMIZATION SPECIFICATION

Sponsor:	Achieve Life Sciences
Protocol Number:	ACH-CYT-10
Protocol Version and Date:	V 3.0, 04-MAY-2022
Specification Version:	V 1.0
Specification Date:	24 MAY 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-10** study. The signatures below represent the approval and acceptance of this document by [redacted] and **Achieve.**

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

Approval (Achieve Life Sciences)	[redacted]

Table of Contents

Revision History

Version	Date	Prepared by	Brief Description of Change
0.1	18MAY2022	[redacted]	Initial Version
1.0	24MAY2022		Accepted track changes from client and updated to version 1.0

1 INTRODUCTION

1.1 Protocol Number:

- ACH-CYT-10

1.2 Study Title:

A Multicenter, Double-blind, Randomized,

Placebo-controlled Phase 2 Trial Evaluating the Efficacy and Safety of Cytisinicline in Adults Using Nicotine-containing E-cigarettes

1.3 Development Phase:

- Phase 2

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]
	RTSM Development Team Lead		Unblinded	
	RTSM, Subject Matter Expert		Unblinded	
	Project Manager		BLINDED	
Achieve Life Sciences	Biometrics		BLINDED	

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			Email of password protected zip file
Achieve Life Sciences	Verification	Dummy ONLY			Email of password protected zip file
[redacted]	Verification	Dummy ONLY			Email of password protected zip file
[redacted]	Verification	Dummy ONLY			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] Development 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	150
Number of sites	N/A
Number of treatment arms	2
Treatment arms description	1. Placebo 12 weeks 2. Cytisinicline 12 weeks
Allocation ratio	2 (Cytisinicline 12 weeks):1(Placebo 12 weeks)
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?	Yes. Subjects will be stratified on whether they have smoked >100 cigarettes in their lifetime (yes vs no).
How is the list stratified?	Stratification dynamically allocated per block
Additional comments	Maximum number of subjects to be randomize at each site is 45

5.2 Subject List File Attributes

File type	CSV (CSV files can be read into SAS datasets where required)
Dummy list filename	Achieve_ACH-CYT-10_Subjects_DUMMY_DDMMMYYYY.csv
Live list filename	Achieve_ACH-CYT-10_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	1-2
4	RG_DESC	Treatment Group Description	Text		Placebo 12 weeks Cytisinicline 12 weeks

Treatment group mapping
1 = Placebo 12 weeks
2 = Cytisinicline 12 weeks

APPENDIX 2. SCORING KEY FOR PENN STATE ELECTRONIC CIGARETTE DEPENDENCE INDEX

1. **How many times per day do you usually use your electronic cigarette? (assume one "time" consists of around 15 puffs, or lasts around 10 minutes)**
   0-4 times/day = 0
   5-9 = 1
   10-14 = 2
   15-19 = 3
   20-29 = 4
   30 or more = 5
2. **On days that you can use your electronic cigarette freely, how soon after you wake up do you first use your electronic cigarette?**
   Less than 5 minutes = 5
   6-15 minutes = 4
   16-30 minutes = 3
   31-60 minutes = 2
   61-120 minutes = 1
   More than 121 minutes = 0
3. **Do you sometimes awaken at night to use your electronic cigarette?**
   Yes = 1
   No = 0
4. **If yes, how many nights per week do you typically awaken to do so?**
   0-1 nights = 0
   2-3 nights = 1
   4 or more nights = 2
5. **Do you use an electronic cigarette now because it is really hard to quit (using e-cigs)?**
   Yes = 1
   No = 0
6. **Do you ever have strong cravings to use an electronic cigarette?**
   Yes = 1
   No = 0
7. **Over the past week, how strong have the urges to use an electronic cigarette been?**
   None/Slight = 0
   Moderate/Strong= 1
   Very Strong/Extremely Strong = 2
8. **Is it hard to keep from using an electronic cigarette in places where you are not supposed to?**
   Yes = 1
   No = 0
9. **(When you haven't used an electronic cigarette for a while or when you tried to stop using one:) Did you feel more irritable because you couldn't use an electronic cigarette?**
   Yes = 1
   No = 0

10. **Did you feel nervous, restless, or anxious because you couldn't use an electronic cigarette?**
    Yes = 1
    No = 0

RESULTS

0-3 = not dependent
4-8 = low dependence
9-12 = medium dependence
13 or more = high dependence