Statistical Analysis Plan

Sponsor Protocol Number: ACH-CYT-01

A Phase 1 Open Label, Randomised, Two-Way Crossover Study in Healthy Volunteers to Investigate the Effect of Food on the Bioavailability of Cytisine

[redacted]

Prepared for:

Achieve Life Sciences, Inc.

Prepared by:

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CONFIDENTIAL

Version	Author
Final Version 2.0	[redacted]

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A Phase 1 Open Label, Randomised, Two-Way Crossover Study in Healthy Volunteers to Investigate the Effect of Food on the Bioavailability of Cytisine

[redacted]

Author: [redacted]

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The undersigned have reviewed and revised this SAP and find it to be consistent with the study requirements:

[redacted] Date

[redacted] Date

[redacted] Date

[redacted] Date

TABLE OF CONTENTS

GLOSSARY OF ABBREVIATIONS

ADaM	Analysis Data Model
AE	Adverse Event
Ae	Amount Excreted
ANOVA	Analysis of Variance
AUC	Area Under the Plasma Concentration Curve
$AUC_{0-\infty}$	Area Under the Plasma Concentration-time Curve calculated from the time of dosing to infinity
AUC_{0-t}	Area Under the Plasma Concentration-time Curve calculated from the time of dosing to the last measurable concentration
BLQ	Below Limit of Quantification
BMI	Body Mass Index
CI	Confidence Interval
C_{max}	Maximum observed plasma concentration
CRF	Case Report Form
CS	Clinically Significant
CSR	Clinical Study Report
CV	Coefficient of Variation
DBL	Database Lock
DMP	Data Management Plan
DRM	Data Review Meeting
ECG	Electrocardiogram
GM	Geometric Mean
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
LLOQ	Lower Limit of Quantification
LSMean	Least Squares Mean
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Millilitre

NCS	Not Clinically Significant
PD	Pharmacodynamic
PK	Pharmacokinetics
PT	Preferred Term
QC	Quality Control
RBC	Red Blood Cell
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TFL	Table/Figure/Listing
T_{max}	Time from dosing to the maximum observed plasma concentration
WBC	White Blood Cell

1 INTRODUCTION

1.1 GENERAL

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analysis of data collected under the ACH-CYT-01 protocol dated 19th May 2017 and should be read in conjunction with the study protocol and case report form (CRF).

This version of the plan has been developed using the protocol version 1.0 dated 19th May 2017 and the annotated CRF. Any further changes to the protocol or CRF will be reviewed for potential impact on the SAP, which will be amended if it is deemed necessary.

Various internal draft versions of the SAP have been developed by [redacted] with input from Achieve. Achieve provided Version 1.0 (dated 20 June 2017) to FDA in support of the cytisine IND. This Version 2.0 has been approved by [redacted] and Achieve prior to Database Lock (DBL).

1.2 CHANGES FROM PROTOCOL

- Inclusion of a summary of vital signs data.
- Randomisation code will be generated using SAS 9.3.
- Individual QT corrections (QTcI) were not performed.
- Inclusion of a summary of ECG outliers.
- Inclusion of an ECG analysis set and ECG-PK analysis set.
- For the statistical analyses of gender and BMI effect, gender and BMI will be included as factors within the ANOVA rather than performing separate analysis within each gender/BMI category.
- Total amount excreted in urine over 24h (Total Ae) will also be included within the statistical analysis of food effect.

1.3 CHANGES FROM PREVIOUS VERSIONS OF THE SAP

The changes from the SAP Version1.0 are as follows:

- Removal of the summary of new ECG abnormalities.
- Individual QT corrections (QTcI) were not performed.
- Total Ae included within the statistical analysis of food effect.
- Inclusion of individual plasma concentration plots with one plot per subject,
- For the statistical analyses of gender effect and BMI, subject nested within sequence will be included as a random effect rather than a fixed effect.
- All PK summary tables and figures will be provided for the Safety Set, in addition to the primary analysis set (PK Set).

2 STUDY OBJECTIVES

Primary Objective:

The primary objective of this study is to compare the bioavailability (C_{max} and $AUC_{0-\infty}$) of cytisine in healthy subjects under fed and fasted conditions, following administration of 3 mg cytisine (2 x 1.5 mg cytisine tablets).

Secondary Objectives:

The secondary objectives of this study are:

- To compare the AUC_{0-t}, $T_{½}$, and T_{max} of cytisine in subjects under fed and fasted conditions, following administration of 3 mg cytisine (2 x 1.5 mg tablets).
- To assess the safety and tolerability of cytisine at the 3 mg dose level under fed and fasted conditions.
- To assess the renal elimination of cytisine via measurement of urinary concentrations of cytisine.
- To explore possible effects of other study parameters on the bioavailability of cytisine (e.g. gender, BMI).
- To explore for cytisine effects on QT/QTc interval prolongation and cardiac safety.

3 STUDY DESIGN

3.1 OVERVIEW

This is an open-label, randomised, 2-period, single-dose crossover Phase I study in 24 healthy volunteers (approximately 12 males and 12 females) to determine the comparative bioavailability of cytisine 3 mg dose under fed and fasted conditions.

The study is comprised of a pre-study screen, followed by 2 treatment periods (1 and 2) and a post-study follow-up. Screening assessments will be carried out within 28 days prior to first administration of IMP. Eligible subjects will be asked to return for the treatment periods. Continued eligibility will be confirmed pre-dose during each treatment period. Each treatment period will be of approximately 2 days duration with at least 72 h between dose administrations. Subjects will arrive at the Clinical Unit on Day -1 and undergo an overnight fast of at least 10 h prior to dosing on Day 1. Randomisation will occur on the morning of Day 1, Period 1, at least 1 h prior to dosing. Subjects will be administered IMP under fasted (after an overnight fast of at least 10 h) or fed (after a high fat breakfast) conditions and will be discharged 24 h post-dose (Day 2).

3.2 INCLUSION AND EXCLUSION CRITERIA

To be eligible for inclusion into this study, each subject must fulfil all inclusion criteria and not violate any exclusion criteria (for the protocol under which they are entered) during screening prior to randomisation. Details of the inclusion and exclusion criteria are presented within the protocol (sections 6.1, 6.2).

3.3 STUDY TREATMENT

Each subject will receive the following over 2 treatment periods in accordance with the randomisation schedule:

- 3 mg Cytisine (2 x 1.5 mg film coated tablets [redacted] under fasted conditions;
- 3 mg Cytisine (2 x 1.5 mg film coated tablets [redacted] under fed conditions.

Cytisine should be administered orally in a single dose application of two 1.5 mg tablets taken with 240 mL water.

3.4 SCHEDULE OF STUDY PROCEDURES

	Screening	**Study Day (Period 1 and Period 2)**			**Post-Study Telephone Call**
Days	-28 to -2	Day -1	1	2	6-8 days after last dose
Written informed consent	X				
Demographic data/height/weight	X				
Randomization			X (Pre-first dose in Period 1)		
Vital signs	X	X	X[1]		
Medical history	X				
Medical history update		X[2]			
Prior and concomitant medication	X	X	X	X	
Physical examination	X				
12-lead ECG	X			X[3]	
Holter monitor for continuous ECG readings[4]		X	X	X	
Pregnancy test for all females	X (Serum)	X (Urine)			
FSH (females only)	X				
Hematology	X			X	
Biochemistry	X			X	
Urinalysis	X			X	
Drugs-of-abuse tests in urine	X	X			
Verification of eligibility criteria	X	X	X		
Cytisine administration			X		
Blood and urine collection for PK analysis			X	X	
Adverse events monitoring		X[5]	X[5]	X[5]	X[5]

[1] Vital signs (supine blood pressure, pulse rate and oral temperature) will be recorded at pre-dose and again approximately 2 hours after administration on Day 1 of each period.
[2] Clinically relevant changes will be reported as adverse events.
[3] Repeat 12-lead ECG and assess prior to discharge.
[4] Attach ECG Holter monitor and begin recording on Day -1 and continue until 24 hours post dose.
[5] Adverse event recording to begin upon admissions on Day -1 of Period 1 to post study.

3.5 SAMPLE SIZE CONSIDERATIONS

A total of approximately 24 subjects will be randomised to the study, with approximately 12 subjects per treatment schedule arm.

Subject numbers are based on the following guidance: No previous pharmacokinetic studies with cytisine have reported the effects of repeated administration, so no estimates of intra-subject variability of C_{max} or AUC are available. A recent bioavailability study in a limited number of dogs[1] ,where cytisine was given in the fed and fasted states, indicated an increased C_{max} in the presence of food of 28%. A previous study[2] reported a total coefficient of variation (%CV) for C_{max} of 42%. Under the assumptions that a similar food effect will be observed in humans and that the intra-subject %CV will be less than the total %CV obtained from the previous study, based on an estimated geometric mean ratio for C_{max} of 1.30 (30% increase) and an estimated %CV of 35%, a sample size of 24 should be sufficient to meet the objectives of the study.

Subjects who withdraw from study at any time after randomisation will not be automatically replaced. Replacement based on the number and reason of withdrawals will be at discretion of the Sponsor, following discussion with the Principal Investigator.

3.6 RANDOMISATION

Subjects will be allocated to a treatment schedule (sequence) in accordance with a randomisation code produced by [redacted] using the PROC PLAN procedure of SAS® version 9.3. Treatment schedules are as follows:

Schedule A (12 subjects):

- Period 1: Cytisine (2 x 1.5 mg tablets) will be administered 30 minutes after the start of a high fat breakfast (fed state) with 240 mL (8 fluid ounces) water. No additional fluids are to be taken until 1 hour post-dosing.

- Period 2: Cytisine (2 x 1.5 mg tablets) will be administered after the overnight fast of at least 10 hours and subject will continue fasting until lunch (fasting state). Dosing will be administered with 240 mL (8 fluid ounces) water. Except for fluids taken for dosing, no fluids will be allowed from 1 hour before dosing until 1 hour post-dosing.

Schedule B (12 subjects):

- Period 1: Cytisine (2 x 1.5 mg tablets) will be administered after the overnight fast of at least 10 hours and subject will continue fasting until lunch (fasting state). Dosing will be administered with 240 mL (8 fluid ounces) water. Except for fluids taken for dosing, no fluids will be allowed from 1 hour before dosing until 1 hour post-dosing.

- Period 2: Cytisine (2 x 1.5 mg tablets) will be administered 30 minutes after the start of a high fat breakfast (fed state) with 240 mL (8 fluid ounces) water. No additional fluids are to be taken until 1 hour post-dosing;

Subjects will be numbered sequentially from 001 (i.e. 001, 002 etc.). Any replacement subjects will be assigned the same randomisation as the subjects they are replacing with 100 added to the subject number (i.e. 101 would replace 001 etc.).

4 STUDY VARIABLES AND COVARIATES

4.1 PRIMARY VARIABLES

The primary plasma cytisine pharmacokinetic endpoints for this study are as follows:

- C_{max} — Maximum observed plasma concentration post dose, obtained from the observed concentration versus time profile.
- $AUC_{0-\infty}$ — Total area under the plasma concentration-time curve (AUC) from zero to infinity, calculated as $AUC_{0-\infty} = AUC_{0-t} + (C_{last}/\lambda_z)$, where C_{last} is the last measureable plasma concentration and λ_z the apparent terminal elimination rate constant.

4.2 SECONDARY VARIABLES

The secondary plasma cytisine pharmacokinetic endpoints for this study are as follows:

- T_{max} — Time of occurrence of maximum observed plasma concentration.
- AUC_{0-t} — AUC from the time of zero to the last sampling time at which concentrations were at or above the lower limit of quantification (LLOQ), calculated by the linear-up/log-down trapezoidal rule.
- %AUC — Residual area or percentage of extrapolated part for the calculation of $AUC_{0-\infty}$, calculated as $100*[1-(AUC_{0-t}/ AUC_{0-\infty})]$.
- λ_z — Apparent terminal elimination rate constant.
- $t_{1/2}$ — Apparent terminal elimination half-life, calculated from $ln\ 2/\lambda_z$.

The secondary urine cytisine pharmacokinetic endpoints for this study are as follows:

- Ae — Amount excreted in urine over time.
- Ae% — Percentage of drug excreted in urine.

The safety endpoints for this study are as follows:

- Adverse events (AEs).
- Laboratory safety data (biochemistry, haematology, urinalysis and microscopy).
- Vital signs (supine systolic/diastolic blood pressure, pulse rate and oral temperature).
- 12-lead ECG (heart rate, PR interval, QRS width, QT interval and QT interval corrected using Fridericia's formula (QTcF interval).
- ECG Holter Monitoring (heart rate, PR interval, QRS width, QT interval and QTcF interval).

5 DEFINITIONS AND DERIVED VARIABLES

Study drug/IMP: Study drug/IMP means 3 mg cytisine (2 x 1.5 mg cytisine tablets).

Treatment: Treatment means 3 mg cytisine in the fed or fasted state.

Baseline: In general, baseline is defined by subject and by variable as the last non-missing value (including repeats) before the first dose of study drug. This is normally the pre-dose assessment on Day 1 but if this assessment is missing (or not planned) then the assessment at the Screening/Day -1 visit will be used instead if available.

For Holter ECG endpoints, a baseline value will be derived for each subject and ECG parameter (heart rate, PR interval, QRS width, QT interval and QTcF interval) by calculating the mean of all individual results recorded prior to the administration of study drug (i.e., at the -45 minute, -30 minute, -15 minute and pre-dose time points).

Study Day: Study day is the number of days since start of treatment where the date of first dose is counted as Day 1.

Bleed Time Deviation: Actual time of blood sample – theoretical time of blood sample.

Protocol Deviation: a deviation related to study inclusion or exclusion criteria, conduct of the trial, subject management or subject assessment. This refers to any change, divergence, or departure from the study design or procedures defined in the protocol. Deviations recorded by the Project Manager or detected by Data Management or by statistical programming checks will be identified and discussed at the Data Review Meeting (DRM) before Database Lock (DBL). All protocol deviations within the study database will be classified as either 'Major' or 'Minor' prior to DBL, details of which will be included within the Protocol Deviations listing.

6 ANALYSIS SETS

Membership of the analysis sets will be reviewed and agreed prior to DBL. These will be reviewed and signed off by the Sponsor, Study Statistician, PK analyst and Project Manager. If PK data is not available at the time of DBL, then subjects will be assumed to be included in the analysis set unless the PK data provide reason to exclude a subject, in which case this will be discussed with the Sponsor and documented within the Analysis Sets listing (Listing 16.2.3.1).

6.1 SAFETY SET

All randomised subjects who receive at least one dose of cytisine will constitute the Safety Set.

This analysis set will be used for baseline and safety summaries as well as for all study listings.

6.2 PK SET

The PK Set will include all subjects who receive both doses of cytisine and comply with the following criteria:

- Do not have an occurrence of vomiting or diarrhoea which renders the concentration profile unreliable;
- Do not use a concomitant medication which renders the concentration profile unreliable;
- Do not have a pre-dose concentration that is greater than 5% of the corresponding C_{max};
- Have at least one evaluable concentration that is preceded by a lower evaluable concentration and followed by a lower evaluable concentration for the calculation of C_{max}, T_{max} and AUCs (i.e. at least 3 evaluable concentrations in total);
- Do not violate the protocol (major protocol deviation) in a way that may invalidate or bias the results.

6.3 ECG SET

The ECG Set will include all subjects who receive at least one dose of cytisine, with at least one available baseline ECG and at least one on-treatment ECG.

6.4 ECG-PK SET

The ECG-PK Set will include all subjects who receive at least one dose of cytisine, with a time-matched ECG-PK pair at baseline and at least one time-matched pair on-treatment.

7 SAFETY MONITORING

Not applicable.

8 INTERIM ANALYSES

Not applicable.

9 DATA

9.1 CRF DATA

CRF data will be provided by [redacted] Data Management to the Statistics department as SAS datasets in [redacted] standard format. SDTM datasets will be derived from the raw database and ADaM from SDTM. Both SDTM and ADaM domains will be used for programming the outputs to be included in the Clinical Study Report (CSR). SDTM/ADaM programming will begin when populated [redacted] standard SAS datasets are available.

9.1.1 Laboratory Data

Transfers of safety laboratory data will be available from the Pathology laboratory and delivered to Data Management via electronic transfer and stored within the study database. Details of laboratory data are

documented in the Data Management Plan (DMP). Populated test transfers will be received before programming can start. The following results will be included:

- ***Haematology***: Haemoglobin (HGB), haematocrit (HCT), mean cell volume (MCV), mean cell haemoglobin (MCH), mean cell haemoglobin concentration (MCHC), red blood cells (RBC), white blood cells (WBC), neutrophils (NEUT), lymphocytes (LYMP), monocytes (MONO), eosinophils (EOS), basophils (BASO) and platelets (PLT).
- ***Biochemistry***: Total protein (TP), albumin (ALB), total bilirubin (BIL-T), alanine transaminase (ALT), aspartate transaminase (AST), gamma glutamyl transferase (GGT), alkaline phosphatase (ALKP), glucose (GLU), sodium (NA), potassium (K), bicarbonate (HCO_3), creatinine (CREA) and urea (UREA).
- ***Urinalysis:*** Glucose, specific gravity, protein, leukocyte esterase, ketones, urobilinogen, bilirubin, nitrites, pH and blood.
- ***Microscopy:*** RBC, WBC, epithelial cells, crystals, bacteria and casts - *if required*.

9.1.2 Pharmacokinetic Data

Plasma and urine concentration data will be received as an Excel file from the Bioanalytical department via an electronic transfer and stored as a SAS dataset. This data will then be stored in the appropriate SDTM domain and subsequent ADaM domain which will be used to produce the file provided to the pharmacokinetic team in order to derive the PK parameters using Phoenix WinNonlin 6.4. Derived PK parameters will be received by the Statistics department from the Project Manager/PK analyst in a SAS.xpt file in an agreed format and then stored as a SAS dataset and subsequently within SDTM/ADaM domains.

9.1.3 ECG Holter Monitoring Data

ECG Holter data will be received as an Excel file from CardioAnalytics (3rd party cardiac monitoring service managed by [redacted] via an electronic transfer and stored as a SAS dataset. This data will then be stored in the appropriate SDTM domain and subsequent ADaM domain.

9.2 RANDOMISATION LIST

The randomisation list will be uploaded to a SAS dataset.

9.3 PROGRAMMING AND DATA REVIEW

Programming of datasets, tables, figures and listings may be ongoing while study data management activities are in progress.

Prior to DBL, a review of the clinical database (i.e. CRF data, laboratory data) in the form of Excel data listings will be conducted. A Data Review Meeting (DRM) will be held to discuss the outcome of this review, any potential impact on the analyses, analysis sets and protocol deviations. Once all data issues

have been resolved and the analysis sets approved, the database will be locked. The SDTM/ADaM datasets will be finalised and the final run of outputs and quality control (QC) will take place.

10 STATISTICAL METHODS

10.1 GENERAL PRINCIPLES

- All statistical methods will be based on the International Conference on Harmonisation (ICH) E9 document "Statistical Principles for Clinical Trials".
- All data collected will be presented within data listings and any unscheduled visits will be listed.
- Data will be summarised by treatment and overall (data from both treatments pooled) where appropriate. The format of the summaries is defined in the shells at the end of this document.
- In summary and analysis tables of continuous variables, standard descriptive statistics (N [number within population], n [number of observations included in analysis], mean, standard deviation [SD], median, minimum and maximum) will be presented. Least squares mean (LS mean) and 90/95% confidence interval (CI) will be presented in the statistical analysis outputs as appropriate. For PK summaries, geometric mean, and coefficient of variation (%CV) will also be used to summarise the data.
- Unless otherwise specified, the minimum and maximum statistics will be presented in summary tables to the same number of decimal places as the original data. The mean, median, LS mean, geometric mean and CI will be presented to one more decimal place than the original data. SD will be presented to two more decimal places than the original data. %CV will be presented to one decimal place.
- In summary tables of categorical variables, the number of non-missing observations by category will be presented along with percentages. Unless otherwise specified, the denominator for each percentage will be the number of non-missing observations. All percentages will be presented to one decimal place.
- All plots will use a linear time scale for the nominal times of the visits and will be labelled by time point.
- Original values will be used in summary tables, unscheduled measurements will be listed only. However, where repeats of baseline values occur, the last assessment will be used within any summary tables and used to calculate change from baseline. In case an unscheduled measurement is performed immediately after the scheduled measurement due to an error in the original measurement, the unscheduled measurement will be included in the analysis and the original erroneous measurement will be excluded.
- The date format for all output presentations will be 'ddMMMyyyy'.
- All statistical analysis will be performed using SAS 9.3 or higher.
- All hypothesis testing will be carried out at the 5% (2-sided) significance level unless stated otherwise.
- P-values will be rounded to four decimal places. P-values less than 0.0001 will be reported as <0.0001 in tables.
- Generally, character values will be left aligned and numeric values will be decimally aligned.

- If any of the assumptions underlying the formal statistical methods proposed are violated during the analysis of the final data, alternative statistical methods will be used and any changes documented in the statistical methods section of the clinical study report (CSR), including the rationale for use.
- For numeric data which includes non-numeric values (e.g. PK data reported as BLQ or laboratory results reported as < 10 or >100) the following principles will be applied when summarising the data:
  - BLQ will be replaced with a zero.
  - Results reported as <*x* or >*x* will be treated as *x*.

10.2 STRATIFICATION AND COVARIATE ADJUSTMENT

In order to investigate any possible effects of gender on the comparative bioavailability of cytisine, the analysis of the pharmacokinetic data will be presented by gender (males, females, overall). Similarly, in order to investigate any potential effects of body mass index (BMI), the analysis of the pharmacokinetic data will also be presented by BMI category (18-22, 23-27, 28-32 kg/m^2), where BMI is rounded to an integer value.

10.3 MISSING DATA

Generally, no methods to impute missing data will be used. However, for the purpose of calculating change from baseline, in the instance of a missing baseline result for Period 1 (generally the assessment at Day 1, Pre-Dose) the results obtained at the Screening/Day -1 visit will be used instead, if available. Missing Period 2 baseline results will not be replaced.

In the instance of missing pharmacokinetic blood samples, the linear-up/log-down trapezoidal rule will be employed between the samples immediately before and after the missing sample for the AUC calculations.

10.4 POOLING OF SITES

Not applicable.

10.5 MULTIPLE COMPARISONS

Not applicable.

10.6 SUBGROUP ANALYSES

Not applicable.

10.7 STATISTICAL ISSUES

None.

11 STATISTICAL OUTPUT

General principles for layout of the statistical output are described in Section 10.1. Layout and specifications are illustrated for each unique table and listing within the shells presented in Section 14.

11.1 SUBJECT DISPOSITION

The subject disposition table will summarise the following data for all randomised subjects:

- The number (%) of subjects within each analysis set;
- The number (%) of subjects receiving each treatment;
- The number (%) of subjects within each treatment schedule (sequence);
- The number (%) of subjects who completed the Day 2 visit, where completion is defined as having PK sample collection at that visit.
- The number (%) of subjects who completed the study/withdrew from the study and the associated reasons for early study termination. A subject is deemed to have completed the study if they complete the Post-Study follow-up telephone contact.

Screening and study completion/termination data will also be listed. A listing of all subjects with protocol deviations will be presented including major/minor category. A data listing presenting subject eligibility for each analysis set and the reason for exclusion from an analysis set will also be presented.

11.2 SUBJECT CHARACTERISTICS AT BASELINE

11.2.1 Demographic and Baseline Characteristics

Demographic data will be listed (including informed consent information) and descriptive statistics for the continuous variables age, height, weight and BMI and frequencies for the categorical variable race will be tabulated. These descriptive statistics will be presented by gender (males, females, overall) and in a separate summary, by BMI category.

Alcohol and cotinine results collected at Screening and Day -1 will be listed and summarised using frequencies (n, %).

Demographic and baseline data will be listed and summarised using the Safety Set. Demographic data may also be summarised using the PK Set, if appropriate.

11.3 EFFICACY ANALYSES

Not applicable.

11.4 PK ANALYSES

The primary analysis set for summaries of PK data will be the PK Set. If the PK Set and the Safety Set are not equivalent, then all PK summaries described below will also be produced for the Safety Set.

11.4.1 Plasma Concentration Data

Plasma PK samples will be collected for measurement of cytisine at the following time points during each period: Pre-dose, 15 min, 20 min, 30 min, 45 min, 1h, 1.5h, 2h, 2.5h, 3h, 4h, 6h, 8h, 12h, 14h, 16h and 24h post-dose.

Cytisine concentrations in plasma will be listed and summarised for each treatment by gender (males, females, overall) using the descriptive statistics N, n, arithmetic mean, arithmetic standard deviation (SD), coefficient of variation (CV%), minimum, median and maximum.

The individual subject plasma cytisine concentration profiles over time will be presented graphically using actual blood sampling times on a linear and semi-logarithmic scale for each subject with both treatments on the same plot and also by treatment and gender (males, females, overall) with all subject profiles presented on the same plot. Arithmetic mean plasma cytisine concentration profiles over time will be presented on linear and semi-logarithmic scales with each treatment by gender (males, females, overall) presented on one plot. In addition, individual and mean plots will be presented in a similar manner by treatment and BMI category (18-22, 23-27, 28-32 kg/m^2).

For inclusion within the summary tables and linear scale plots, concentrations below the limit of quantification (BLQ) will be assigned a value of zero. Concentrations above the upper limit of quantification (ULOQ) will be obtained via dilution into the calibration range and are valid results. For inclusion within the semi-logarithmic scale plots, concentrations below the limit of quantification (BLQ) will be set to missing.

Plasma concentration data listings and individual plots will be presented using the Safety Set. Plasma concentration data summaries and mean plots will be presented using the PK Set and the Safety Set. All plasma concentration data included in listings and summaries will be presented to three significant figures.

11.4.2 Urine Concentration Data

Urine PK samples will be collected for measurement of cytisine at the following time intervals during each study period: Pre-dose, 0-2h, 2-4h, 4-8h, 8-12h and 12-24h post-dose.

Cytisine concentrations in urine will be listed and summarised for each treatment by gender (males, females, overall) using the descriptive statistics N, n, arithmetic mean, arithmetic standard deviation (SD), coefficient of variation (CV%), minimum, median and maximum. In addition, a similar summary will be presented by treatment and BMI category (18-22, 23-27, 28-32 kg/m^2).

11.4.3 Derived PK Parameters

The derived pharmacokinetic parameters of cytisine in plasma (listed in section 4) will be determined using WinNonlin Phoenix 6.3 from the individual concentration versus time data using standard non-compartmental methods. The derived urine pharmacokinetic parameters, Ae and Ae% (individual and cumulative), will be determined from the individual concentration versus time data using SAS version 9.3.

The terminal elimination rate constant (λ_z) will be determined by plotting the concentration data versus time on a semi-logarithmic scale. The parameter will be estimated by linear least square regression analysis, using the last three (or more) non-zero concentrations. The upper and the lower time points, as well as the number of time points, used for λ_z estimation will be reported.

AUC_{0-t} will be calculated using the linear-up/log-down trapezoidal method.

The derived urine PK parameter Ae will be calculated as: urine volume * urine cytisine concentration. AE% will be derived as: 100*Ae/Dose. The cumulative parameters are the sum of the individual values from 0h to 24h.

Values of λ_z, $AUC_{0-\infty}$, %AUC and $t_{½}$ will not be reported for cases where λ_z cannot be reliably determined.

For the calculation of derived pharmacokinetic parameters, concentrations below the limit of quantification (BLQ) will be assigned a value of zero. In case of a deviation from the theoretical time, the actual time of blood sample will be used in the calculation of the derived pharmacokinetic parameters.

Derived pharmacokinetic parameters will be listed and summarised for each treatment and gender (males, females, overall). The descriptive statistics presented will be N, n, arithmetic mean, arithmetic standard deviation (SD), coefficient of variation (CV%), minimum, median, maximum and geometric mean (with the exception of T_{max}).

In addition, derived pharmacokinetic parameters will be listed and summarised in the same manner for each treatment and BMI category (18-22, 23-27, 28-32 kg/m^2).

If no reliable PK parameter can be determined for more than a third of the subjects, only n, minimum and maximum values will be presented for that parameter and all other descriptive statistics will be omitted.

PK parameter data listings will be presented using the Safety Set. PK data summaries will be presented using the PK Set and the Safety Set. All PK parameter data included in listings and summaries will be presented to three significant figures with the exception of the CV% which will be presented to one decimal place.

11.4.3.1 Statistical Analysis of PK Parameters

Following logarithmic transformation, C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ and Total Ae values will be subjected to an analysis of variance (ANOVA) including fixed effects for sequence (treatment schedule), period, treatment and subject nested within sequence. Point estimates and 90% confidence intervals (CI) will be constructed for the contrasts between fed and fasted states using the residual mean square error obtained from the ANOVA. The point and interval estimates will be back-transformed to give estimates of the ratios of the geometric least squares means (LSmean) and corresponding 90% CI. In addition, estimated geometric means will be presented.

An assessment of T_{max} will be performed using the Wilcoxon Signed-Rank test. In addition, the Hodges-Lehmann estimate of the median difference in T_{max} and 95% CI will be presented.

For the purpose of exploring whether gender may have an effect on bioavailability, following logarithmic transformation, C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ values will be subjected to an analysis of variance (ANOVA) including fixed effects for sequence (treatment schedule), period, treatment, gender and gender*treatment interaction and a random effect of subject nested within sequence.

In addition, for the purpose of exploring whether BMI may have an effect on bioavailability, following logarithmic transformation, C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ values will be subjected to an analysis of covariance (ANCOVA) including fixed effects for sequence (treatment schedule), period and treatment, a random effect of subject nested within sequence and BMI as a covariate.

11.5 PD ANALYSES

Not applicable.

11.6 SAFETY ANALYSES

11.6.1 Adverse Events

All AEs will be coded using the MedDRA dictionary using the version specified in the Data Management Plan (DMP).

All AEs, including those which occurred prior to the first dose of study drug, will be listed. Only treatment emergent adverse events (TEAEs), i.e., existing conditions that worsen or events that occur during the course of the study after administration of IMP, will be included within the summary tables. AEs occurring post-dose on Period 1 up to immediately prior to dosing on Period 2 will be assigned to the corresponding Period 1 treatment. Similarly, any AEs occurring post-dose on Period 2 up to Post-Study will be assigned to the corresponding Period 2 treatment. TEAEs will be summarised by treatment and overall.

An overall summary of AEs will be produced including the number of TEAEs; the number and % of subjects reporting at least 1 TEAE, serious TEAE (where SAE is reported as 'Yes'), TEAE leading to withdrawal from study drug (Action recorded as 'Study Drug Discontinued'); the number and % of subjects reporting TEAEs by severity and relationship to study drug. A subject with multiple occurrences of any AE is counted only once at the maximum level of severity or the highest association to study drug.

The number of TEAEs and the number and % of subjects reporting at least one TEAE will be tabulated by system organ class (SOC) and preferred term (PT). A subject reporting multiple episodes of a particular AE within a treatment period will only contribute one count towards the corresponding SOC and preferred term. The number of TEAEs and the number and % of subjects reporting at least one TEAE will also be tabulated by preferred term (PT), with the PTs sorted in descending order of frequency. A subject reporting multiple episodes of a particular AE within a treatment period will only contribute one count towards the corresponding PT.

In addition, the number and % of subjects reporting TEAEs will be tabulated by maximum severity and strongest relationship to study drug. For the summary of TEAEs by severity, if a subject has multiple events occurring within the same SOC or preferred term the event with the highest severity will be counted. Similarly, for TEAEs by relationship to study drug, if a subject has multiple events occurring within the same SOC or PT, the event with the highest association to study drug will be counted.

Data will be listed by treatment. For any adverse event taken prior to first administration of study drug, treatment will be described as 'Prior to Treatment'.

Where there are only partial dates/times recorded for adverse events, adverse events will be assigned to treatment unless it can be ruled out based on the partial information.

The derived variables, 'Time from Dose' and 'Duration' will be presented where full date and time are present. If partial dates are present for any parameter required in the calculation, then the variable will not be populated. The following will be used to calculate the variables:

Duration: (Date/Time of Resolution-Date/Time of Onset) + 1 minute;

Time from Dose: (Date/Time of Onset-Date/Time of Start of Dose).

The following will be presented in listing format within the data summaries:

Serious Adverse Events – If there are none present, the listing will be produced stating: 'No subjects experienced any serious adverse events'.

Adverse Events which Led to Withdrawal of Study Drug – If there are none present, the listing will be produced stating: 'No subjects experienced any adverse events that led to withdrawal of study drug'.

Adverse event data will be summarised and listed using the Safety Set.

11.6.2 Laboratory Data

Routine safety laboratory tests will be carried out at Screening and Day 2 of each study period.

The laboratory parameters required for this study are listed in section 9.2.1.

Laboratory data listings will be presented in two ways:

- Out of range values - any values that fall outside of the normal/alert ranges (presented in listing format within the data summaries)
- All laboratory data (including physician's review (Normal, Abnormal-NCS, Abnormal-CS)) with any out of range values flagged (presented within the data listings).

Laboratory data will be listed using the Safety Set.

11.6.3 Vital Signs

Vital signs will be taken at Screening, Day -1 and pre-dose and 2h post-dose on Day 1 of each study period.

Vital signs parameters (supine systolic and diastolic blood pressure and pulse rate and oral temperature) will be listed with any out of normal range values (see Appendix 1) flagged (flag 'H' or 'L' appended to relevant result). Descriptive statistics (N, n, mean, SD, minimum, median and maximum) of absolute and change from pre-dose on Day 1 to post-dose on Day 1 will be tabulated by treatment.

Vital signs data will be summarised and listed using the Safety Set.

11.6.4 Electrocardiogram

11.6.4.1 12-Lead ECG

A 12-lead ECG will be performed at Screening and prior to discharge on Period 2, Day 2.

12-lead ECG parameters (heart rate, PR interval, QRS width, QT interval and QTcF interval) will be listed with any out of normal range values (see Appendix 16.1) flagged (flag 'H' or 'L' appended to relevant result). The ECG results will also be assessed as either 'normal' or abnormal' with comments on abnormal results also presented.

12-lead ECG data will be listed using the Safety Set.

11.6.4.2 Holter Monitoring

The ECG extraction time points will be from extraction windows which precede the PK blood draws. ECG parameters (heart rate, PR interval, QRS width, QT interval and QTcF interval) will be extracted in triplicate from Holter recordings at 45, 30 and 15 minutes prior to pre-dose and at pre-dose, 0.5h, 1h, 2h, 3h, 4h, 6h, 8h, 12h and 24h post dose on both study periods.

The extracted ECG parameters will be listed with any out of normal range values (see Appendix 1) flagged (flag 'H' or 'L' appended to relevant result). The ECG results will also be assessed as either 'normal' or abnormal' with comments on abnormal results also presented.

The mean of the triplicate recordings at each time point will be calculated for use in the summary tables and plots. Descriptive statistics (N, n, mean, SD, minimum, median and maximum) of absolute and change from baseline (see definition, Section 5) values at each time point up to 24h, will be tabulated by treatment. The change from baseline ECG results will also be plotted over time from Day 1, pre-dose up to 24h by treatment.

In addition, frequencies of QTcF data will be calculated according to the following categories:

For absolute values:

- QTcF ≤ 450 mSec
- 450 < QTcF ≤ 480 mSec
- 480 < QTcF ≤ 500 mSec
- QTcF > 500 mSec.

For change from baseline:

- QTcF increase ≤ 30 mSec
- 30 < QTcF increase ≤ 60 mSec
- QTcF increase > 60 mSec.

The presence of outliers will be explored for heart rate, PR interval, QRS width, QT interval and QTcF interval). The outlier analysis will use the time-averaged baseline (see definition, Section 5) and compare that baseline value to each of the individual on-treatment ECG time point values. Outliers are defined as follows for this analysis:

- Heart rate: A value for a subject will be considered to be an outlier at a pre-defined post dose time point if the heart rate measurement at that time point is <50 bpm and the measure is at least a 25% decrease from the subject's baseline mean heart rate (i.e., a bradycardic event) or if the heart rate measurement at the pre-defined post dose time point is >100 bpm and the measure is at least a 25% increase from the baseline mean heart rate (i.e., a tachycardic event).
- PR interval: A value for a subject will be considered to be an outlier at a pre-defined post dose time point if the PR interval at that pre-defined post dose time point is >200 mSec and it is at least a 25% increase from the subject's baseline mean PR interval.
- QRS width: A value for a subject will be considered to be an outlier at a pre-defined post dose time point if the QRS width at that pre-defined post dose time point is >100 mSec and it is at least a 25% increase from the subject's baseline mean QRS width.
- QT interval: A value for a subject will be considered to be an outlier at a pre-defined post dose time point if the QT interval at that pre-defined post dose time point is >500 mSec and the subject's baseline mean QT interval is ≤500 mSec.
- QTcF interval: A value for a subject will be considered to be an outlier at a pre-defined post dose time point if the QTcF interval at that pre-defined post dose time point is >500 mSec and the subject's baseline mean QTcF interval is ≤500 mSec. Outlier values will also be presented if the QTcF interval at a pre-defined post dose time point is >480 mSec when the subject's baseline mean QTcF interval is ≤480 mSec and when a pre-defined post dose time point is >450 mSec when the subject's baseline mean QTcF interval is ≤450 mSec.

The number (%) of subjects with at least one outlier will be summarized by treatment for each ECG parameter. For heart rate, separate summaries will be provided for bradycardic events (i.e., decreases) and tachycardic events (i.e. increases).

Holter ECG data will be listed for the Safety Set and summarised using the ECG Set.

11.7 PK/PD

In order to explore the effects of cytisine on QTc prolongation, individual cytisine concentrations in plasma and individual absolute and change from baseline Holter QTcF values will be presented together in a listing. A scatter plot will be presented for each of the Holter extraction time points (0.5h, 1h, 2h, 3h, 4h, 6h, 8h, 12h and 24h) with the individual change from baseline QTcF value plotted against the corresponding cytisine concentration. Both treatments will be presented on the same plot along with their correlation coefficients.

Holter ECG versus plasma concentration data will be listed and plotted for subjects in the ECG-PK Set.

There are currently no plans for a statistical analysis of the paired plasma concentrations (PK) and QTc (ECG). The Sponsor may conduct such an analysis at a later date. In that case, a formal, prospective statistical analysis plan document will be authored that describes those planned analyses and prospectively details the PK-PD model to be used.

11.8 ALL OTHER DATA

All data will be listed, including the following: Tobacco and Alcohol Use, Visit Dates, Medical History, Menstrual and Obstetric History, Pregnancy Test Results, Physical Examination, Concomitant Medication, Physician's Review of Laboratory Safety Data, Inclusion/Exclusion Criteria Failures, Virology Results, Drugs of Abuse Results, Dose Administration, Urine Volumes and Additional Notes.

Derivations within listings:

PK Blood Sampling Time Deviations: Calculate sample time deviation as: actual time – theoretical time, display in minutes.

Analysis Sets: Detail whether subject should be included in each of the analysis sets along with corresponding comments if not included.

Inclusion/Exclusion Criteria: Only failures to be recorded. If no failures display '*All subjects passed inclusion/exclusion criteria*'.

Protocol Deviations: Major/Minor category to be assigned and confirmed by Sponsor.

Prior and Concomitant Medication: Calculation of the treatment period on which the concomitant medication was taken (prior to treatment/study drug) will be calculated as per adverse events specification, using the concomitant medication start and stop dates. A medication will be regarded as '*prior*' if it stops prior to dosing, '*prior and ongoing*' if it starts prior to dosing and continues after dosing and '*concomitant*' if it starts after dosing. All medications will be coded using the WHO Drug Dictionary (version as specified in the DMP) and listed using the ATC Level 4 class, Preferred Term and verbatim text.

12 VALIDATION

All tables, figures and listings will be subject to independent quality control and visual review. Unique tables will be independently programmed. Findings will be documented in an Output Summary file quality control form and actions taken will also be documented.

The study summary sheet of the Output Summary file will be completed and signed by all persons who performed QC. The final version of the Output Summary, including the signed summary sheet, will be printed and stored in the Data Management File. The study summary sheet of the Output Summary file will be completed and signed by all persons who performed QC. The final version of the Output Summary, including the signed summary sheet, will be printed and stored in the Data Management File (DMF).

13 LITERATURE CITATIONS/REFERENCES

[1] SRI Study No. M261-16.

[2] Jeong SH, Newcombe D, Sheridan J, Tingle M. Pharmacokinetics of cytisine, an alpha4 beta2 nicotinic receptor partial agonist, in healthy smokers following a single dose. Drug testing and analysis 2015;7:475-82.

14 LIST OF TABLES, FIGURES AND LISTINGS

List of Tables and Figures Contained in Report Section 14

14.1 Disposition and Demographic Data

14.1.1 Disposition Data

Table 14.1.1.1	Summary of Study Disposition	Safety Set

14.1.2 Demographic Data

Table 14.1.2.1	Summary of Demographic Data by Gender	Safety Set
Table 14.1.2.2	Summary of Demographic Data by BMI Category	Safety Set

14.2 Efficacy Data

Not Applicable.

14.3 Safety Data

14.3.1 Adverse Events

Table 14.3.1.1	Summary of Treatment Emergent Adverse Events	Safety Set
Table 14.3.1.2	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety Set
Table 14.3.1.3	Summary of Treatment Emergent Adverse Events by Preferred Term	Safety Set
Table 14.3.1.4	Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Severity	Safety Set
Table 14.3.1.5	Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Relationship	Safety Set
Table 14.3.1.6	Serious Adverse Events	Safety Set
Table 14.3.1.7	Adverse Events Leading to Withdrawal of Study Drug	Safety Set

14.3.2 Laboratory Safety

Table 14.3.2.1	Biochemistry Out of Range Data	Safety Set
Table 14.3.2.2	Haematology Out of Range Data	Safety Set
Table 14.3.2.3	Urinalysis Out of Range Data	Safety Set

14.3.3 Vital Signs

Table 14.3.3.1	Summary of Absolute and Change from Pre-Dose to Post-Dose Vital Signs Data	Safety Set

14.3.4 ECG

Table 14.3.4.1	Summary of Absolute and Change from Baseline Holter ECG Data	ECG Set
Table 14.3.4.2	Summary of Holter ECG QTcF Categories	ECG Set
Table 14.3.4.3	Summary of Treatment-Emergent Holter ECG Abnormalities	ECG Set
Table 14.3.4.4	Summary of Holter ECG Outliers	ECG Set
Figure 14.3.4.1	Mean Change from Baseline Holter ECG Data	ECG Set
Figure 14.3.4.2	Individual Change from Baseline Holter ECG QTcF versus Plasma Cytisine Concentration Data.	ECG-PK Set

14.4 Pharmacokinetics

14.4.1 Concentration-Time Data

Table 14.4.1.1	Summary of Plasma Cytisine Concentration Data by Treatment and Gender	PK Set
Table 14.4.1.2	Summary of Plasma Cytisine Concentration Data by Treatment and Gender	Safety Set
Table 14.4.1.3	Summary of Plasma Cytisine Concentration Data by Treatment and BMI Category	PK Set
Table 14.4.1.4	Summary of Plasma Cytisine Concentration Data by Treatment and BMI Category	Safety Set
Table 14.4.1.5	Summary of Urine Cytisine Concentration Data by Treatment and Gender	PK Set
Table 14.4.1.6	Summary of Urine Cytisine Concentration Data by Treatment and Gender	Safety Set
Table 14.4.1.7	Summary of Urine Cytisine Concentration Data by Treatment and BMI Category	PK Set
Table 14.4.1.8	Summary of Urine Cytisine Concentration Data by Treatment and BMI Category	Safety Set
Figure 14.4.1.1	Mean Plasma Cytisine Concentration-Time Curves by Treatment and Gender - Linear Scale	PK Set
Figure 14.4.1.2	Mean Plasma Cytisine Concentration-Time Curves by Treatment and Gender - Linear Scale	Safety Set

Figure 14.4.1.3	Mean Plasma Cytisine Concentration-Time Curves by Treatment and Gender - Semi-Logarithmic Scale	PK Set
Figure 14.4.1.4	Mean Plasma Cytisine Concentration-Time Curves by Treatment and Gender - Semi-Logarithmic Scale	Safety Set
Figure 14.4.1.5	Mean Plasma Cytisine Concentration-Time Curves by Treatment and BMI Category - Linear Scale	PK Set
Figure 14.4.1.6	Mean Plasma Cytisine Concentration-Time Curves by Treatment and BMI Category - Linear Scale	Safety Set
Figure 14.4.1.7	Mean Plasma Cytisine Concentration-Time Curves by Treatment and BMI Category - Semi-Logarithmic Scale	PK Set
Figure 14.4.1.8	Mean Plasma Cytisine Concentration-Time Curves by Treatment and BMI Category - Semi-Logarithmic Scale	Safety Set

14.4.2 Derived Pharmacokinetic Data

Table 14.4.2.1	Summary of Derived Cytisine Pharmacokinetic Parameters by Treatment and Gender	PK Set
Table 14.4.2.2	Summary of Derived Cytisine Pharmacokinetic Parameters by Treatment and Gender	Safety Set
Table 14.4.2.3	Summary of Derived Cytisine Pharmacokinetic Parameters by Treatment and BMI Category	PK Set
Table 14.4.2.4	Summary of Derived Cytisine Pharmacokinetic Parameters by Treatment and BMI Category	Safety Set
Table 14.4.2.5	Summary of Statistical Analysis of Cytisine C_{max}, AUC and Total Ae	PK Set
Table 14.4.2.6	Summary of Statistical Analysis of Cytisine C_{max}, AUC and Total Ae	Safety Set
Table 14.4.2.7	Summary of Statistical Analysis of Cytisine T_{max}	PK Set
Table 14.4.2.8	Summary of Statistical Analysis of Cytisine T_{max}	Safety Set
Table 14.4.2.9	Summary of Statistical Analysis: Effect of Treatment and Gender on C_{max} and AUC	PK Set
Table 14.4.2.10	Summary of Statistical Analysis: Effect of Treatment and Gender on C_{max} and AUC	Safety Set
Table 14.4.2.11	Summary of Statistical Analysis: Effect of Treatment and BMI on C_{max} and AUC	PK Set
Table 14.4.2.12	Summary of Statistical Analysis: Effect of Treatment and BMI on C_{max} and AUC	Safety Set

14.5 Pharmacodynamics

Not applicable.

14.6 Other

14.6.1 Alcohol and Cotinine Results

Table 14.6.1.1	Summary of Alcohol and Cotinine Results	Safety Set

Subject Data: Listings Contained in Report Appendix 16.2

16.2.1 Visit Dates, Dosing Information and Disposition

Listing 16.2.1.1	Visit Dates	Safety Set
Listing 16.2.1.2	Dose Administration	Safety Set
Listing 16.2.1.3	Subject Disposition	Safety Set
Listing 16.2.1.4	Additional Notes	Safety Set

16.2.2 Protocol Deviations

Listing 16.2.2.1	Protocol Deviations	Safety Set

16.2.3 Analysis Sets

Listing 16.2.3.1	Analysis Sets	Safety Set

16.2.4 Demographic Data and Other Baseline Characteristics

Listing 16.2.4.1	Demographic Data	Safety Set
Listing 16.2.4.2	Medical History and Concurrent Conditions	Safety Set
Listing 16.2.4.3	Virology Results	Safety Set
Listing 16.2.4.4	Tobacco and Alcohol Use	Safety Set
Listing 16.2.4.5	Drugs of Abuse Results	Safety Set
Listing 16.2.4.6	Menstrual and Obstetric History	Safety Set
Listing 16.2.4.7	Pregnancy Test Results	Safety Set
Listing 16.2.4.8	Inclusion/Exclusion Criteria Failures	Safety Set

16.2.5 Drug Concentration Data and Pharmacokinetics

Listing 16.2.5.1	Plasma Cytisine Concentration Data	Safety Set
Listing 16.2.5.2	Urine Cytisine Concentration Data	Safety Set
Listing 16.2.5.3	Individual Derived Cytisine Pharmacokinetic Parameters	Safety Set

Figure 16.2.5.1	Individual Plasma Cytisine Concentration-Time Curves - Linear Scale	Safety Set
Figure 16.2.5.2	Individual Plasma Cytisine Concentration-Time Curves - Semi-Logarithmic Scale	Safety Set
Figure 16.2.5.3	Individual Plasma Cytisine Concentration-Time Curves by Gender - Linear Scale	Safety Set
Figure 16.2.5.4	Individual Plasma Cytisine Concentration-Time Curves by Gender - Semi-Logarithmic Scale	Safety Set
Figure 16.2.5.5	Individual Plasma Cytisine Concentration-Time Curves by BMI Category - Linear Scale	Safety Set
Figure 16.2.5.6	Individual Plasma Cytisine Concentration-Time Curves by BMI Category - Semi-Logarithmic Scale	Safety Set

16.2.6 Efficacy

Not applicable.

16.2.7 Adverse Events

Listing 16.2.7.1	Adverse Events	Safety Set

16.2.8 Individual Laboratory Safety Measurements

Listing 16.2.8.1	Biochemistry Data	Safety Set
Listing 16.2.8.2	Haematology Data	Safety Set
Listing 16.2.8.3	Urinalysis Data	Safety Set
Listing 16.2.8.4	Microscopy Data	Safety Set
Listing 16.2.8.5	Physician's Review of Laboratory Safety Data	Safety Set

16.2.9 Vital Signs

Listing 16.2.9.1	Vital Signs Data	Safety Set

16.2.10 Physical Examination

Listing 16.2.10.1	Physical Examination Data	Safety Set

16.2.11 ECG

Listing 16.2.11.1	12-Lead ECG Data	Safety Set
Listing 16.2.11.2	Holter Monitoring ECG Data	Safety Set

Listing 16.2.11.3	Change and Percentage Change from Baseline Holter ECG Data	Safety Set
Listing 16.2.11.4	Holter ECG QTcF and Plasma Cytisine Concentration Data	Safety Set
Listing 16.2.11.5	Holter Monitoring Information	Safety Set

16.2.12 Prior and Concomitant Medication

Listing 16.2.12.1	Prior and Concomitant Medication Use	Safety Set

16.2.13 Pharmacodynamics

Not applicable.

15 SHELLS FOR TABLES, FIGURES AND LISTINGS

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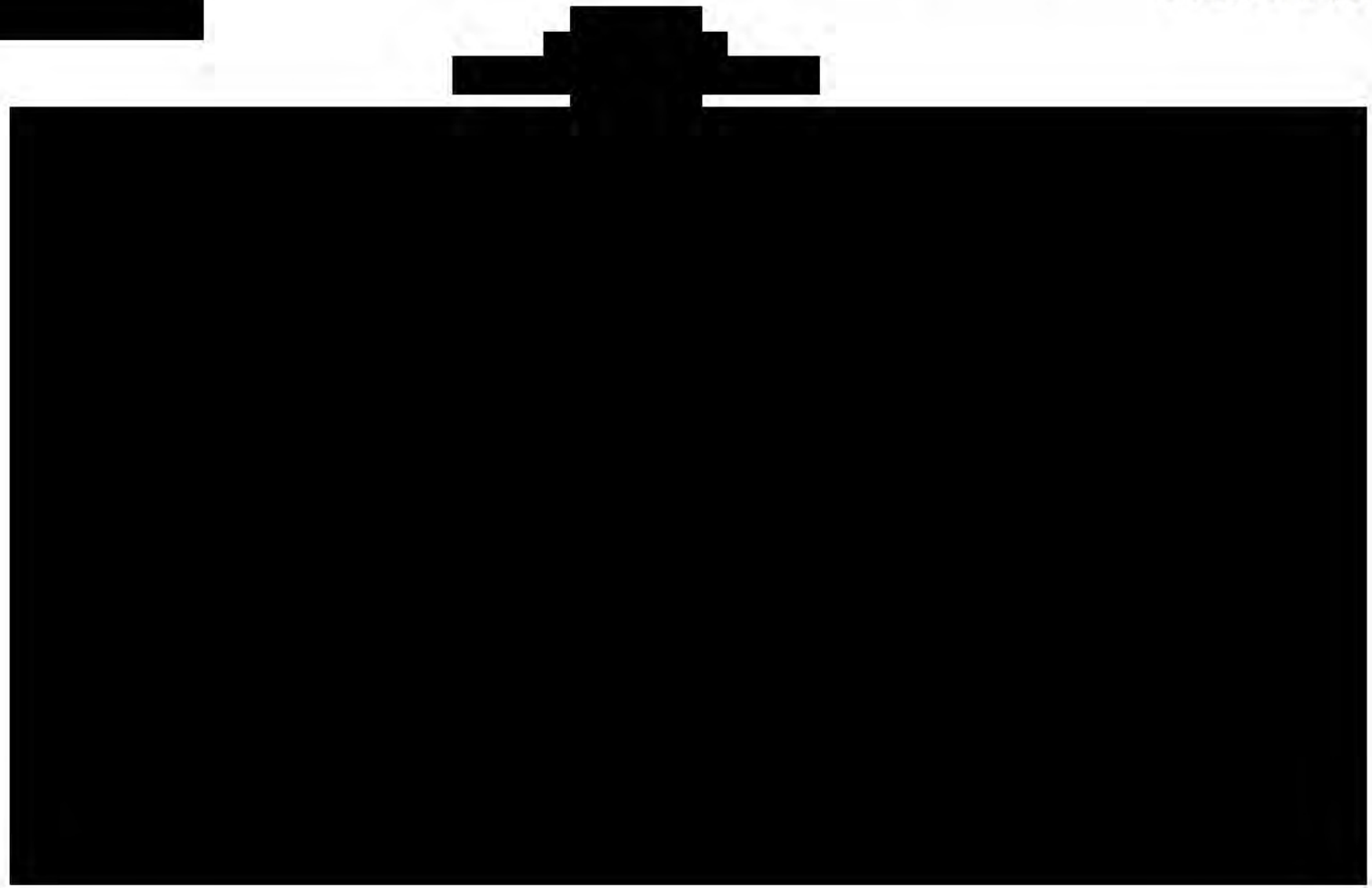

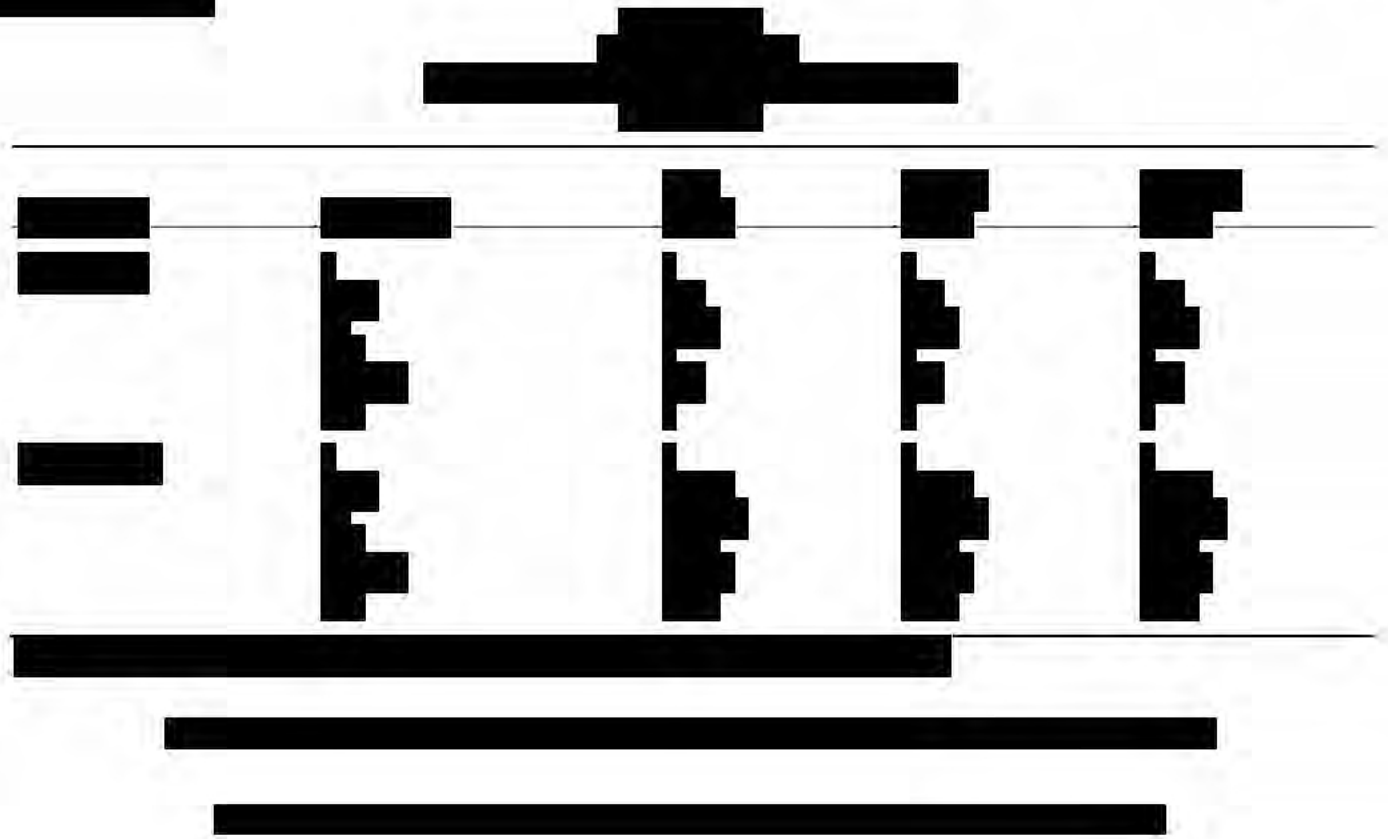

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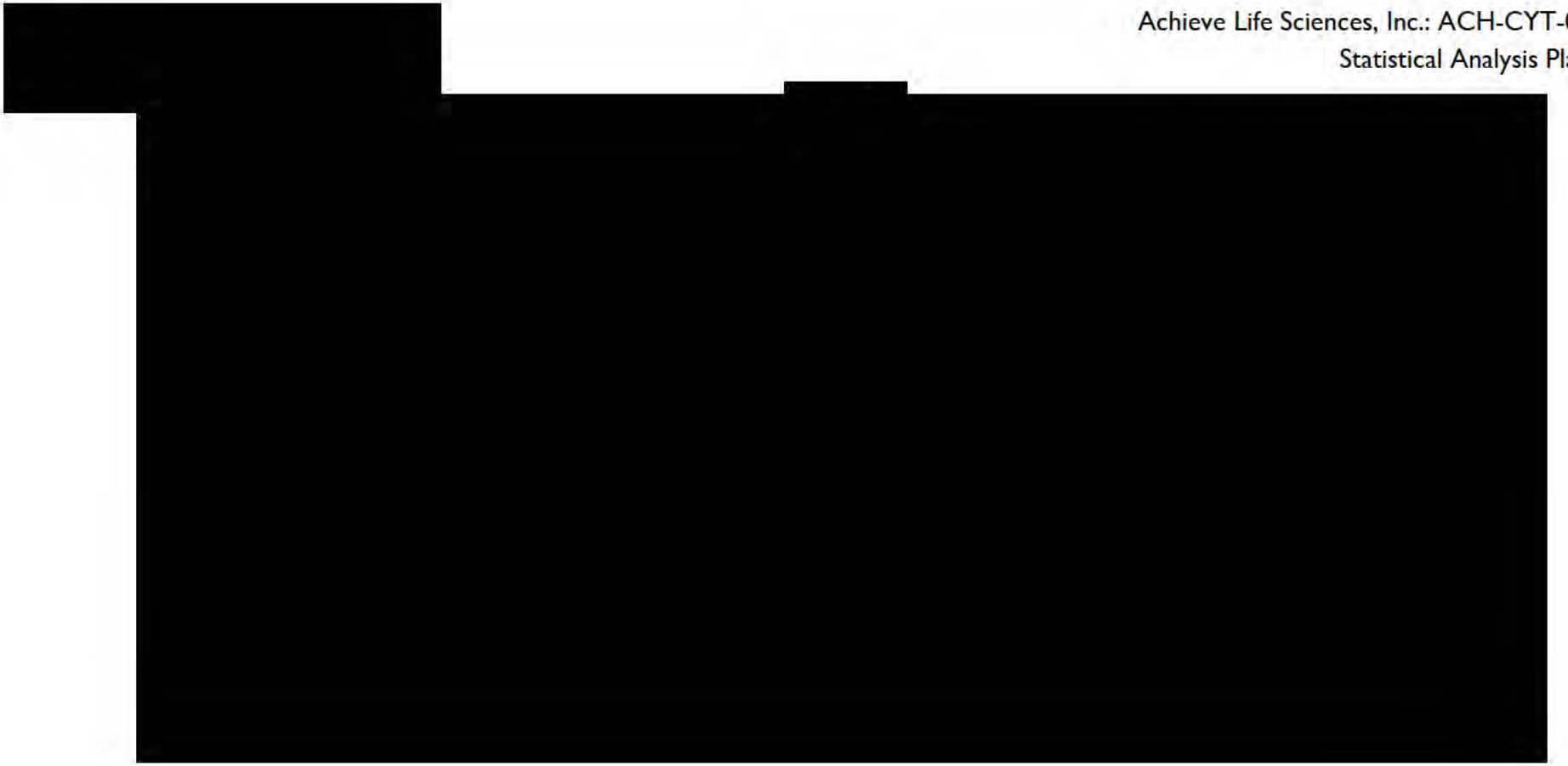

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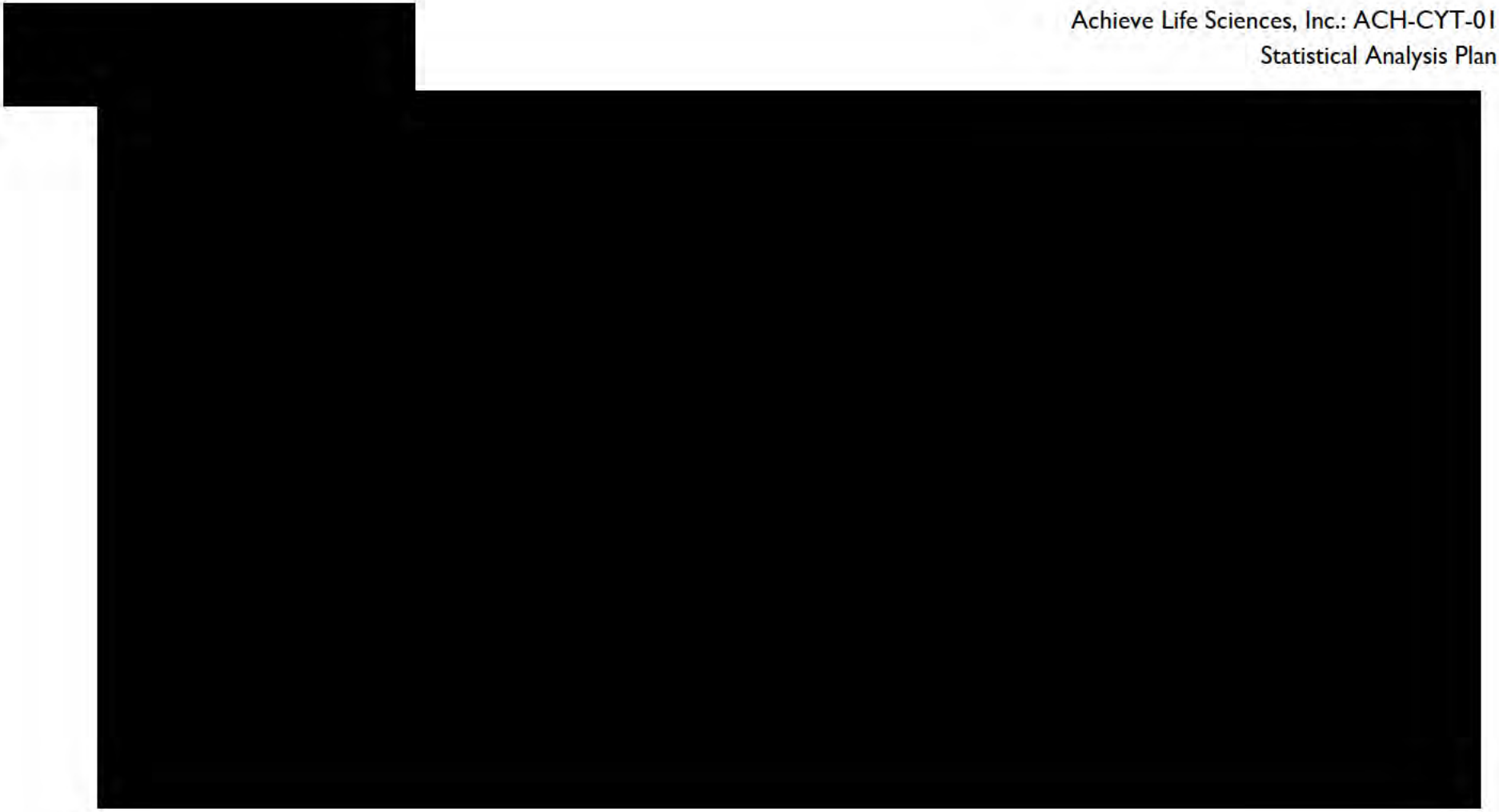

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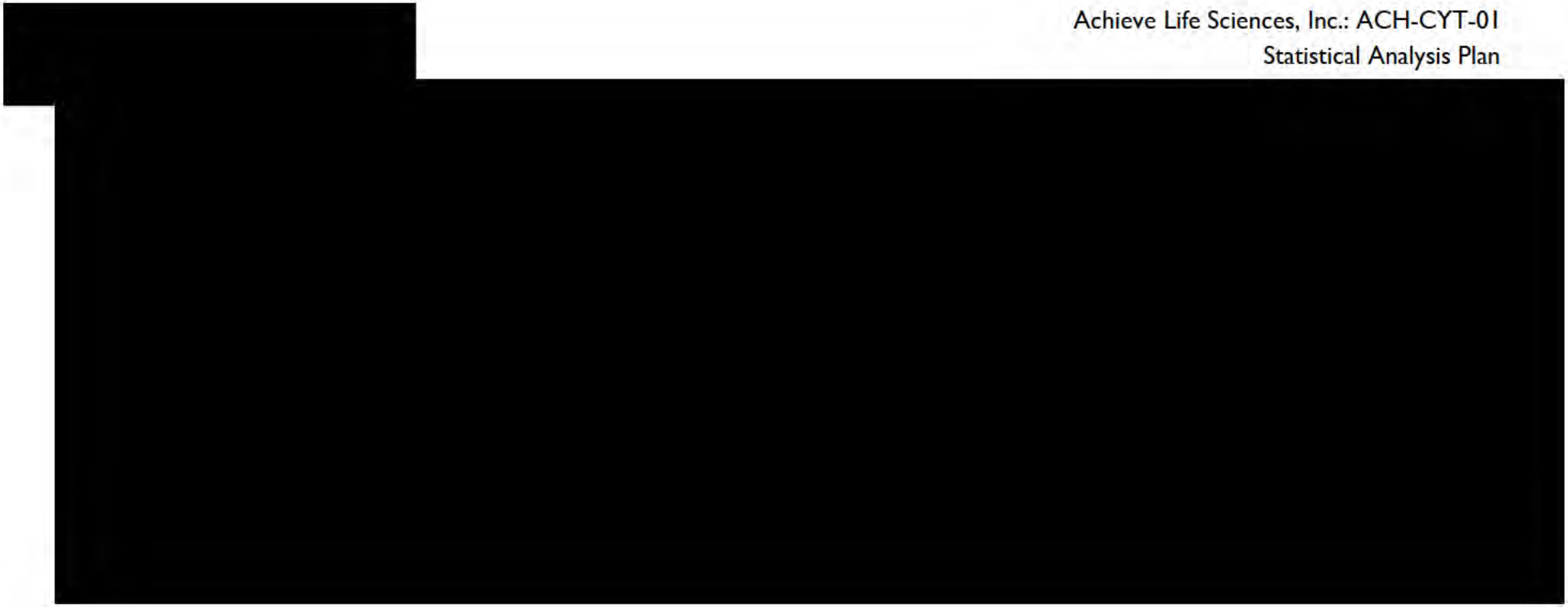

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16 APPENDICES

16.1 NORMAL RANGES

Vital Signs Normal Ranges:

Parameter	Normal Range	Units
Pulse Rate	40-110	Beats per minute (bpm)
Systolic Blood Pressure	90-150	mmHg
Diastolic Blood Pressure	50-90	mmHg
Respiratory Rate	12-18	Breaths per minute
Oral Temperature	35.0-37.5	Degrees Celsius (°C)
Pulse Oximetry	94-100	%

12-Lead ECG Normal Ranges:

Parameter	Normal Range	Units
Heart Rate	40-110	Beats per minute (bpm)
PR Interval	120-220	mSec
QRS Width	70-120	mSec
QT Interval	N/a	N/a
QTc Interval (=QTcF) (Fridericia's)	350-430 (males)	mSec
	350-450 (females)	mSec