STATISTICAL ANALYSIS PLAN

PROTOCOL NUMBER: CT-005

NCT04411940

TITLE: A single center, single dose, open-label, randomized, two period crossover pivotal study to determine the bioequivalence of two formulations containing haloperidol 2 mg in healthy males and females under fasting conditions

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1. INTRODUCTION

This document details the planned statistical analyses for the Cycle Pharmaceuticals CT-005 study titled "a single center, single dose, open-label, randomized, two period crossover pivotal study to determine the bioequivalence of two formulations containing haloperidol 2 mg in healthy males and females under fasting conditions".

The proposed analyses are based on the contents of the protocol, version Final 2.0, 25Sep2019.

This will be a single dose, open-label, laboratory-blind, randomized, two period crossover study with orally administered haloperidol 2 mg conducted under fasting conditions in at least 24 healthy males and females at a single study center.

The study will comprise:

- a screening period of maximum 21 days;
- two treatment periods (each of which will include a profile period of 192 hours) separated by a wash-out period of at least 14 calendar days (minimum number of days based on half-life of the analyte) between consecutive administrations of the IP;
- an interim visit 2 days before admission to Treatment Period 2, and
- a post-study visit will be performed when the subjects attend the last PK sampling visit (192 hours post-dose) or within 72 hours after the subject withdrew/was withdrawn from the study.

Subjects will receive either the test or reference product, according to the randomization schedule, under fasting conditions. Subjects will receive each product once.

Subjects will be pre-medicated with benztropine mesylate tablets, 1 mg every 10 to 12 hours beginning 4 to 6 hours before dosing with haloperidol and continuing for a total of 4 doses to provide coverage during periods of substantial haloperidol levels. The start time for administration of the pre-medication will be recorded in the individual subject CRFs. The pre-medication will be administered with 240 mL of water. In the event of breakthrough acute dystonia, diphenhydramine hydrochloride 50 mg (up to 100 mg, but not exceeding a daily dose of 400 mg) could be administered intramuscular or intravenous.

2. STUDY OBJECTIVES

2.1 Primary Objective

To determine whether the test product, Haloperidol Tablets, 2 mg (Cycle Pharmaceuticals Ltd.), and the reference product, Haloperidol Tablets, USP, 2 mg (Mylan Pharmaceuticals Inc.) are bioequivalent.

For this purpose, the PK profile of haloperidol will be compared after administration of a single dose of 2 mg of each of the two formulations, under fasting conditions.

2.2 Secondary Objective

To evaluate the safety and tolerability of Haloperidol Tablets, 2 mg in healthy males and females.

3. ENDPOINTS

The primary pharmacokinetic (PK) parameters are:

Parameter	Unit	Description
C_{max}	ng/mL	Maximum observed plasma concentration
$AUC_{(0-t)}$	h*ng/mL	Area under the plasma concentration versus time curve, from time zero to t, where t is the time of the last quantifiable concentration
$AUC_{(0-\infty)}$	h*ng/mL	Area under the plasma concentration versus time curve, with extrapolation to infinity

The secondary PK parameters are:

Parameter	Unit	Description
T_{max}	h	Time to maximum observed plasma concentration
λz	1/h	Terminal elimination rate constant
$T_{(1/2)}$	h	Apparent terminal elimination half-life

4. SAMPLE SIZE

Based on a bioequivalence range of 80.00% to 125.00% for C_{max}, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$, a within-subject CV% of 22.5%, and a "test/reference" mean ratio between 0.95 and 1.05, 24 subjects are needed to achieve a power of 80% at an alpha level of 0.05 to show bioequivalence.

Up to 32 eligible subjects will be enrolled in the study to complete the study with at least 24 evaluable subjects.

5. RANDOMIZATION

A randomization schedule will be provided by Biostatistics. The randomization schedule will be generated utilizing the PROC PLAN procedure of SAS® software or appropriate equivalent.

Subjects will be randomized to one of two treatment sequences (AB or BA) and will be assigned randomization numbers 01 - 32, sequentially.

Subjects who withdraw or are withdrawn from the study will not be replaced, unless fewer complete the study than the estimated number of evaluable subjects.

This is an open-label, laboratory-blind study.

6. PLANNED ANALYSES

This statistical analysis plan (SAP) describes all pre-planned analyses as specified in the protocol, adding clarification and details where appropriate.

The data listings, descriptive statistics, statistical analysis and graphs of this study will be generated using SAS/STAT® and SAS/GRAPH® software version 9.4 (or higher).

Calculation of the PK parameters will be performed with Certara Phoenix® WinNonlin® version 8.1 (or higher).

If circumstances should arise during the study rendering the analysis inappropriate, or if in the meantime improved methods of analysis should come to light, different analyses may be made. Any deviations from the statistical methodology, reasons for such deviations and all alternative or additional statistical analyses that may be performed, will be described in the clinical study report (CSR).

6.1 ANALYSIS POPULATIONS

6.1.1 SAFETY POPULATION

All subjects who received at least one dose of IP will be included in the safety analysis for the study.

6.1.2 PK POPULATION

All subjects who complete the PK sampling in all periods and for whom primary PK parameters can be calculated for all treatment periods, and who have no major protocol deviations thought to impact the analysis of the PK data will be included in the statistical PK analysis for the study.

Data from subjects who experienced vomiting during the course of the study may be deleted from the statistical analysis if vomiting occurred at or before 2 times median T_{max} of the reference product.

For subjects with pre-dose plasma concentrations, the subject's data may be included without any adjustments in all PK measurements and calculations if the pre-dose concentration is ≤ 5% of C_{max}. If the pre-dose value is > 5% of C_{max}, the subject's data may be dropped from all bioequivalence evaluations.

6.2 DERIVED DATA

This section describes the derivations required for statistical analysis.

6.2.1 BASELINE

- Study Baseline is defined as the last non-missing measurement (scheduled, unscheduled or repeat) collected before the first administration of IP;
- Period Baseline is defined as the last non-missing measurement (scheduled, unscheduled or repeat) collected before the first administration of IP in each period.

6.2.2 STUDY DAY

Day 1 is defined as the day of the first administration of IP. Study day will be calculated as the number of days from first administration of IP, as follows:

- Events on or after the first administration of IP: Date of event – date of first administration of IP + 1
- Events before the first administration of IP: Date of event – date of first administration of IP

6.2.3 MISSING/PARTIAL DATA

Unless otherwise specified, missing/partial data will not be imputed.

6.2.4 INEXACT VALUES

In the event of results recorded as "> x", "≥ x", "< x" or "≤ x", a value of x will be taken for analysis purposes.

6.2.5 BLQ VALUES

PK concentrations below the lower limit of quantification (LLOQ) will be indicated as below the limit of quantification (BLQ). These BLQ concentrations will be handled as follows:

- For descriptive statistics, pre-dose BLQ concentrations will be substituted by zeros; all other BLQ values will be substituted by ½LLOQ value before the calculation of the summary statistics; values reported as 'NS' (no sample) will be set to "missing".
- For parameter estimation,
    - BLQ values at pre-dose and in the absorption phase, before the first reported concentration, will be substituted by zeros; the BLQ values between evaluable concentrations will be substituted by ½LLOQ before the calculation of the PK parameters; the terminal BLQ values will be set to missing. These measures are taken to prevent an over estimation of AUC.
    - missing concentrations will be deleted, resulting in an interpolation between the nearest two concentration values.

6.2.6 OUTLIERS

No outlier testing will be performed, and outliers will not be deleted from the analysis.

6.3 GENERAL CONSIDERATIONS

Summaries will be presented by treatment sequence or treatment group, unless otherwise stated. Listings will be sorted in the following order: subject number, parameter, and visit; unless otherwise stated.

For demographic and safety data, continuous variables will be summarized using the number of non-missing observations (n), mean, standard deviation (SD), minimum (min), median, and maximum (max).

PK data (concentrations and parameters), continuous variables will be summarized using n, arithmetic mean, geometric mean, SD, min, median, max and coefficient of variation percentage (CV%).

Categorical variables will be summarized by presenting the frequency and percent. Percentages will be based on the subject population unless otherwise specified. For each variable, all categories will be shown. Zero frequencies (but not the percent) within a category will be presented.

All post-baseline repeat/unscheduled assessments will be listed only. Only scheduled post-baseline safety measurements will be summarized, if appropriate.

6.3.1 DECIMAL PLACES

The following rules will be followed with regards to the number of decimal places and presentation of data in the tables and listings of clinical data:

- All data will be listed according to the number of decimal places presented in the source data.
- Mean and median will be presented to one more decimal place than the source data.
- Min and max values will be presented to the same number of decimal places as the source data.
- SD will be presented to two more decimal places than the source data.
- A maximum of three decimal places will apply to all summary statistics.

The following rules will be followed with regards to the number of decimal places and presentation of data in the tables and listings of concentration data:

- The individual concentrations will be reported to the same precision as the source data (for example, if the source data is presented to five significant digits, the individual values will be presented to five significant digits).

- The arithmetic mean, geometric mean, SD, and median will be tabulated to one more significant digit compared to the source data, but with a maximum of four significant digits.
- Min and max values will be tabulated to the same precision as the source data, but with a maximum of four significant digits.
- CV% will be presented to one decimal place.

The following rules will be followed with regards to the number of decimal places and presentation of data in the tables and listings of PK parameters:

- Individual PK parameters will be presented to four significant digits, with the exception of T_{max}, which will be presented to two decimal places. In addition, parameters directly derived from source data (e.g., C_{max},) will be reported with the same precision as the source data (if this is not four significant digits).
- The arithmetic mean, geometric mean, SD, and median values will be reported to four significant digits; all other descriptive statistics will be reported to three significant digits except for CV% which will be presented to one decimal place.
- For T_{max} the minimum and maximum will be presented to two decimals places and the rest of the descriptive statistics to three decimal places.
- P-values will be presented to four decimal places.
- Estimates and confidence intervals in the form of percentages will be presented to two decimal places.

7. STATISTICAL ANALYSIS

7.1 SUBJECT DISPOSITION

Subject disposition will be summarized by treatment sequence and overall for all enrolled subjects as follows:

- The number of subjects who were enrolled, who were randomized and who are in each analysis population;
- The number of early withdrawals and the reasons for withdrawals.

All disposition data, including reasons for exclusion from analysis populations, will be listed for all enrolled subjects.

7.2 PROTOCOL DEVIATIONS

All protocol deviation data will be listed for all enrolled subjects.

7.3 DEMOGRAPHIC DATA

Demographic characteristics will be summarized by treatment sequence and overall for the Safety and PK populations, for each of the following variables:

- Age (years)
- Age group (>=18 to <=35; >=36 to <=55)
- Race (Black, Caucasian, Mixed Race, Other)
- Gender (Male, Female)
- Height (cm)
- Weight (kg)
- BMI (kg / m^2)
- BMI group (≤25, 25-≤30, 30-≤35, >35)

If the Safety and PK populations are the same, a single Demographics table will be produced for the Safety/PK populations.

All demographic data will be listed for all subjects in the Safety population.

7.4 MEDICAL HISTORY

All medical history data will be listed for all subjects in the Safety population.

Medical history data will be coded using the Medical Dictionary of Regulated Activities (MedDRA® Version 22.1) primary System Organ Class (SOC) and Preferred Term (PT).

7.5 PRIOR AND CONCOMITANT MEDICATION

All prior and concomitant medications will be listed separately for all subjects in the Safety population.

A prior medication is a medication which stopped before first administration of IP, while a concomitant medication is a medication which is ongoing at end of study or stopped after first administration of IP. Medications will be coded using the World Health Organization (WHO) Drug Dictionary Version Sep2019.

In situations with missing medication start/end dates/times, available data will be used for prior/concomitant assignment. If the assignment is inconclusive, worst-case will be assumed and the medication will be assigned as concomitant.

7.6 DOSING INFORMATION

All dosing information will be listed for all subjects in the Safety population.

7.7 PK ANALYSIS

7.7.1 PK Concentrations

All PK blood sampling times, including time deviations, will be listed for all subjects in the Safety population (to ensure data for subjects excluded from the PK population are listed).

PK concentration data will be summarized descriptively (n, arithmetic mean, geometric mean, SD, min, median, max, CV%) by treatment group for the PK population.

The arithmetic and geometric mean plasma concentrations versus scheduled time profiles for each treatment group, as well as the combined individual plasma concentrations versus actual time profiles for

each subject, will be presented graphically on a linear (concentration) – linear (time) and log (concentration) – linear (time) scale. The time axis will be presented in equal intervals (e.g. 0h, 4h, 8h etc.).

All PK concentration data will be listed for all subjects in the Safety population (to ensure data for subjects excluded from the PK population are listed).

7.7.2 PK Parameters

The Day 1 pre-dose concentrations of haloperidol will be used for baseline. Where possible, the PK parameters will then be estimated on baseline subtracted plasma concentrations of haloperidol. Pharmacokinetic parameters will be calculated on the baseline subtracted concentrations (even if some values are negative, they are used for computing AUC as they are).

Source data shall be used in all derived PK parameter calculations without prior rounding.

The PK parameters will be calculated for each subject using non-compartmental analysis and using the actual sampling time (relative to IP administration).

PK parameter data will be summarized descriptively (n, arithmetic mean, geometric mean, SD, min, median, max, CV%) by treatment group for the PK population. For T_{max} only the median, min and max, and for $T_{1/2}$ the mean, median, min and max values will be presented.

All PK parameter data will be listed for all subjects in the Safety population (to ensure data for subjects excluded from the PK population are listed).

7.7.3 Analysis of Bioequivalence

The test product will be compared to the reference product by means of statistical analysis with respect to the primary PK parameters using an analysis of variance (ANOVA) with sequence, subject(sequence), product and period effects after logarithmic transformation of the data. Point estimates and 90% CIs for the "test/reference" geometric mean ratios of these parameters will be obtained by taking the antilog of the “test - reference” difference.

Bioequivalence of the test and reference products will be assessed on the basis of the 90% CIs for estimates of the geometric mean ratios between the primary PK parameters of the test and reference products in relation to the conventional bioequivalence range of 80.00% to 125.00%.

Code similar to the following SAS® code will be used, with the treatments sorted as test then reference:

```
PROC GLM DATA=pk;
        BY param;
        *where param = Cmax, AUC(0-t), and AUC(0-inf);
        CLASS product period subject sequence;
        MODEL log_result = product period sequence subject(sequence);
        *where log_result = log[Cmax], log[AUC(0-t)], and log[AUC(0-inf)];
        OUTPUT OUT = routput R=res P=pred;
        LSMEANS product / pdiff=control(reference) cl alpha = 0.1;
        ESTIMATE "Test versus Reference" product 1 -1;
RUN;
```

Additionally, a non-parametric Wilcoxon signed rank test will be performed on the variable T_{max} after logarithmic transformation of the data.

Code similar to the following SAS® code will be used:

```
PROC UNIVARIATE DATA = pk;
        BY param;
        *where param = Tmax;
        VAR log_diff;
        *where log_diff = the log difference test minus reference;
        ODS output testsforlocation = wilcoxon;
RUN;
```

7.8 SAFETY ANALYSIS

7.8.1 ADVERSE EVENTS (AEs)

Adverse events (AEs) will be classified as treatment emergent AEs (TEAEs) if they started on or after the first administration of IP.

AEs will be assigned to a treatment based on the last IP received prior to the onset of the AE.

In situations with missing AE start/end dates/times, available data will be used for TEAE classification and treatment assignment. If the TEAE classification is inconclusive, worst-case will be assumed and the AE will be classified as a TEAE. If the treatment assignment is inconclusive, the earliest of the possible treatments will be assigned.

The Investigator is responsible for determining the seriousness (yes, no), severity (mild, moderate, severe) and causality (reasonable possibility, no reasonable possibility) of AEs.

In situations with missing data, worst-case will be applied, that is, seriousness will be assigned as yes if seriousness is missing, severity will be assigned as severe if severity is missing, and causality will be assigned as related.

All AEs will be coded using MedDRA® Version 22.1.

The following summaries will be presented for AEs:

- Incidence of all TEAEs; serious AEs (SAEs); treatment-related TEAEs; treatment-related SAEs; Mild, Moderate and Severe TEAEs; TEAEs leading to study withdrawal; TEAEs leading to death;
- Incidence of TEAEs by SOC and PT;
- Incidence of Treatment-Related TEAEs by SOC and PT;
- Incidence of Serious TEAEs by SOC and PT;
- Incidence of TEAEs by SOC and PT, by Worst Causality;
- Incidence of TEAEs by SOC and PT, by Maximum Intensity.

In counting the number of TEAEs reported, a subject reporting multiple events within the same SOC and PT will only be counted once within that SOC and PT, at the worst causality and the maximum intensity. SOC will be presented in descending order of overall frequency and then alphabetically, followed by PT in descending order of overall frequency and then alphabetically within SOC.

All AEs will be listed for all subjects in the Safety population.

Separate listings of AEs leading to death, SAEs and AEs leading to treatment discontinuation will be provided.

7.8.2 LABORATORY DATA

Hematology, and clinical chemistry results will be summarized for the Safety population. Urinalysis, serology, drugs of abuse, tobacco use, and alcohol breath test data will be listed only.

Abnormal hematology and clinical chemistry results (for all visits including unscheduled visits) will be flagged as "Low" (values lower than the lower limit of the reference range), “Normal” (values within the limits of the reference range) and "High" (values higher than the upper limit of the reference range). Clinical significance will be indicated as "NCS" (abnormal, not clinically significant) or "CS" (abnormal, clinically significant). Where possible and applicable, repeat measurements will be marked as “Rep”.

Descriptive statistics for each hematology and clinical chemistry test will be presented, along with changes from study baseline to post-treatment assessments by treatment sequence. Shifts from study baseline to post-treatment assessments will be presented based on the Low, Normal or High classification for each laboratory test, as applicable.

All laboratory data will be listed for all subjects in the Safety population.

A separate listing of any clinically significant laboratory measurements recorded throughout the study will be provided.

7.8.3 VITAL SIGNS DATA

Descriptive statistics for each vital sign parameter will be summarized, along with changes from period baseline to post-baseline assessments for the Safety population by treatment sequence.

All vital sign data will be listed for all subjects in the Safety population.

7.8.4 ELECTROCARDIOGRAM (ECG) DATA

Descriptive statistics for each ECG parameter will be summarized, along with changes from study baseline, for the Safety population by treatment sequence.

All ECG data, including details of any abnormalities of the overall ECG assessment, will be listed for all subjects in the Safety population.

7.8.5 PHYSICAL EXAMINATION DATA

All physical examination data will be listed for all subjects in the Safety population.

8. REFERENCES

1. Certara USA, Inc., 100 Overlook Center, Suite 101, Princeton, NJ 08540 USA
2. SAS Institute Inc., Cary, NC, 27513, USA

9. APPENDIX

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