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STATISTICAL ANALYSIS PLAN
11 September 2019

A RANDOMIZED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY AND TOLERABILITY OF TWO DOSING REGIMENS OF CTP-543 IN ADULT PATIENTS WITH MODERATE TO SEVERE ALOPECIA AREATA

PROTOCOL NUMBER CP543.2002

SPONSORED BY

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LIST OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
AE	Adverse event
ATC	Anatomical-Therapeutic-Chemical
BID	Twice daily dosing
CI	Confidence interval
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
ECG	Electrocardiogram
eCRF	Electronic case report form
HDL	High-density lipoprotein
ICH	International Conference on Harmonisation
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
QD	Once daily dosing
QT	QT interval
QTcF	QT interval corrected for heart rate (Fridericia's method)
SAE	Serious Adverse Event
SALT	Severity of Alopecia Tool
SAP	Statistical Analysis Plan
SD	Standard deviation
SI	International System of Units
SOC	System organ class
TEAE	Treatment-emergent adverse events
VAS	Visual Analog Scale
WHO	World Health Organization

LIST OF IN-TEXT TABLES

1. PURPOSE OF THE STATISTICAL ANALYSIS PLAN

This statistical analysis plan (SAP) contains detailed information to aid in the implementation of the statistical analyses and reporting of the study data for use in the clinical study report (CSR) for study CP543.2002. This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline, entitled Guidance for Industry: Statistical Principles for Clinical Trials, and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports.

This SAP describes the data sets that will be used for analysis, as well as patient characteristics, efficacy, safety, and clinician-reported and patient-reported perception of disease severity and improvement parameters. The details of the specific statistical methods stated in the protocol will be provided and any changes from the protocol-specified analyses will be documented in the SAP prior to database lock. If additional analyses are required to supplement the planned analyses described in this SAP after the database lock, they may be completed and will be described in the CSR. Table, figure, and listing specifications are provided as an attachment in a separate document. This SAP is based on the latest version of the protocol (Amendment 1), dated 03 January 2019.

2. PROTOCOL SUMMARY

2.1 Study Objectives

The overall objective of the study is to compare the efficacy and tolerability of a 16 mg total daily dose of CTP-543 utilizing two different dosing regimens in adult patients with chronic, moderate to severe alopecia areata.

The secondary/exploratory objectives of the study will be to assess the patient reported outcomes of hair coverage and hair coverage quality.

2.2 Study Design

This is a randomized, parallel group multicenter study to evaluate the efficacy and tolerability of two dosing regimens of CTP-543 (8 mg twice daily dosing (BID) vs 16 mg once daily dosing (QD)), in adult patients with chronic, moderate to severe alopecia areata. Patients will be between 18 and 65 years of age and experiencing an episode of alopecia areata lasting at least 6 months and not exceeding 10 years, with at least 50% hair loss as measured by the Severity of Alopecia Tool (SALT) at Screening and Baseline, and are not concurrently being treated for alopecia areata with other treatments that might affect hair regrowth or immune response. Up to approximately 75% of alopecia areata patients with alopecia totalis or universalis, and no more than 10% with only alopecia ophiasis will be enrolled.

Patients may be screened up to 28-days prior to initiation of study drug. The Treatment Period is a 24-week dosing period where patients will be randomized to receive either CTP-543 8 mg BID, or CTP-543 16 mg QD and will be analyzed for the primary endpoints of the study. To minimize bias in the evaluation of study endpoints, patients, investigators, and site personnel will be unaware of the active drug dosing regimen by administering one 16 mg tablet and one placebo tablet 12 hours apart from each other for the 16 mg QD study group.

Patients will take the first dose of study drug in the clinic on Day 1. Patients will be instructed to take study drug every 12 hours. Patients should dose study drug in the clinic on all Study Visit Days after clinical laboratory blood draws are completed.

Patient safety will be monitored throughout the trial. The patient will be tested to ensure they do not have the Hepatitis B or C virus, thyroid function abnormalities or latent or active Tuberculosis, during the screening period. During the first 8 weeks of the Treatment Period, hematology and serum chemistry will be conducted every 2 weeks, followed by an assessment every 4 weeks thereafter through completion of the study at 24 weeks. Lipid levels will be assessed every 12 weeks throughout the Treatment Period. Significant cytopenias or other hematologic abnormalities will be managed by severity through dose interruption, or discontinuation, and signs and symptoms of infection will be closely monitored and treated promptly. Patients who experience intolerable symptoms during treatment may discontinue the study at the discretion of the Investigator. Patients may withdraw consent at any time. The Treatment Period will last 24 weeks to assess BID and QD doses, in parallel. Assessment of treatment response with SALT for efficacy will occur at 4, 8, 12, 16, 20 and 24 weeks. Upon completion of the 24-week Treatment Period patients will be eligible to either complete

treatment and exit the study following the safety follow-up visit, or roll-over into a long-term open-label extension study.

Approximately 60 patients are planned to be enrolled in the study; approximately 30 patients per dosing regimen.

2.3 Study Population

The study population will consist of male and female patients of any ethnicity between 18 and 65 years of age, inclusive, with diagnosis of alopecia areata with a current episode lasting at least 6 months and not exceeding 10 years at the time of Screening. Total disease duration greater than 10 years is permitted. Patients must also exhibit at least 50% scalp hair loss, as defined by a SALT $\geq$ 50, at Screening and Baseline.

A full list of the inclusion and exclusion criteria can be found in Sections 7.1 and 7.2 in the CP543.2002 Protocol.

2.4 Treatment Regimens

CTP-543 will be dosed orally as tablets. Doses and frequency will be allocated as follows:

- CTP-543 8 mg BID (every 12 hours)
- CTP-543 16 mg QD (16 mg in the morning and placebo tablet in the evenings)

2.5 Treatment Group Assignments or Randomization

Patients meeting all inclusion criteria and none of the exclusion criteria will be randomized to CTP-543 8 mg BID or CTP-543 16 mg QD in a 1:1 ratio. Randomization will be stratified by classification of alopecia areata subtype into one of the following three categories: 1) alopecia areata, 2) alopecia totalis or alopecia universalis, or 3) alopecia ophiasis.

2.6 Sample Size Determination

A sample size of 25 patients (completers) per group provides adequate precision for the estimated dosing regimen difference for relative change in SALT score from baseline at Week 24. Precision of the estimated difference is quantified by the width of the 90% confidence interval (CI) for the dosing regimen difference.

3. GENERAL ANALYSIS AND REPORTING CONVENTIONS

The following is a list of general analysis and reporting conventions to be applied to this study, unless otherwise specified.

All data displays (tables, listings, and figures) will have a header showing the sponsor company name, protocol number, page number, and display status (i.e. "DRAFT" or "FINAL"), as well as a footer indicating file name and run date/time. Summary tables and data listings will be summarized by dosing regimen and overall, as appropriate. All data collected per-protocol and all derived variables will be listed.

Categorical variables will be summarized using counts (n) and percentages (%) and will be presented in the form "n (xx.x)." If a count is 0, 0% will be shown for the percentage. If a percentage is 100%, 100% will be shown with no decimal place. To ensure completeness, summaries for categorical variables will include all categories, even if no patients had a response in a particular category. Unless otherwise specified, the denominator for each percentage will be based on the number of patients in the population being summarized (header n). If missing values are present, counts will be shown but will not be included in percentage calculations.

Continuous variables will be summarized using mean, standard deviation (SD), minimum, maximum, median, and number of patients. The mean and median will be reported to an additional level of precision than the original observations, and the SD will be reported to two additional levels of precision than the original observations. The minimum and maximum will be the same precision as the original data. In general, any calculated values, such as those due to unit conversion, will be rounded to the same number of decimal places as the original data.

Confidence intervals will be 90%. No formal hypothesis tests will be performed. Testing will be performed only for the Treatment Period. Estimates and confidence intervals may be reported to 1 more decimal than the original data.

Summary tables and data listings:

- No preliminary rounding will be performed; rounding will only occur after analysis.
- Data from patients excluded from an analysis population will be presented in the data listings but will not be included in the calculation of summary statistics, where applicable.
- Data from each patient will be separated by a blank line. Within a data listing, if a descriptive item appears line after line (e.g., repetition of a patient number, date, visit, etc.), only the first occurrence will be displayed (e.g., in Listing of Vital Signs, patient number, date and visit will only be displayed on first row when presenting all parameters collected at same visit). Repetition of actual results or outcomes (e.g., Adverse Events (AEs), lab results, vital sign values, etc.) will not be collapsed.
- Data listings will be sorted by dosing regimen, patient, and week and/or time of assessment, as applicable.

- When change from baseline or change to baseline is calculated, baseline is the last observation obtained prior to dosing of the study drug.

Mock tables and data listings will be provided as attachments to this analysis plan. Minor changes to the mocks after formal SAP approval will not necessitate re-approval unless changes to the text of the SAP are required.

All statistical deliverables will be produced, validated, and reviewed for accuracy/consistency in accordance with [redacted] standard operating procedures and the processes described in the statistical validation plan.

SAS® (SAS Institute, Cary, North Carolina) statistical software, version 9.4 or later, will be used for all analyses. Adverse Events and Medical History will be coded in Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1. Concomitant medications will be coded in World Health Organization (WHO) Drug Version E (2016.01) and Anatomical-Therapeutic-Chemical (ATC) classification and preferred term.

4. ANALYSIS POPULATIONS

Analysis populations will be summarized and listed for each patient, by dosing regimen.

4.1 Efficacy Population

The Efficacy Population will include all patients who receive study drug and have at least 1 post-treatment SALT assessment during the Treatment Period. Patients in the Efficacy Population will be analyzed according to their randomized dosing regimen.

4.2 Safety Population

The Safety Population will include all patients who receive study drug during the Treatment Period. Patients in the Safety Population will be analyzed according to the actual dosing regimen received during the study.

5. STUDY PATIENTS

5.1 Disposition of Patients

Disposition will be summarized by randomized dosing regimen for all patients screened in the study. The following disposition information will be summarized (percentages based on the number randomized, with the exception of the reasons for discontinuation):

- The number of patients screened.
- The number of patients randomized.
- The number and percentage of patients treated within the Efficacy and Safety Populations.
- The number and percentage of patients who completed the study (defined as completing all study visits through Visit 11), completed Visit 10 and rolled into the open-label extension, and who completed 24 weeks of treatment but did not roll into the open-label extension and did not complete the safety follow up visit.
- The number and percentage of patients who prematurely discontinued, and the frequency and percentage of each discontinuation reason. The denominator for the percentage of each discontinuation reason will be the number of patients who discontinued.

Disposition and patient visits will also be presented for each patient in patient data listings. Patient data listings will list date of informed consent, date of first/last treatment, date of end of study/early termination, and reasons for discontinuation. A Kaplan Meier curve of time to study completion or early termination will also be presented. Patients who have completed the study will be censored.

5.2 Protocol Deviations

Protocol deviations will be collected at both the site and patient level on the electronic Case Report Form (eCRF). A data review will be conducted before database lock by the sponsor to classify protocol deviations as minor or major. Deviations that may alter or confound interpretation of the study results will be classified as major deviations. Protocol deviations will be summarized by deviation classification and category for all randomized patients and listed by patient in a data listing.

6. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic characteristics (ie, sex, ethnic origin, race, date of birth, and calculated body mass index) will be collected at the Screening Visit, between Day -28 and -1, and detailed on the eCRF. Demographic characteristics will be summarized using descriptive statistics for all randomized patients.

Baseline characteristics will be summarized using descriptive statistics for all randomized patients and will include the following:

- baseline total SALT score.
- alopecia areata type (current episode; defined below).
- alopecia areata type (at disease onset; defined below).
- duration of current episode in months (calculated as: [date of randomization – date of current episode onset + 1] / 30.4375).
- duration of disease at onset in months (calculated as: [date of randomization – date of disease onset + 1] / 30.4375).
- current nail involvement.
- current eyelash/eyebrow involvement.
- current other facial hair involvement.
- prior Herpes Zoster vaccination.
- time since Herpes Zoster vaccination in months.

Other co-morbidities may be identified and included as baseline characteristics.

The patient's alopecia areata will be classified by the Investigator into one of three categories defined for this study:

1) Alopecia areata: patchy type hair loss,

2) Alopecia totalis or universalis: complete hair loss on the scalp with or without body hair loss,

3) Alopecia ophiasis: band-like hair loss limited to the periphery of the scalp along the back of the hair line in the occipital region and possibly extending over each ear in temporal regions.

The alopecia totalis and alopecia universalis category will be separated into each individual subtype for summaries. Alopecia areata category at baseline, defined as the current episode, and

alopecia areata category at disease onset will be summarized with the number and percent of patients in each category.

All demographics and baseline characteristics will also be listed within a by-patient data listing for all randomized patients.

Medical history will be summarized by frequencies of System Organ Class (SOC) and preferred term and will be coded using MedDRA Version 19.1. All medical history for each patient in the Safety Population will be included in a data listing.

6.1 Prior and Concomitant Medications

Prior and concomitant medications will be summarized by WHO Drug ATC classification level 2 and preferred term and listed within a by-patient data listing.

Medications are classified as prior if the medication started and stopped prior to the first dose date of study drug or as concomitant if used on or after the first dose date of study drug. Concomitant medications will be recorded from Screening through the Follow-Up Visit at Week 28.

Partial and completely missing dates will be imputed for the purposes of classifying concomitant medications as follows:

- Partial dates will be imputed following the same algorithm as in Section 9.2 for Treatment-emergent adverse events (TEAEs).

- For an entirely missing start date (i.e. day, month, and year are missing), the start date will be set to the date of administration of study drug unless the stop date is prior to the date of administration of study drug, in which case the start date will be set to the stop date.

For an entirely missing stop date (i.e. day, month, and year are missing), the medication will be treated as ongoing.

7. MEASUREMENTS OF TREATMENT COMPLIANCE

Patients will strive for 100% compliance with the daily dosing schedule. Treatment compliance will be summarized as time on treatment as well as percent of planned dose received for each dosing regimen. Time on treatment will be defined as date of last dose in the treatment period minus the date of first dose in the treatment period + 1. Percent of planned dose received will be calculated for the entire treatment period as follows:

$$100 * \frac{Tablets\ Dispensed - Tablets\ Returned}{Tablets\ Expected}$$

Tablets Expected is defined as the time on treatment multiplied by the expected number of active dose pills taken daily (x2 for the 8 mg BID group; x2 for the 16 mg QD group). Dose interruptions will be ignored in this calculation. Derived patient compliance, compliance per the eCRF (80% or higher versus less than 80%), and dosing exceptions will be listed in by-patient data listings.

8. EFFICACY EVALUATION

8.1 Primary Efficacy Endpoint

The primary efficacy endpoint will be the relative change in SALT score for each dose regimen from baseline at Week 24.

8.1.1 Severity of Alopecia Tool

The SALT is a measure of hair absence that quantifies the amount of scalp surface without hair in a pre-specified quadrant of the scalp (right side, top, left side, back), that is further summed after applying a quadrant-specific multiplier indicative of scalp surface area contribution, to provide an overall score of total hair loss. Total SALT score is computed as [(left quadrant raw score x 0.18) + (right quadrant raw score x 0.18) + (top quadrant raw score x 0.40) + (back quadrant raw score x 0.24)]. The SALT assessment will occur via live examination of the patient during clinic visits.

As the SALT score is by nature a measurement of total surface without hair, it is important to note that in the context of this SAP, endpoints will follow these definitions:

- Absolute change = difference in SALT measurements (baseline SALT score minus follow-up SALT score)
- Relative change = percent change of the follow-up SALT score, where baseline SALT score is the denominator (i.e. absolute change divided by the baseline score, multiplied by 100)

8.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

- Proportion of patients achieving at least a 90%, 75%, and 50% relative reduction in SALT score from baseline at Weeks 4, 8, 12, 16, 20, and 24;
- Absolute change in SALT scores from baseline at Weeks 4, 8, 12, 16, 20, and 24 in the Treatment Period;
- Relative change in SALT scores from baseline at Weeks 4, 8, 12, 16, 20, and 24 in the Treatment Period;
- Change in satisfaction of hair coverage as reported by patient

8.2.1 Satisfaction of Hair Coverage

Results of the patient satisfaction questions will be collected on Day 1 and at Week 24. Patients will answer the question “How satisfied are you with the hair coverage on your scalp today?”.

Responses range from 1-5 as follows: 1 (very dissatisfied), 2 (dissatisfied), 3 (somewhat satisfied), 4 (mostly satisfied), 5 (very satisfied).

8.3 Exploratory Efficacy Endpoints

Exploratory efficacy endpoints include:

- Change in patient's eyebrows as measured by the patient's Visual Analog Scale (VAS);
- Change in satisfaction of hair coverage quality as reported by patient;
- Proportion of patients achieving an absolute SALT score of ≤10, ≤20, and ≤25 at Weeks 4, 8, 12, 16, 20 and 24;

8.3.1 Visual Analog Scale

The VAS is a scale of continuous measure initially developed for pain that has been used in a variety of clinical settings where the endpoint of interest is based on a subjective perception. The VAS is a distinct 100 millimeter line anchored on the left end at full degree of impairment and on the right end at no degree of impairment, where indication of the degree of impairment perceived at the time of assessment is captured by marking the appropriate position on the line between the anchor points. The measured distance of the mark from the left anchor will be recorded in millimeters.

As specified in the Schedule of Events, patients will rate his/her eyebrows on the patient VAS. The left and right anchor points for the patient's eyebrow VAS are "None" and "Full", respectively. The patient VAS will measure the patient's eyebrows at the time of completion.

Since the VAS was measured right to left in terms on increasing impairment, the VAS analysis value will be calculated by taking 100 minus the collected value

8.3.2 Satisfaction of Hair Coverage Quality

Results of the patient satisfaction of quality questions will be collected on Day 1 and at Week 24. Patients will answer 7 questions with responses ranging from 1-5 as follows: 1 (very dissatisfied), 2 (dissatisfied), 3 (somewhat satisfied), 4 (mostly satisfied), 5 (very satisfied). The list of questions is provided in the protocol, Appendix 16.2.2.

8.4 Overview of Efficacy Analysis Issues

8.4.1 Handling of Dropouts or Missing Data

The Last Observation Carried Forward (LOCF) approach will be implemented for missing SALT score data, e.g., if the SALT score in the Week 16 visit window is missing, the next and closest available on-treatment SALT score measurement before the Week 16 visit window will be used for all remaining SALT assessments: Week 16, Week 20 and Week 24. Missing baseline values will not be carried forward. If a SALT assessment is missing between two non-missing SALT

assessments visits, the SALT score at that visit will be interpolated using the mean of the closest pre- and post-assessments.

If the number of discontinuations due to adverse events is substantial, other methods will be explored.

8.4.2 Multicenter Studies

Patients will be enrolled at approximately 10 sites. To reduce variability, one rater should perform each clinician dependent assessments (SALT) for the patient for the duration of the study. All investigators using the SALT will be trained prior to use. Data from all sites will be pooled.

8.4.3 Assessment Visit Windows

The visit schedule for all study assessments is provided in Appendix 17.2. Patients will be considered completed for efficacy analyses after Week 24 (Visit 10). Patients will either complete treatment at Week 24 and have a Safety Follow-up visit at Week 28 prior to exiting the study, or if eligible, may enroll into an open-label extension study of CTP-543 at their Week 24 visit.

For scheduled visits, there will be no reassignment of the analysis visit based on date, and all data will appear in summary tables based on the nominal timepoint.

Both unscheduled visits and repeat visits will be reassigned to the closest prior visit. If an assessment was already documented at that visit, the scheduled data will be used in summaries. If the scheduled data was missing, then the re-assigned unscheduled visit/repeat visit will be used in summaries. All visits will be included in by-patient data listings.

8.5 Analysis Methods

No formal hypothesis tests will be conducted. All confidence intervals will be 90%. Testing will be based on the Efficacy Population and performed only for the Treatment Period.

Table 8-1 gives an overview of the analysis methods that will be used for each of the efficacy variables.

Table 8-1 Efficacy Variables and Analysis Methods

Efficacy Variables	Collection Times	Method
Primary		
SALT (relative change)	Baseline, Week 24	Mean and 90% confidence interval (t-distribution)
Secondary		
Responder Analysis SALT (90%, 75%, 50% relative reduction)	Baseline, Week 4, 8, 12, 16, 20, 24	Proportion and 90% confidence interval (binomial approximation)
SALT (absolute change)	Baseline, Week 4, 8, 12, 16, 20, 24	Mean and 90% confidence interval (t-distribution)
SALT (relative change)	Baseline, Week 4, 8, 12, 16, 20, 24	Mean and 90% confidence interval (t-distribution)
Satisfaction of hair coverage	Baseline, Week 24	Proportion and 90% confidence interval (binomial approximation); Shift table
Exploratory		
VAS for Eyebrows (percent change)	Baseline, Week 24	Mean and 90% confidence interval (t-distribution)
Satisfaction of hair coverage quality	Baseline, Week 24	Proportion and 90% confidence interval (binomial approximation); Shift table
SALT (≤10, ≤20, ≤25 absolute score)	Baseline, Week 4, 8, 12, 16, 20, 24	Proportion and 90% confidence interval (binomial approximation)

8.5.1 Primary Efficacy Analysis

The aim of this study is to compare 16 mg doses of CTP-543 taken in 2 different dosing regimens (8 mg BID or 16 mg QD). Comparisons between dosing regimens will be assessed using the mean relative change from baseline at Week 24 with 90% confidence intervals.

8.5.2 Secondary Efficacy Analyses

Descriptive statistics and 90% confidence intervals will be reported for the SALT score (observed values, relative change, and absolute change) at each time point for each dosing regimen and by subtype. By-patient data listing will also be presented for patient SALT scores. The mean of observed value, absolute change, and relative change SALT scores along with 90% confidence intervals for each dosing regimen will be presented using line graphs.

Responders at 90%, 75%, and 50% by visit will be summarized with proportions and 90% confidence intervals (using the binomial approximation with a Wald continuity correction). Responders are defined as patients with at least 90%, 75%, or 50% reduction in SALT score by visit. Percent reduction is calculated as the baseline SALT score minus the current value, divided by the baseline value, multiplied by 100. Responders will be presented graphically by dosing regimen as a bar graph at 24 Weeks and as a line graph across time.

Responses to the patient satisfaction question will be summarized with proportions and 90% confidence intervals (using the binomial approximation with a Wald continuity correction). Responses will be also categorized as "Satisfied" (including responses of "Very satisfied," "Mostly satisfied," and "Somewhat satisfied") and "Dissatisfied" (including responses of "Very dissatisfied" and "Dissatisfied") and presented as a 2 x 2 shift table from baseline to Week 24. Response will also be listed in the by-patient data listings.

8.5.3 Exploratory Efficacy Analyses

VAS for Eyebrows scores will be summarized using percent change from baseline at Week 24. Descriptive statistics will be presented with 90% confidence intervals around the mean (t-distribution). Results will also be listed in the by-patient data listings.

The satisfaction of hair quality questions will be summarized with descriptive statistics at baseline and Week 24, and will be listed in the by-patient data listings. Responses to the patient satisfaction question will be summarized as proportions with 90% confidence intervals. Responses will be also categorized as "Satisfied" (including responses of "Very satisfied," "Mostly satisfied," and "Somewhat satisfied") and "Dissatisfied" (including responses of "Very dissatisfied" and "Dissatisfied") and presented as a 2 x 2 shift table from baseline to Week 24.

Additional analyses by dosing regimens will be performed at Weeks 4, 8, 12, 16, 20, and 24 for patients who achieve an absolute SALT score of $\leq$10, $\leq$20, or $\leq$25. Responders by visit will be summarized with proportions and 90% confidence intervals (using the binomial approximation with a Wald continuity correction).

8.6 Examination of Subgroups

Descriptive statistics will be provided by alopecia subtype.

9. SAFETY EVALUATION

9.1 Overview of Safety Analysis Methods

Safety and tolerability of CTP-543 will be assessed by evaluating the following for the Safety Population:

- Adverse events
- Clinical laboratory results
- Vital signs
- Electrocardiogram (ECG) results
- Concomitant medications
- Physical examinations

All safety summaries will be descriptive with no statistical hypothesis testing and based on the Safety Population. Patients will be summarized according to the study drug received (i.e., as treated), should it differ from the randomized dosing regimen. All safety endpoints will be listed in by-patient data listings.

9.2 Adverse Events

Adverse events will be coded using MedDRA and summarized by system organ class and preferred term. Clinically significant deteriorations in physical examination findings will be reported and summarized as adverse events.

An adverse event reported after informed consent, but before the first dose of study drug (i.e., Day 1), will be considered a pre-treatment adverse event. Treatment-emergent adverse events will be defined as any adverse event that occurs after administration of the first dose of study drug. The number and percentage of patients who report TEAEs will be summarized by system organ class and preferred term.

Treatment emergent adverse events will also be summarized by intensity as well as relationship to study drug.

Partial dates will be imputed for the purposes of defining TEAEs as follows:

- For a missing start day where the month and year are present, the start day will be set to the first day of the month, unless 1) the first day of the month is before the date of administration of study drug and the month and year are the same as the month and year of the date of administration of study drug, and 2) the end date is on or after the date of

administration of study drug or the end date is completely missing, in which case the start day will be set to the first day of administration of study drug.

- For a missing start day and month where the year is present, the start day and month will be set to January 1st, unless 1) January 1st is before the date of administration of study drug, and 2) the end date is on or after the date of administration of study drug or the end date is completely missing, in which case the start day and month will be set to that of the first date of administration of study drug.

- For a missing end day where the month and year are present, the end day will be set to the last day of the month, unless the month and year are the same as the month and year of the last contact date for the patient, in which case the end day will be set to that of the patient's last contact date.

- For a missing end day and month where the year is present, the end day and month will be set to the patient's last contact date, unless the year of the patient's last contact date is greater than the end year, in which case the end day and month will be set to December 31st.

For an entirely missing stop date (i.e. day, month, and year are missing), the TEAE will be treated as ongoing.

Patients who report the same preferred term on multiple occasions will be counted once for the preferred term: under the highest severity when summarized by severity and under the closest relationship to study drug when summarized by relationship. Missing severity or relationship will not be imputed. If a patient reports multiple preferred terms for a SOC, the patient will be counted only once for that SOC.

The number and percentage of patients who experience TEAEs will be summarized by dosing regimen for the following:

- By SOC and preferred term.

- By severity/intensity, SOC, and preferred term.

- By relationship to study drug, SOC, and preferred term.

- Serious adverse events (SAEs) by SOC and preferred term.

- SAEs by relationship to study drug, SOC and preferred term.

- AEs resulting in discontinuation of study drug by SOC and preferred term.

- AEs that result in study drug dose interruption by SOC and preferred term.

- AEs that meet Grade 3-4 Common terminology criteria for adverse events (CTCAE) hematology results by system organ class and preferred term.

- AEs that meet Grade 3-4 CTCAE serum chemistry results by system organ class and preferred term.

By-patient listings will be provided for all AEs, SAEs, and AEs related to the study drug, as well as AEs leading to study drug withdrawal or death. A by-patient listing will also be created for any pregnancies that occur. TEAEs that result in dose interruption will also be identified.

9.3 Clinical Laboratory Evaluation

Observed measurements along with change from baseline for each assessment will be summarized descriptively by dosing regimen and visit for each clinical laboratory parameter.

Hematology parameters for patients that meet Grade 3 or Grade 4 toxicity criteria from the CTCAE v4.0 will be summarized for each scheduled visit and overall for all post-baseline visits. In addition, hematology parameters of interest will be plotted as mean values over time. Serum chemistry parameters for patients that meet Grade 3 or Grade 4 toxicity criteria from the CTCAE v4.0 will be summarized for each scheduled visit and overall for all post-baseline visits.

Laboratory values will be converted to International System of Units (SI) before analysis. If laboratory values are recorded as above or below a threshold (i.e. "<2", ">30", etc.), they will be counted as missing for continuous summaries. Abnormal, clinically significant laboratory values (per Investigator judgment) will be reported and summarized as AEs.

All laboratory parameter results will be included in by-patient data listings. Reference ranges for each clinical laboratory parameter will also be summarized in a data listing.

9.4 Vital Signs, Physical Findings, and Other Observations Related to Safety

9.4.1 Vital Signs

Baseline will be defined as the last vital sign value obtained before the first dose of study drug on Day 1; if Day 1 values are unavailable, then values obtained at the Screening Visit will be used. Observed vital sign measurements along with change from baseline for each assessment will be summarized descriptively by dosing regimen and visit for each vital sign variable specified in the protocol (Systolic Blood Pressure, Diastolic Blood Pressure, Pulse Rate, Respiratory Rate, and Oral Temperature). Vital signs will also be presented for each patient in a data listing.

9.4.2 ECG

Observed Overall ECG Interpretations will be summarized as Normal, Abnormal and Not Clinically Significant, or Abnormal and Clinically Significant for each scheduled visit by dosing regimen. In addition, observed and change from baseline measurements of ECG intervals (PR, QT, QTcF, QRS, and RR) for each scheduled assessment will be summarized descriptively by dosing regimen and visit as well as listed within a by-patient data listing. Patients receiving study drug will be identified and summarized by dosing regimen and visit, as well as overall for the following clinically notable categories:

- QTcF > baseline and > 450 msec
- QTcF > baseline and > 480 msec
- QTcF > baseline and > 500 msec
- QTcF increase from baseline > 30 msec
- QTcF increase from baseline > 60 msec

9.4.3 Physical Examinations

A listing of physical examinations will be provided. Deteriorations from baseline on physical examination will be coded as adverse events and summarized as such.

10. PHARMACOKINETIC EVALUATION

Pharmacokinetic endpoints will not be collected for this study.

11. INTERIM ANALYSES AND DATA MONITORING

No interim analyses or data monitoring committee are planned for this study.

12. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

The following alterations were made to the original analyses planned in the protocol:

- Additional analyses of patients who achieve absolute SALT scores of ≤10, ≤20, or ≤25 at Weeks 4, 8, 12, 16, 20, and 24 were added.

13. REFERENCES

Mendoza TR, Osei JS, Shi Q, Duvic M. Development of the alopecia areata symptom impact scale. J Investig Dermatol Symp Proc. 2013 Dec;16(1):S51-2.

Olsen EA, Hordinsky MK, Price VH, et al. Alopecia areata investigational assessment guidelines--Part II. National Alopecia Areata Foundation. J Am Acad Dermatol. 2004 Sep;51(3):440-7.

14. LIST OF PLANNED TABLES

[redacted] Table ID	Table No.	Title	Population	Unique?
DS_TAA	14.1.1	Summary of Patient Disposition	All Screened Patients	Y
DS_TAB	14.1.2	Summary of Protocol Deviations	All Randomized Patients	Y
DM_TAA	14.1.3	Summary of Demographics	All Randomized Patients	Y
DM_TAB	14.1.4	Summary of Baseline Characteristics	All Randomized Patients	Y
MH_TAA	14.1.5	Summary of Medical History by System Organ Class and Preferred Term	Safety Population	Y
EX_TAA	14.1.6	Summary of Study Drug Administration and Compliance by Dosing Regimen	Safety Population	Y
CM_TAA	14.1.7.1	Summary of Prior Medications	Safety Population	Y
CM_TAB	14.1.7.2	Summary of Concomitant Medications	Safety Population	N
EF_TAA	14.2.1	Summary of Relative Change from Baseline in Total SALT Score at Week 24	Efficacy Population	Y
EF_TAC	14.2.2.1	Summary of Total SALT Scores by Dosing Regimen and Visit	Efficacy Population	Y
EF_TAE	14.2.2.2	Summary of 90%, 75%, and 50% Responders (SALT Relative Change) by Visit	Efficacy Population	Y
EF_TAG	14.2.2.3	Summary of Satisfaction of Hair Coverage Question	Efficacy Population	Y
EF_TAH	14.2.2.4	Shift from Baseline to Week 24 Satisfaction of Hair Coverage Question	Efficacy Population	Y
EF_TAI	14.2.3.1	Summary of Visual Analog Scale for Eyebrows (mm)	Efficacy Population	Y
EF_TAJ	14.2.3.2	Summary of Satisfaction of Hair Coverage Quality Questions	Efficacy Population	N
EF_TAK	14.2.3.3	Shift from Baseline to Week 24 Satisfaction of Hair Coverage Quality Questions	Efficacy Population	N

EF_TAL	14.2.3.4	Analysis of Patients Achieving ≤10, ≤20, or ≤25 Absolute SALT Scores by Visit	Efficacy Population	Y
AE_TAA	14.3.1.1	Summary of Treatment-Emergent Adverse Events	Safety Population	Y
AE_TAB	14.3.1.2	Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population	Y
AE_TAC	14.3.1.3	Summary of Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term	Safety Population	N
AE_TAD	14.3.1.4	Summary of All Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug System Organ Class and Preferred Term	Safety Population	N
AE_TAE	14.3.1.5	Summary of Treatment-Emergent Adverse Events Resulting in Study Dose Interruption by System Organ Class and Preferred Term	Safety Population	N
AE_TAF	14.3.1.6	Summary of CTCAE Grade 3-4 Hematology Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population	N
AE_TAG	14.3.1.7	Summary of CTCAE Grade 3-4 Serum Chemistry Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population	N
AE_TAH	14.3.1.8	Summary of Treatment-Emergent Adverse Events by Severity/Intensity, System Organ Class, and Preferred Term	Safety Population	Y
AE_TAI	14.3.1.9	Summary of Treatment-Emergent Adverse Events by Relationship to Study Drug, System Organ Class, and Preferred Term	Safety Population	N
AE_TAJ	14.3.1.10	Summary of Treatment-Emergent Serious Adverse Events by Relationship to	Safety Population	N

		Study Drug, System Organ Class, and Preferred Term		
LB_TAA	14.3.4.1.1	Summary of All Clinical Laboratory Values: Hematology	Safety Population	Y
LB_TAB	14.3.4.1.2	Summary of All Clinical Laboratory Values: Serum Chemistry	Safety Population	N
LB_TAC	14.3.4.2.1	Summary of CTCAE Grade 3-4 Key Clinical Laboratory Values: Hematology	Safety Population	Y
LB_TAD	14.3.4.2.2	Summary of CTCAE Grade 3-4 Key Clinical Laboratory Values: Serum Chemistry	Safety Population	N
VS_TAA	14.3.5.1	Vital Signs Summary	Safety Population	Y
EG_TAA	14.3.5.2	12-Lead Electrocardiogram Summary	Safety Population	N
EG_TAB	14.3.5.3	Summary of Abnormal, Clinically Significant 12-Lead Electrocardiogram Values by Dosing Regimen and Visit	Safety Population	Y
EG_TAC	14.3.5.4	Summary of Clinically Notable 12-Lead Electrocardiogram Values by Dosing Regimen and Visit	Safety Population	Y

15. LIST OF PLANNED FIGURES

[redacted] Figure ID	Figure No.	Title	Population	Unique?
DS_FAA	14.1.1	Kaplan-Meier Plot for Time to Study Completion or Early Termination	Safety Population	Y
EF_FAA	14.2.1.1	Relative Change in SALT Scores by Dosing Regimen across Time	Efficacy Population	Y
EF_FAB	14.2.1.2	Responders by Dosing Regimen at Week 24	Efficacy Population	Y
EF_FAC	14.2.1.3	Responders by Dosing Regimen across Time	Efficacy Population	Y
EF_FAD	14.2.1.4	Mean SALT Scores by Dosing Regimen across Time	Efficacy Population	Y
EF_FAE	14.2.1.5	Mean Absolute Change in SALT Scores by Dosing Regimen across Time	Efficacy Population	N
LB_FAA	14.3.4.1.1	Key Clinical Laboratory Values: Hematology Parameters	Safety Population	Y

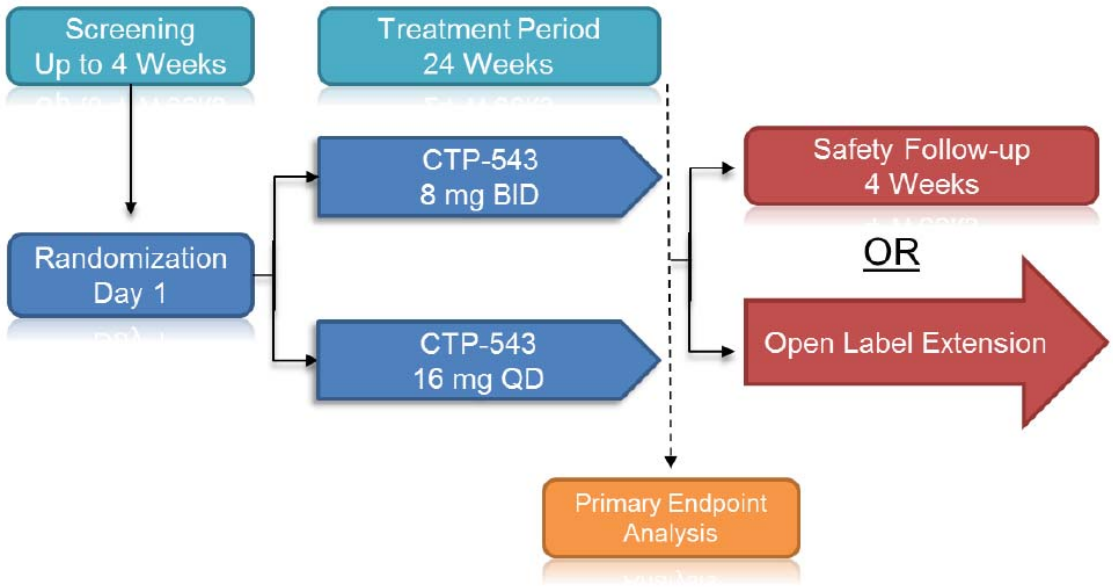
16. LIST OF PLANNED DATA LISTINGS

[redacted] Listing ID	Listing No.	Title	Population	Unique?
RN_LAA	16.1.1	Randomization Codes	All Randomized Patients	Y
LB_LAA	16.1.10.1	Clinical Laboratory Reference Range	N/A	Y
DS_LAA	16.2.1.1	Patient Disposition	All Randomized Patients	Y
DS_LAB	16.2.1.2	Screen Failures	N/A	Y
DS_LAC	16.2.1.3	Patient Visits	All Randomized Patients	Y
DS_LAD	16.2.2	Protocol Deviations	All Randomized Patients	Y
DS_LAE	16.2.3	Analysis Sets	All Randomized Patients	Y
DM_LAA	16.2.4.1	Patient Demographic and Baseline Characteristics	All Randomized Patients	Y
DM_LAB	16.2.4.2	Alopecia Areata History	All Randomized Patients	Y
MH_LAA	16.2.4.3	Medical History	Safety Population	Y
CM_LAA	16.2.4.4	Prior and Concomitant Medications	Safety Population	Y
EX_LAA	16.2.5.1	Treatment Compliance	Safety Population	Y
EX_LAB	16.2.5.2	Dosing Exceptions	Safety Population	Y
EF_LAA	16.2.6.1	SALT Score	Efficacy Population	Y
EF_LAB	16.2.6.2	Visual Analog Scale (VAS) for Eyebrows	Efficacy Population	Y
EF_LAC	16.2.6.3	Satisfaction of Hair Coverage Question	Efficacy Population	N
EF_LAD	16.2.6.4	Satisfaction of Hair Coverage Quality Questions	Efficacy Population	N
AE_LAA	16.2.7.1	All Adverse Events	Safety Population	Y
AE_LAB	16.2.7.2	Serious Adverse Events	Safety Population	N
AE_LAC	16.2.7.3	Adverse Events Related to Study Drug	Safety Population	N
AE_LAD	16.2.7.4	Adverse Events Leading to Study Drug Discontinuation	Safety Population	N
AE_LAE	16.2.7.5	Adverse Events Leading to Study Drug Interruption	Safety Population	N
AE_LAF	16.2.7.6	Adverse Events Leading to Death	Safety Population	N

AE_LAG	16.2.7.7	Pregnancy	Safety Population	N
PE_LAA	16.2.8	Physical Examinations	Safety Population	Y
LB_LAB	16.2.9.1	Clinical Laboratory Data: Hematology	Safety Population	Y
LB_LAC	16.2.9.2	Clinical Laboratory Data: Serum Chemistry	Safety Population	N
VS_LAA	16.2.10.1	Vital Signs	Safety Population	Y
EG_LAA	16.2.10.2	12-Lead Electrocardiogram	Safety Population	Y

17. APPENDICES

17.1 Study Flow Chart



17.2 Schedule of Events

Event	Screening	Randomization[1]	Treatment Period					Safety Follow-Up
	Day -28 to Day -1[12] (Visit 1)	Day 1[2] (Visit 2)	Week 2, 6 (Visit 3, 5)	Week 4, 8 (Visit 4, 6)	Week 12 (Visit 7)	Week 16, 20 (Visit 8, 9)	Week 24[3] (Visit 10)	Week 28[4] (Visit 11)
Informed consent	X							
Eligibility assessment	X	X						
Demographics	X							
Medical history	X	X						
Randomization		X						
Physical examination	X	X					X	X
Brief physical examination				X	X	X		
Height	X							
Weight	X	X		X	X	X	X	X
Pregnancy test[5]	X	X		X	X	X	X	
Tuberculosis test	X							
Clinical laboratory testing[7,8]	X[4]	X	X	X	X	X	X	X
Lipid assessment[10]		X			X		X	X
HBV and HCV test	X							
12-lead electrocardiogram	X	X		X	X	X	X	X
Vital signs	X	X		X	X	X	X	X
Severity of Alopecia Tool assessment[11]	X	X		X	X	X	X	
Photographs[12]	X	X		X	X	X	X	
Visual Analog Scale (VAS) for Eyebrows								
Patient Satisfaction Questions								
Dispense study drug		X		X	X	X		
Study drug accountability				X	X	X	X	
Adverse events[13]	X	X	X	X	X	X	X	X
Concomitant medications[13]	X	X	X	X	X	X	X	X

HBV= hepatitis B virus; HCV = hepatitis C virus

[1] Randomization/Day 1 may occur any time after Screening laboratory results are available and reviewed by the investigator.

[2] All subsequent visits and week increments should be based on the date of Visit 2. All visit windows are ±3 days.

[3] Also serves as the Early Termination Visit for patient withdrawal in this period.

[4] The Safety Follow-Up Visit is intended for those patients who do not roll over into an open-label extension and for patients who have been discontinued from the study and completed the Early Termination Visit (Week 24).

[5] Serum pregnancy test for females of childbearing potential only.

[6] Urine pregnancy test should be performed at the randomization visit.

[7] Includes hematology and serum chemistry.

[8] Collected pre-dose, except on Visit 11.

[9] Will include thyroid stimulating hormone and hemoglobin A1c at Screening only.

[10] Includes total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglycerides.

[11] Should be performed by the same rater for the patient for the duration of the study.

[12] Sites will take photographs of patient's scalps and eyebrow/eyelashes, if involved, to provide visual support of baseline SALT as well as potential SALT changes throughout the study.

[13] Collection is ongoing.

18. ATTACHMENTS

Attachment A: “CP543.2002 – TLF Shells” – Shells for Planned Tables, Figures, and Listings