Official Title:	**A Double-Blind, Randomized, Placebo-Controlled, Parallel Dose Study to Evaluate the Safety and Efficacy of CTP-543 In Adult Patients With Moderate to Severe Alopecia Areata**
NCT Number:	NCT03137381
Document Date:	SAP Version 2: 07 May 2019

STATISTICAL ANALYSIS PLAN
07 May 2019

A DOUBLE-BLIND RANDOMIZED, PLACEBO-CONTROLLED STUDY TO EVALUATE THE SAFETY AND EFFICACY OF CTP-543 IN ADULT PATIENTS WITH MODERATE TO SEVERE ALOPECIA AREATA

PROTOCOL NUMBER CP543.2001

SPONSORED BY

Concert Pharmaceuticals, Inc.
99 Hayden Avenue, Suite 500
Lexington, MA 02421
Telephone: (781) 860-0045

DOCUMENT VERSION CONTROL

Version Number	Date	Comments/Changes
0.1	11 September 2017	DRAFT 1
0.2	20 October 2017	DRAFT 2
0.3	20 February 2018	DRAFT 3
0.4	10 May 2018	DRAFT 4
1.0	04 June 2018	VERSION 1.0
2.0	07 May 2019	VERSION 2.0

APPROVALS

Approved: DocuSigned by: [redacted] Date: _____

Signer Name: [redacted]
[redacted]ning Reason: I am the author of this document
[redacted]ning Time: 5/14/2019 1:37:55 PM EDT
[redacted]\8FD9B40F656D28C3
[redacted]

DocuSigned by: [redacted] Date: _____

Signer Name: [redacted]
[redacted]g Reason: I approve this document
[redacted]g Time: 5/14/2019 1:45:44 PM EDT
[redacted]58088AA6147794D

Concert Pharmaceuticals, Inc.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
AASIS	Alopecia Areata Symptom Impact Scale
AE	Adverse event
ANCOVA	Analysis of Covariance
ATC	Anatomical-Therapeutic-Chemical
BID	Twice daily dosing
CGI-I	Clinical Global Impression of Improvement
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel Test
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
DMC	Data monitoring committee
ECG	Electrocardiogram
eCRF	Electronic case report form
HDL	High-density lipoprotein
ICH	International Conference on Harmonisation
LDL	Low-density lipoprotein
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effects Model of Repeated Measures
PD	Pharmacodynamic
PGI-I	Patient Global Impression of Improvement
PK	Pharmacokinetic
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
SOC	System organ class

TEAE	Treatment-emergent adverse events
VAS-S	Visual Analog Scale of Severity
WHO	World Health Organization
χ^2	Chi-squared test

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 CP543.2001. 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, pharmacokinetic (PK), pharmacodynamic (PD), 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. Pharmacokinetic analyses are outside the scope of this document and will be performed and reported separately. 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. The CP543.2001 protocol amendment 2.0 was finalized on 05 July 2017. The purpose of this amendment was to revise for a new sequential cohort study design, where a parallel active dose comparison would no longer be conducted. Amendment 3.0, dated 25 September 2017, further clarifies this revised approach. Amendment 4.0, dated 17 August 2018, included an additional Cohort of subjects to assess a 12 mg BID dose of CTP-543 compared to placebo. The sample size calculations were updated to reflect the additional patients enrolled. Amendment 5.0, dated 21 January 2019, included language for allowing eligible patients who completed dosing for 24 weeks to enter an open-label extension study of CTP-543. This SAP is based on the latest protocol amendment.

2. PROTOCOL SUMMARY

2.1 Study Objectives

The overall objectives of the study are to assess the safety and efficacy of a 24-week regimen of administration of CTP-543 in adult patients with chronic, moderate to severe alopecia areata.

2.1.1 Primary Objective

- To assess the effect of CTP-543 on treating hair loss as measured by the Severity of Alopecia Tool (SALT);
- To assess the safety of administration of CTP-543 in adult patients with chronic, moderate to severe alopecia areata.

2.1.2 Exploratory Objectives

- To assess the change in alopecia areata severity as measured by the clinician Visual Analog Scale of Severity (VAS-S) from baseline;
- To assess the Clinical Global Impression of Improvement (CGI-I);
- To assess the change in alopecia areata severity as measured by the patient VAS-S from baseline;
- To assess the Patient Global Impression of Improvement (PGI-I);
- To assess the change in patient reported outcomes as measured by the Alopecia Areata Symptom Impact Scale (AASIS) and exploratory questions from baseline.

2.2 Study Design

This is a double-blind, randomized, placebo-controlled multicenter study to evaluate the safety and efficacy of CTP-543 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 SALT at Screening and Baseline, and are not concurrently being treated for alopecia areata or with other treatments that might affect hair regrowth or immune response. Approximately 50% of alopecia areata patients with alopecia totalis or universalis, and approximately 10% with only alopecia ophiasis will be enrolled.

The study consists of up to 3 cohorts initiated sequentially in ascending dose order. An independent data monitoring committee (DMC) will determine if there are adequate safety data to support each subsequent higher dose cohort. Patients will not dose escalate within a cohort and may only participate in one cohort.

The Screening Period may last up to 28 days prior to randomization and initiation of study drug. The Treatment Period is the initial 24-week, double-blind, placebo-controlled period to define efficacy and safety of CTP-543 compared to placebo. The Post-Treatment Safety Follow-up Period is the final 4 weeks of each cohort to assess safety following treatment completion. Patients enrolled in Cohort 3 (12 mg BID) will have the option to continue receiving treatment in an open-label extension study following the treatment period. If patients do not wish to continue into the open-label extension study, they will complete treatment at Week 24 and return in 4 weeks for the Post-Treatment Safety Follow-up to assess safety following treatment completion.

The DMC will perform regular safety assessments for each cohort based on review of collective safety data. After the last patient has completed the Week 12 Visit within a cohort, the DMC will convene to review accumulated safety data to assess if initiation of the subsequent cohort is supported. The DMC may advise treatment arm cessation due to intolerability at any time.

Patients will provide appropriately obtained informed consent prior to completing any screening procedures. Patients meeting screening criteria will be eligible to continue to the Day 1 visit for review of eligibility and baseline assessments, including SALT, physical examination, clinical laboratory assessments, vital signs, and electrocardiogram (ECG). For each cohort, patients meeting all inclusion criteria and none of the exclusion criteria will be randomized to CTP-543 treatment or placebo. The first 2 cohorts will be randomized in a 2:1 ratio (active:placebo) and the third cohort will be randomized in a 5:1 ratio (active:placebo) in order to provide a similar number of patients across each CTP-543 dose and overall placebo (pooled) group. 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.

The double-blind, placebo-controlled Treatment Period for each cohort will last 24 weeks. Assessment of treatment response with SALT for efficacy will occur at 4, 8, 12, 16, 20 and 24 weeks. The final efficacy analysis will be conducted when all patients in the 12 mg cohort have completed Week 24.

For Cohorts 1 and 2, patients will stop taking study medication upon completion of treatment at Week 24 and enter a 4-week Post-Treatment Safety Follow-Up Period. Patients will be assessed for safety through Week 28. For Cohort 3, 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.

Patients enrolled into each cohort will take the first dose of study drug in the clinic on Day 1 and will be instructed to take study drug every 12 hours for the duration of the Treatment Period. Patients will dose study drug in the clinic on all Study Visit Days after clinical laboratory blood draws are completed. Blood samples for pharmacokinetic and pharmacodynamic assessment will be taken periodically. Scheduled assessment of patient and clinician perception of disease

severity and improvement will also occur. Patient safety will be monitored throughout the trial and supported by regular review by the DMC.

Hematology parameters will be monitored closely for the duration of the study. For each cohort, hematology will be conducted every 2 weeks during the first 8 weeks of the Treatment Period, followed by an assessment every 4 weeks thereafter through completion of the study. Lipid levels will be assessed every 12 weeks throughout the Treatment Period and at the Post-Treatment Safety Follow-Up Visit, if applicable. Significant cytopenias or other hematologic abnormalities will be managed by dose interruption and signs and symptoms of infection will be 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.

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 8.1 and 8.2 in the CP543.2001 Protocol.

2.4 Treatment Regimens

CTP-543 will be dosed orally as tablets at doses 4 mg, 8 mg, 12 mg, or matching placebo, every 12 hours during the Treatment Period. Doses will be allocated to each cohort as follows:

- Cohort 1: 4 mg (2:1 CTP-543 4 mg : placebo)
- Cohort 2: 8 mg (2:1 CTP-543 8 mg : placebo)
- Cohort 3: 12 mg (5:1 CTP-543 12 mg : placebo)

2.5 Treatment Group Assignments or Randomization

Patients meeting all inclusion criteria and none of the exclusion criteria will be randomized to CTP-543 treatment or placebo. The first 2 cohorts will be randomized in a 2:1 ratio (active:placebo) and the third cohort will be randomized in a 5:1 ratio (active:placebo) in order to provide a similar number of patients across each CTP-543 dose and the overall placebo (pooled) group. 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. Approximately 50% of alopecia areata patients with alopecia totalis or universalis, and approximately 10% with only alopecia ophiasis will be enrolled.

2.6 Sample Size Determination

There are very few studies in the literature to provide reliable estimates of active treatment or placebo response rates using SALT, or the estimate of variances around these measures, in patients with alopecia areata. Power calculations assume a 2-sided chi-squared test and significance level of 0.05 and are based on an active treatment response rate of 45% and a placebo response rate of 10%.

Although patients will be randomized in an unbalanced ratio of active drug to placebo within each cohort, the placebo patients from the 3 cohorts will be combined for statistical comparisons to each active treatment group. The first 2 cohorts will be randomized in a 2:1 ratio (active:placebo) and the third cohort will be randomized in a 5:1 ratio (active:placebo). Based on estimated completion rates, this randomization scheme is expected to provide a similar number of patients in each CTP-543 dose group and the pooled placebo group. Thus, power calculations for the comparison to placebo are based on a 1:1 treatment ratio of each CTP-543 dose group to placebo. Power calculations assume a 2-sided test and significance level of 0.05 and are based on an active treatment response rate of 45% and a placebo response rate of 10%. Based on estimated completion rates as of Amendment 4, this randomization scheme is expected to provide a similar number of patients in the 12 mg group and the pooled placebo group.

A sample size of 28 patients in the 12 mg group and 28 patients in the pooled placebo group will provide >80% power for the chi-squared test when comparing each dose group to the combined placebo group (28 active, 28 placebo). Approximately 150 patients will be randomized in order to provide 120 patients who complete treatment.

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 path, file name, and run date/time. Summary tables and data listings will be summarized by treatment 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.

All statistical tests will be 2-sided with a significance value of 0.05. Testing will be performed only for the Treatment Period. Estimates and confidence intervals will be reported to 1 more decimal than the original data. P-values will be reported to 3 decimal places.

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 cohort within treatment, patient, and week and/or time of assessment, as applicable.
- Placebo groups will be separated by cohort within data listings and pooled within summary tables.
- When change from 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 treatment and cohort.

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 treatment group.

4.2 Pharmacokinetic Population

The Pharmacokinetic Population will include all patients who receive study drug and have at least 1 pharmacokinetic sample taken during the Treatment Period. Patients who receive placebo will be excluded from the Pharmacokinetic Population.

4.3 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 treatment received during the study.

4.4 Per Protocol Population

The Per Protocol Population will include all patients in the Efficacy Population who were dosed according to protocol, have a week 24 SALT score, and have no major protocol deviations. The procedure for defining major protocol deviations is described in Section 5.2.

5. STUDY PATIENTS

5.1 Disposition of Patients

Disposition will be summarized by randomized treatment group 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, Pharmacokinetic, Safety, and Per Protocol Populations.
- The number and percentage of patients who completed the study (defined as completing all study visits) and who completed 24 weeks of treatment.
- 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. Additionally, screen failures post and prior to Amendment 2 will be presented in separate listings. A Kaplan Meier curve of time to last dose will also be presented.

5.2 Protocol Deviations

Protocol deviations will be collected at both the site and patient level on the Electronic case report form (eCRF). A blinded 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. Protocol deviations that are identified as major will be used to exclude patients from the Per Protocol population.

6. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic characteristics (i.e., 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.

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. In addition, baseline SALT score will be presented as a baseline characteristic. The duration of the current episode in months and the duration of disease in months will also be summarized.

Duration of current episode will be calculated as: (date of randomization – date of current episode onset + 1) / 30.4375.

Duration of disease at onset will be calculated as: (date of randomization – date of disease onset + 1) / 30.4375.

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

Thorough medical history, including current medications, nail and facial hair involvement, co-morbidities, as well as history of vaccination against herpes zoster collected at the Screening and Randomization Visits, will be summarized and listed.

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 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 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 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 treatment group. 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 4 mg cohort, x2 for the 8 mg cohort, and x 2 for the 12 mg cohort). Dose interruptions will be ignored in this calculation. Patient compliance 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 proportion of responders, defined as patients achieving at least a 50% relative reduction in SALT score, from baseline at Week 24.

8.1.1 Severity of Alopecia Tool (SALT)

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 (follow-up SALT score minus baseline 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 Exploratory Efficacy Endpoints

Exploratory efficacy endpoints include:

- The proportion of responders at Weeks 4, 8, 12, 16 and 20;
- Proportion of responders who have at least 75%, 90% and 100% 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 Blinded Treatment Period;
- Relative change in SALT scores from baseline at Weeks 4, 8, 12, 16, 20, and 24 in the Blinded Treatment Period;
- Absolute SALT scores at Weeks 4, 8, 12, 16, 20, and 24 in the Blinded Treatment Period;
- Proportion of patients achieving an absolute SALT score of $\leq$10, $\leq$20, and $\leq$25 at Weeks 4, 8, 12, 16, 20 and 24;
- Percent change in alopecia areata severity from baseline as measured by the clinician VAS-S at Weeks 12 and 24;

- Changes in alopecia areata from baseline as measured by the clinician rated 7-point Likert scale CGI-I at Weeks 12 and 24;
- Proportion of subjects worsening in alopecia areata from baseline to Weeks 12 and 24 as measured by responses of "Very Much Worse" or "Much Worse" on the clinician rated CGI-I;
- Proportion of subjects improving from baseline to Weeks 12 and 24 as measured by responses of "Very Much Improved" or "Much Improved" on the clinician rated CGI-I;
- Percent change in alopecia areata severity from baseline as measured by the patient VAS-S at Weeks 12 and 24;
- Changes in alopecia areata from baseline as measured by the patient rated 7-point Likert scale PGI-I at Weeks 12 and 24;
- Proportion of subjects worsening in alopecia areata from baseline to Weeks 12 and 24 as measured by responses of "Very Much Worse" or "Much Worse" on the patient rated PGI-I;
- Proportion of subjects improving from baseline to Weeks 12 and 24 as measured by responses of "Very Much Improved" or "Much Improved" on the patient rated PGI-I;
- Patient-reported outcomes: Changes in symptoms from baseline as measured by AASIS and exploratory questions at Week 24.

8.2.1 Visual Analog Scale (VAS)

The VAS is a scale initially developed for pain that has been used in a variety of clinical settings where the endpoint of interest is based on patient 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. 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.

Clinician VAS of Severity (VAS-S)
The Investigator will complete a VAS-S regarding the severity of the patient's alopecia areata at the time of completion as indicated in the Schedule of Events. The left and right anchor points for the clinician VAS-S are "Extremely Apparent" and "Not At All Apparent", respectively.

Patient VAS of Severity (VAS-S)
Patients will rate perception of his/her alopecia areata severity on the patient VAS-S. The left and right anchor points for the patient's alopecia areata VAS-S are "Extremely Apparent" and

"Not At All Apparent", respectively. The patient VAS-S will measure the patient's perception of his/her alopecia areata at the time of completion.

8.2.2 Clinical Global Impression of Improvement (CGI-I)

Compared to the patient's alopecia areata prior to treatment at baseline, the patient's current state of alopecia areata will be assessed according to the Investigator's perceived change. The Investigator may select one of seven numeric choices from 1 to 7, with 1 representing "Very Much Improved" to 7 representing "Very Much Worse".

8.2.3 Patient Global Impression of Improvement (PGI-I)

Compared to the patient's alopecia areata prior to treatment at baseline, the patient's current state of alopecia areata will be assessed according to his/her perceived change. The patient may select one of seven numeric choices from 1 to 7, with 1 representing "Very Much Improved" to 7 representing "Very Much Worse".

8.2.4 Patient Reported Outcomes: Alopecia Areata Symptom Impact Scale (AASIS) and Exploratory Questions

The AASIS is a questionnaire designed to measure the quality of life, symptoms, and their impact for patients with alopecia areata [Mendoza 2013]. Three dimensions related to alopecia areata are assessed: impact of alopecia areata, hair loss, and physical skin symptoms. All responses will be summed to produce the AASIS score.

In addition to the AASIS, exploratory questions will be used to attempt to define clinically meaningful outcomes for patients with alopecia areata.

8.3 Overview of Efficacy Analysis Issues

8.3.1 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.

8.3.2 Multicenter Studies

Patients will be enrolled at up to 15 sites. To reduce variability, one rater should perform each clinician dependent assessment (SALT, VAS-S, and CGI-I) for the patient for the duration of the study. All investigators using the SALT will be trained prior to use.

8.3.3 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). For Cohorts 1 and 2, patients will stop taking study medication upon completion of treatment at Week 24 and enter a 4-week Post-Treatment Safety Follow-Up Period. For Cohort 3, 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.

Unscheduled and repeat safety visits will be assigned to the closest prior planned visit. If the closest planned visit is already documented, the unscheduled or repeat visit will only be listed and will not be summarized.

8.4 Analysis Methods

All statistical tests will be 2-sided with a significance value of 0.05. Testing will be based on the Efficacy population and performed only for the Treatment Period. An analysis of the primary efficacy endpoint and exploratory SALT endpoints will also be performed for the Per Protocol population. The final efficacy analysis will be conducted when all patients in the 12 mg cohort have completed Week 24. The placebo groups from all 3 cohorts will be pooled and compared to each active dose (4 mg, 8 mg, and 12 mg) individually. Active doses, 4 mg, 8 mg, and 12 mg, will also be compared. There will be no adjustment for multiple treatment group comparisons in this dose-ranging Phase 2 study.

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		
Responder Analysis SALT (50% relative reduction)	Baseline, Week 24	χ^2 Test
Exploratory		
Responder Analysis SALT (50% relative reduction)	Baseline, Week 4, 8, 12, 16, 20	χ^2 Test
Responder Analysis SALT (75%, 90%, and 100% relative reduction)	Baseline, Week 4, 8, 12, 16, 20, 24	χ^2 Test
SALT (≤10, ≤20, ≤25 absolute score)	Baseline, Week 4, 8, 12, 16, 20, 24	χ^2 Test
SALT (absolute change)	Baseline, Week 4, 8, 12, 16, 20, 24	MMRM
SALT (relative change)	Baseline, Week 4, 8, 12, 16, 20, 24	MMRM
SALT (absolute score)	Baseline, Week 4, 8, 12, 16, 20, 24	MMRM
Clinician VAS-S (percent change)	Baseline, Week 12, 24	ANCOVA
Patient VAS-S (percent change)	Baseline, Week 12, 24	ANCOVA
CGI-I	Week 12, 24	χ^2 Test
CGI-I Responder ("Very Much/Much Improved" and "Much/Very Much Worse")	Week 12, 24	χ^2 Test
PGI-I	Week 12, 24	χ^2 Test
PGI-I Responder ("Very Much/Much Improved" and "Much/Very Much Worse")	Week 12, 24	χ^2 Test
AASIS	Baseline, Week 24	Descriptive Statistics
Exploratory Questions	Baseline, Week 24	Descriptive Statistics
Responder Analysis, Exploratory Questions, Satisfied v. Unsatisfied	Baseline, Week 24	χ^2 Test

χ^2 = Chi-Squared Test; ANCOVA = analysis of covariance; CMH = Cochran-Mantel-Haenszel; MMRM = mixed-effect model for repeated measures

8.4.1 Primary Efficacy Analysis

The aim of this study is to demonstrate that in terms of the primary efficacy endpoint, 50% relative reduction in SALT score at Week 24, CTP-543 is superior to the placebo. Pairwise treatment group differences will be assessed with the χ^2 test.

The active treatment will be considered effective if $p \leq 0.05$.

Number and percentage, as well as p-values based on the χ^2 test, will be reported for the responders, defined as a patient meeting at least 50% relative reduction in SALT score at Week 24. Additionally, the number and percentage of responders will be reported by alopecia areata subtype.

Responders will be presented graphically by treatment group as a bar graph at 24 Weeks and as a line graph across time.

8.4.2 Exploratory Efficacy Analyses

Treatment differences for absolute score, absolute change, and relative change in SALT score from baseline to Weeks 4, 8, 12, 16, 20, and 24 will be assessed with a mixed-effect model of repeated measures (MMRM). The model will include fixed factors for treatment group, study visit, treatment by study visit interaction, and alopecia areata subtype, with baseline SALT score as a covariate. An unstructured variance-covariance matrix will be used. If convergence is not achieved, an alternative autoregressive covariance structure will be used. If the MMRM model does not converge, other covariance structures will be explored. If convergence is still not met, only descriptive statistics will be presented.

Point estimates and standard errors will be presented for each treatment group at each time point. P-values for the treatment by visit interaction will be presented at Week 24 for each active treatment compared to the placebo. A comparison of the active doses (4 mg vs. 8 mg, 4 mg vs. 12 mg, 8 mg v. 12 mg) will be presented as well. Treatments will be compared overall and by visit.

Descriptive statistics will be reported for the SALT score at each time point for each treatment group and by subtype. By-patient data listing will also be presented for patient SALT scores and collection of SALT photographs. The mean of observed value, absolute change, and relative change SALT scores along with standard errors for each treatment group will be presented using line graphs.

Responders, as defined for the primary endpoint, will be analyzed per section 8.4.1 for Weeks 4, 8, 12, 16, and 20. Additionally, the following responder groups will be analyzed per section 8.4.1 at Weeks 4, 8, 12, 16, 20, and 24: 1) patients who meet at least 75%, 90%, and 100% relative change; 2) patients who meet an absolute SALT score of ≤10, ≤20, or ≤25.

The percent change in clinician and patient VAS-S from baseline will be assessed using the analysis of covariance (ANCOVA) for Week 12 and 24 with fixed factors for treatment, alopecia areata subtype, and baseline VAS-S. The least squares mean score estimates with 95% CI will be presented along with p-values for each treatment comparison at each time point. Descriptive statistics will also be reported by treatment and subtype.

A χ^2 trend test will be used to analyze CGI-I and PGI-I between treatment groups overall. Responses for PGI-I and CGI-I categorized as achieving "Very Much/Much Improved" or "Much/Very Much Worse" will also be compared between treatment groups with the χ^2 test. Descriptive statistics and by-patient data listings will also be presented for the 7 response categories for each assessment.

Mean and mean change from baseline for total AASIS score will be reported. Number and percentage of subjects in each response category of AASIS will also be summarized. Individual responses will be listed in categories of "Severity" and "Interference".

The exploratory questions will be summarized with descriptive statistics at baseline and Week 24, and will be listed in the by-patient data listings. Responses will be categorized as "Satisfied" (including responses of "Very satisfied" and "Satisfied") and "Unsatisfied" (including responses of "Unsatisfied" and "Very unsatisfied") and presented as a 2 x 2 shift table from baseline to Week 24, compared with a χ^2 Test by cohort.

8.5 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
- 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 treatment arm. 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 treatment group 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.

Additionally, TEAEs will be summarized by time interval: 0 to 12 weeks, and 12 to 24 weeks. For each time interval, an incidence table will summarize only TEAEs with an onset date within the interval and a prevalence table will summarize all TEAEs that have an onset date within the interval or continue into the interval. Differences between the incidence and prevalence tables can provide insight into the duration of TEAEs as well as the recurrence of TEAEs. A preferred term for an individual patient will be reported in multiple time intervals if there are multiple adverse event reports. The denominator for each time interval will be the number of patients who received at least 1 dose of study drug within the interval. These incidence and prevalence tables will be repeated for key hematology and serum chemistry AEs categorized as CTCAE Grade 3-4 results.

9.3 Clinical Laboratory Evaluation

Observed measurements along with change from baseline for each scheduled assessment will be summarized descriptively by treatment group 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 for neutrophils, platelets, and hemoglobin will be summarized for each scheduled visit and overall for all post-baseline visits. In addition, hematology parameters of interest that meet Grade 3 or Grade 4 toxicity criteria 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 for total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL), and triglycerides will be summarized for each scheduled visit and overall for all post-baseline visits.

Laboratory values will be converted to the project-defined unit of measurement, as applicable, 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 scheduled assessment will be summarized descriptively by treatment group 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 treatment group. 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 treatment group and visit as well as listed within a by-patient data listing. Patients receiving study drug will be identified and summarized by treatment group 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

10.1 Pharmacokinetic and Pharmacodynamic Methods

The collection status of pharmacokinetic and pharmacodynamic samples will be listed for each visit with scheduled sampling by patient using the Safety Population. Plasma concentrations of study drug may be summarized separately, as appropriate, for the Pharmacokinetic Population.

11. INTERIM ANALYSES AND DATA MONITORING

When SALT data through Week 24 of treatment was available for all patients in Cohort 1 (4 mg) and Cohort 2 (8 mg), an interim analysis was performed. The purpose was to review selected efficacy and safety results in those 2 cohorts for planning purposes regarding the clinical development of the compound. While the results showed aggregate comparisons between the patients who received active CTP-543 and those who received placebo, all blinded study personnel remained blinded to treatment assignment. Since no further enrollment occurred in these 2 cohorts, there will be no adjustment for multiple treatment group comparisons. See Section 14 and 15 for summary tables and figures that were generated for this interim analysis.

A Data Monitoring Committee will monitor safety at regular intervals as defined in the DMC Charter. After the last patient in a cohort has completed the Week 12 Visit, the DMC will convene to review accumulated safety data to assess if initiation of the subsequent cohort is supported, as applicable. Specifications of data to be supplied to the Committee are outside the scope of this document. Further details are provided in the latest version of the DMC Charter.

12. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

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

- SALT 50% reduction analysis changed from Cochran-Mantel-Haenszel Test (CMH) to χ^2 test and will not be stratified by Alopecia Areata subtype.
- VAS-S analysis method changed from CMH to ANCOVA.
- CGI-I and PGI-I analysis method changed from CMH test to χ^2test.
- AASIS and Exploratory Question analysis method changed from ANCOVA to descriptive statistics and χ^2 test, respectively.
- Alopecia Areata subtype used as a fixed effect within the MMRM.
- TEAE definition modified so that all AEs that occur after study dosing will be counted, rather than only those that occur up to Week 24 or the Early Termination Visit.

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?	Interim Analysis
DS_TAA	14.1.1	Summary of Patient Disposition	All Screened Patients	Y	X
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	X
DM_TAB	14.1.4	Summary of Baseline Characteristics	All Randomized Patients	Y	X
MH_TAA	14.1.5	Summary of Medical History by System Organ Class and Preferred Term	Safety Population	Y	
EX_TAA	14.1.6.1	Summary of Study Drug Administration and Compliance by Treatment Group	Safety Population	Y	
CM_TAA	14.1.7.1	Summary of Prior Medications	Safety Population	N	
CM_TAB	14.1.7.2	Summary of Concomitant Medications	Safety Population	N	
EF_TAA	14.2.1.1	Chi-Squared Analysis of Responders at Week 24	Efficacy Population	Y	X
EF_TAB	14.2.1.2	Chi-Squared Analysis of Responders at Week 24	Per Protocol Population	N	
EF_TAC	14.2.1.3	Chi-Squared Analysis of Responders by Visit	Efficacy Population	N	X
EF_TAD	14.2.1.4	Chi-Squared Analysis of	Per Protocol Population	N	

		Responders by Visit			
EF_TAT	14.2.1.5	Chi-Squared Analysis of Patients Achieving ≤10, ≤20, or ≤25 Absolute Salt Scores by Visit	Efficacy Population	N	
EF_TAU	14.2.1.6	Chi-Squared Analysis of Patients Achieving ≤10, ≤20, or ≤25 Absolute Salt Scores by Visit	Per Protocol Population	N	
EF_TAE	14.2.1.7.1	Summary of Total SALT Scores by Treatment Group and Visit	Efficacy Population	Y	X
EF_TAI	14.2.1.7.2	Summary of Total SALT Scores of Responders at Week 24 by Treatment Group	Efficacy Population	Y	X
EF_TAF	14.2.1.8	MMRM Analysis for Absolute Change in SALT Scores	Efficacy Population	Y	X
EF_TAG	14.2.1.9	MMRM Analysis for Absolute Change in SALT Scores	Per Protocol Population	N	
EF_TAH	14.2.1.10	MMRM Analysis for Relative Change in SALT Scores	Efficacy Population	N	X
EF_TAS	14.2.1.11	MMRM Analysis for Relative Change in SALT Scores	Per Protocol Population	N	
EF_TAY	14.2.1.12	MMRM Analysis for Absolute SALT Scores	Efficacy Population	N	
EF_TAZ	14.2.1.13	MMRM Analysis for Absolute SALT Scores	Per Protocol Population	N	

EF_TAJ	14.2.2.1	Summary of Clinician VAS-S (mm)	Efficacy Population	Y	
EF_TAK	14.2.2.2	Summary of Patient VAS-S (mm)	Efficacy Population	N	
EF_TAL	14.2.3.1	Summary of CGI-I	Efficacy Population	Y	
EF_TAM	14.2.3.2	Summary of CGI-I Improvement	Efficacy Population	Y	
EF_TAN	14.2.3.3	Summary of CGI-I Worsening	Efficacy Population	N	
EF_TAO	14.2.3.4	Summary of PGI-I	Efficacy Population	N	
EF_TAP	14.2.3.5	Summary of PGI-I Improvement	Efficacy Population	N	
EF_TAQ	14.2.3.6	Summary of PGI-I Worsening	Efficacy Population	N	
EF_TAR	14.2.4.1	Summary of Exploratory Questions at Week 24	Efficacy Population	Y	
EF_TAV	14.2.4.2	Shift from Baseline to Week 24 Exploratory Questions	Efficacy Population	Y	
EF_TAW	14.2.5.1	Summary of AASIS Responses	Efficacy Population	Y	
EF_TAX	14.2.5.2	Mean and Mean Change from Baseline in AASIS Responses	Efficacy Population	Y	
AE_TAA	14.3.1.1	Summary of Treatment-Emergent Adverse Events	Safety Population	Y	X
AE_TAB	14.3.1.2	Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population	Y	X
AE_TAC	14.3.1.3	Summary of Treatment-Emergent Serious Adverse Events by System Organ	Safety Population	N	

		Class and Preferred Term			
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	Safety Population	Y	

		Events by System Organ Class and Preferred Term: Incidence by Time Interval			
AE_TAJ	14.3.1.10	Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term: Prevalence by Time Interval	Safety Population	N	
AE_TAK	14.3.1.11	Summary of CTCAE Grade 3-4 Treatment-Emergent Hematology Adverse Events System Organ Class and Preferred Term: Incidence by Time Interval	Safety Population	N	
AE_TAL	14.3.1.12	Summary of CTCAE Grade 3-4 Treatment-Emergent Hematology Adverse Events System Organ Class and Preferred Term: Prevalence by Time Interval	Safety Population	N	
AE_TAM	14.3.1.13	Summary of CTCAE Grade 3-4 Treatment-Emergent Serum Chemistry Adverse Events System Organ Class and Preferred Term: Incidence by Time Interval	Safety Population	N	
AE_TAN	14.3.1.14	Summary of CTCAE Grade 3-4 Treatment-	Safety Population	N	

		Emergent Hematology Adverse Events by System Organ Class and Preferred Term: Prevalence by Time Interval			
AE_TAO	14.3.1.15	Summary of Treatment-Emergent Adverse Events by Relationship to Study Drug, System Organ Class, and Preferred Term	Safety Population	N	
AE_TAP	14.3.1.16	Summary of Treatment-Emergent Serious Adverse Events by Relationship to Study Drug, System Organ Class, and Preferred Term	Safety Population	N	
LB_TAA	14.3.4.1.1	Summary of All Clinical Laboratory Values: Hematology	Safety Population	Y	X
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	X
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 Treatment Group and Visit	Safety Population	Y	
EG_TAC	14.3.5.4	Summary of Clinically Notable 12-Lead Electrocardiogram Values by Treatment Group and Visit	Safety Population	Y	

15. LIST OF PLANNED FIGURES

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

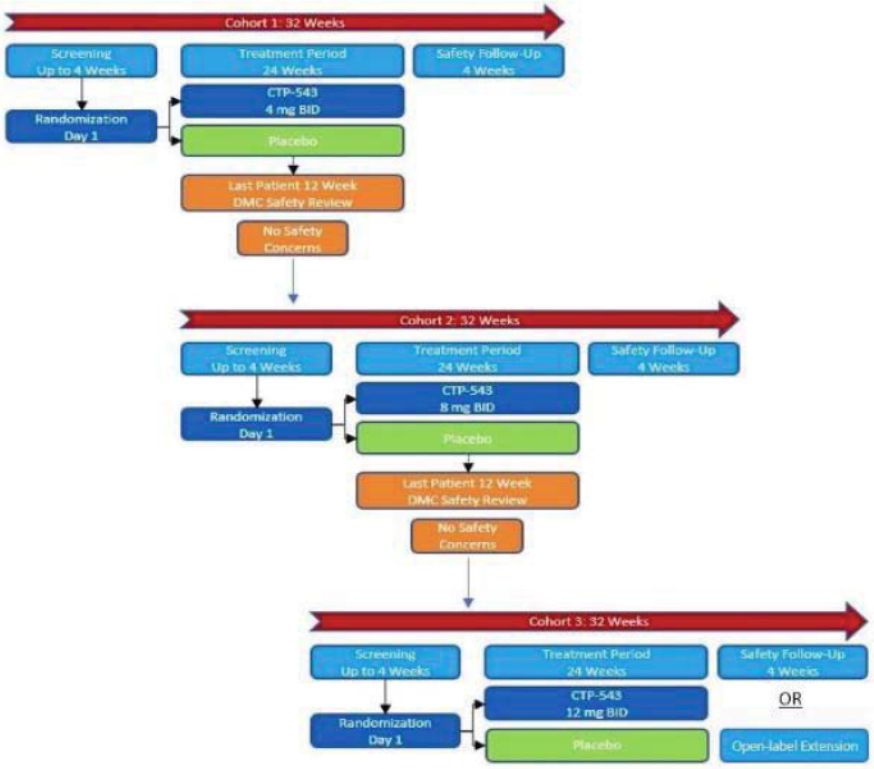
16. LIST OF PLANNED DATA LISTINGS

[redacted] Listing ID	Listing No.	Title	Population	Unique?	Interim Analysis
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		Y	
DS_LAC	16.2.1.3	Screen Failures Prior to Amendment 2		N	
DS_LAD	16.2.1.4	Patient Visits	All Randomized Patients	Y	
DS_LAE	16.2.2	Protocol Deviations	All Randomized Patients	Y	
DS_LAF	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	SALT Photographs	Efficacy Population	Y	
EF_LAC	16.2.6.3	Clinician and Patient VAS-S	Efficacy Population	Y	
EF_LAD	16.2.6.4	CGI-I and PGI-I	Efficacy Population	Y	
EF_LAE	16.2.6.5	AASIS	Efficacy Population	Y	

EF_LAF	16.2.6.6	Exploratory 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	
PK_LAA	16.2.10.3	Pharmacokinetic Blood Samples	Pharmacokinetic Population	Y	
PD_LAA	16.2.10.4	Pharmacodynamic Blood Samples	Pharmacokinetic Population	Y	

17. APPENDICES

17.1 Study Flow Chart



17.2 Schedule of Events

Event	Screening	Randomization	Treatment Period					Safety Follow-Up
	Day -28 to Day -1[12] (Visit 1)	Day 1[1] (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[11] (Visit 10)	Week 28 (Visit 11)[13]
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[2]	X	X		X	X	X	X	
Tuberculosis test	X							
Clinical laboratory testing[3,8]	X[4]	X	X	X	X	X	X	X
Lipid assessment[5]		X			X		X	X
HBV and HCV test	X							
Pharmacokinetic blood sampling		X[6]	X[6]	X[6]			X[6]	
Pharmacodynamic blood sampling		X[7]	X[7]	X[7]			X[7]	
12-lead electrocardiogram	X	X		X	X	X	X	X
Vital signs	X	X		X	X	X	X	X
Severity of Alopecia Tool assessment[9]	X	X		X	X	X	X	
Photographs	X	X		X	X	X	X	
Clinician Visual Analog Scale – Severity[9]		X			X		X	
Clinician Global Impression of Improvement[9]					X		X	
Patient Visual Analog Scale - Severity		X			X		X	
Patient Global Impression of Improvement					X		X	
AASIS and exploratory questions		X					X	
Dispense study drug		X		X	X	X		
Study drug accountability				X	X	X	X	
Adverse events[10]	X	X	X	X	X	X	X	X
Concomitant medications[10]	X	X	X	X	X	X	X	X

AASIS = Alopecia Areata Symptom Impact Scale; HBV= hepatitis B virus; HCV = hepatitis C virus

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

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

[3] Includes hematology and serum chemistry.

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

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

[6] Collected at Day 1 and Week 4 (pre-dose, and post-dose at end of visit), and Weeks 2 (pre-dose with clinical labs), and Weeks 8, 24 (post-dose at end of visit).

[7] Collected at Day 1 and Week 2 (pre-dose with clinical labs), and Weeks 4, 8, 24 (post-dose at end of visit).[8] Collected pre-dose.

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

[10] Collection is ongoing.

[11] Also serves as the Early Termination Visit for patient withdrawal.

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

[13] The Safety Follow-Up Visit is intended for those patients in Cohort 1 and Cohort 2, and those patients in Cohort 3 who do not roll over into the Open-label Extension.

18. ATTACHMENTS

Attachment A: "CP543.2001 – TLF Shells" – Shells for Planned Tables, Figures, and Listings