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Document: Statistical Analysis Plan

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STATISTICAL ANALYSIS PLAN

STUDY TITLE:

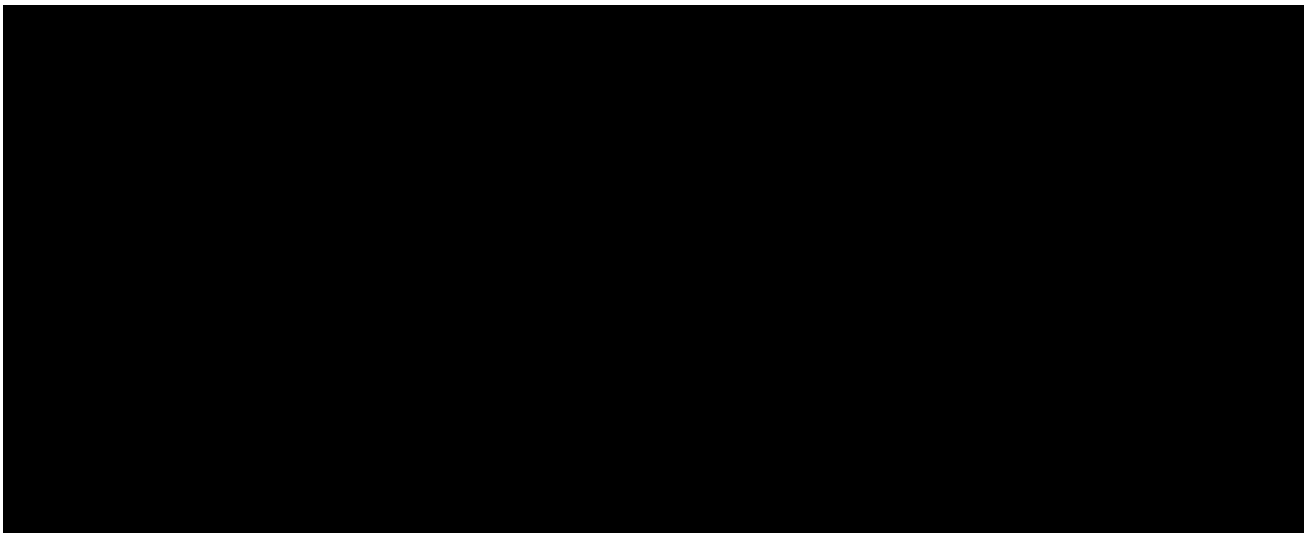
A MULTICENTER, OPEN-LABEL, EXTENSION STUDY TO ASSESS THE LONG-TERM SAFETY AND EFFICACY OF CTP-543 IN ADULT PATIENTS WITH MODERATE TO SEVERE ALOPECIA AREATA

PROTOCOL NUMBER:

CP543.5002

SPONSOR: Sun Pharmaceutical Industries, Inc.

ACKNOWLEDGEMENT AND SIGNATURE SHEET



VERSION HISTORY

SAP Version	Version Date	Change(s)	Rationale
1.0	2021-11-30	Not applicable	Original Version
2.0	2024-08-14	Updated for Protocol Amendment 5.2. Added Section 8.2.3.1 for SALT post-dose reduction analyses. Also added additional comments/questions in Section 9.2. Updated Section 8.2.3.1 for SALT post-dose reduction analyses. Added clarifications to Section 9.5. Also added questions throughout. Added SALT<50 category to baseline alopecia areata classification. Added clarification to Section 8.2.3.1. Removed duration of continuous study drug exposure (with gaps) paragraph and non-qualifying dose changes paragraph from Section 9.2. Updated Section 9.5 to align with ISS.	Protocol update and sponsor request

TABLE OF CONTENTS

LIST OF TABLES

1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
AE	Adverse event
ALT	Alanine aminotransferase
ATC	Anatomical-Therapeutic-Chemical
BID	Twice daily dosing
BMI	Body mass index
COVID-19	Coronavirus disease of 2019
CPK	Creatine phosphokinase
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
ECG	Electrocardiogram
eCRF	Electronic case report form
e.g.	Exempli gratia
i.e.	Id est
IQR	Interquartile Range
IWRS	Interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
OLE	Open-label extension
PCS	Potentially clinically significant
PML	Progressive multifocal leukoencephalopathy
QTcF	QT interval corrected for heart rate (Fridericia's method)
SALT	Severity of Alopecia Tool
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
TB	Tuberculosis
TEAE	Treatment-emergent adverse events
WHO	World Health Organization

2. PURPOSE OF THE ANALYSES

This statistical analysis plan (SAP) provides a detailed description of the strategy and statistical methodology to be used for analysis of data from the CP543.5002 current protocol version.

The purpose of the SAP is to describe the pre-specified statistical approaches to the analysis of study data prior to database lock. This analysis plan is meant to supplement the study protocol. If differences occur between analyses described in the SAP and the current protocol, those found in this SAP will assume primacy. Any deviations from this plan will be described in the Clinical Study Report (CSR).

3. PROTOCOL SUMMARY

The overall objectives of the study are to evaluate long-term safety of CTP-543 and to assess long-term effects of CTP-543 on treating hair loss in adult subjects with moderate to severe alopecia areata.

Subjects with alopecia areata who previously participated in a qualifying Phase 3 clinical trial (study CP543.3001 or study CP543.3002) with CTP-543 and who complete the 24-week Treatment Period on Study Medication (active or placebo), have the opportunity to enroll in this open-label extension (OLE) study in which they will receive daily treatment with CTP-543. Only subjects in the European Union will be included in this OLE study. At the Week 52 visit, patients will be assessed for treatment success (Responders) defined as patients having an absolute SALT score of ≤20 at Week 52. These Responders will be eligible to continue in the OLE extension for up to a maximum of an additional 52 weeks. Non-responders will complete the study at Week 52.

Safety will be evaluated by clinical laboratory measurements, adverse events (AEs) and physical exams. SARS-CoV-2 testing will be performed at all visits. Severity of Alopecia Tool (SALT) assessments will be performed periodically for efficacy, as described in the Schedule of Events Tables in Section 14.1.

Subjects will provide written informed consent prior to completing any eligibility procedures for the OLE study. Following the Day 1 visit, eligible subjects were enrolled and study drug was dispensed. Initially, subjects were assigned to receive daily treatment with CTP-543 at a dose of 8 mg BID or 12 mg BID according to the following criteria:

Previous Treatment in Qualifying Trial	**Treatment Assignment in OLE**
Placebo BID	8 mg BID or 12 mg BID
8 mg BID	8 mg BID
12 mg BID	12 mg BID

Placebo subjects were randomized via the study Interactive Web Response System (IWRS) in a 1:1 ratio to 8 mg BID or 12 mg BID. The randomization schedule was generated prior to subject enrollment from studies CP543.3001 and CP543.3002.

Following reports of thrombosis with 12 mg BID after long-term administration of CTP-543 and discussions with the US Food and Drug Administration (FDA), the 12 mg BID dose was immediately discontinued and communicated under an Urgent Safety Measure. Due to implementation of this urgent safety measure, all patients previously assigned to the 12 mg BID dose will be dose reduced to the 8 mg BID dose, should they elect to continue in the trial, for the duration of the trial up to a total of 52 weeks for non-responders or a maximum of 108 weeks for responders.

At the Week 52 visit, subjects will be assessed for treatment success (Responders) defined as subjects having an absolute SALT score of ≤20. These Responders will continue in the OLE extension for an additional 52 weeks. Non-responders will complete the study at Week 52. Additionally, subjects should be withdrawn from the study if in the Investigator's opinion

continued study participation is undesirable or the risk-benefit profile has become unfavorable. Additional withdrawal criteria can be found in Section 7.3 of the protocol.

Subject safety will be monitored throughout the study. During the first 12 weeks, hematology, serum chemistry, and lipids will be conducted under fasted conditions every 4 weeks. Following 12 weeks on treatment, subjects will return to the clinic every 8 weeks for safety assessments until the completion of the study or until withdrawal from the study. At each study visit, an assessment should also be undertaken for any changes in the physical exam, or symptoms such as pain, swelling or tenderness in leg(s), persistent breathing difficulties or shortness of breath, or severe headache, that are suggestive of an increased risk of thromboembolism. Patients must be withdrawn if they have a prior history of thrombotic event(s) or experience a thromboembolic event.

Serum pregnancy testing will be performed at all in-clinic visits. To minimize subject burden of additional clinic visits, urine pregnancy testing will be performed by the subject at home on Weeks 16, 24, 32, 40, 48 and 4-weeks post the final study visit. For responders, additional home pregnancy testing will be performed at Weeks 56, 64, 72, 80, 88, 96, 104 and 4-weeks post the final study visit. The test date and result will be documented in a subject diary and brought to each in-clinic study visit by the subject. 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. Less significant changes in laboratory values may warrant clinical intervention and the Investigator should use his/her best clinical judgement when considering a dose interruption, whether for singular or aggregate laboratory results outside of the normal range, or for other clinical signs, symptoms, or considerations that suggest dose interruption is in the best interest of the subject. Subjects who experience intolerable symptoms during treatment may discontinue the study at any time. Subjects may withdraw consent at any time.

Assessment of treatment response with SALT for efficacy will occur every 4 weeks for the first 12 weeks, then every 8 weeks thereafter until study completion.

4. 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. Departures from these general policies will be described, if applicable, in the appropriate sections of this SAP. When this situation occurs, the rules set forth in the specific section take precedence over the general policies.

All data displays (tables, listings, and figures) will have a header showing the sponsor company name, protocol number, and page number, as well as a footer indicating file name, run date/time, and display status (i.e. "DRAFT" or "FINAL"). Unless otherwise noted, summary tables and data listings will be summarized by treatment group CTP-543 8 mg BID, CTP-543 12 mg BID, and Total CTP-543. All data for analysis will be listed by-subject and by CTP-543 8 mg or 12 mg BID.

Categorical variables will be summarized using counts (n) and percentages (%) and will be presented in the form "n (xx.x)", with percentages rounded to one decimal place. If a count is 0, no percentage will be shown. If a percentage is 100%, 100.0 will be shown. To ensure completeness, summaries for categorical variables will include all categories, even if no subjects had a response in a particular category. Unless otherwise specified, the denominator for each percentage will be based on the number of subjects in the population being summarized (i.e. header N).

Continuous variables will be summarized using mean, standard deviation (SD), minimum, maximum, median, and number of subjects. The mean and median will be reported to an additional level of precision than the original observations, and the standard deviation 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 collected data. The precision for some original collected data and derived variables are longer than required for clinical interpretation (e.g., >15 decimals). In these situations, the number of decimal places will be determined by the table of precision that will be included with the table shells.

Summary tables and data listings:

- No preliminary rounding will be performed; rounding will only occur after analysis.
- Data from each subject will be separated by a blank line. Within a data listing, if a descriptive item appears line after line, only the first occurrence will be displayed (e.g., in Listing of Vital Signs, subject 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., AEs, lab results, vital sign values) will not be collapsed.
- Data listings will be sorted by CTP-543 dose, subject, and date and/or time of assessment, as applicable, unless otherwise specified.
- Whenever change from baseline or change to baseline is calculated, baseline will be defined and presented in two different ways, with a "pre-zero baseline" and a "CP543.5002 study baseline" as described in Section 6.2. Assessments for physical exams, clinical laboratory tests, 12-lead electrocardiograms (ECG), and SALT will be carried over from the preceding clinical trial database into this study database and be used as the subject's baseline assessment.

4.1. Treatment Group Presentation by Analysis

For analyses of disposition, demographics, baseline characteristics, concomitant medications, and medical history, subjects will be analyzed under their first actual treatment received (8 mg BID or 12 mg BID) in CP543.5002. The following treatment columns will be used:

- CTP-543 8 mg BID
- CTP-543 12 mg BID
- Total CTP-543

Summary tables for the laboratory evaluations, vital signs, and ECGs will include the following treatment columns referring to the starting dose in CP543.5002 and modified dose, if applicable (CP543.5002 initial treatment to CP543.5002 modified treatment):

- CTP-543 8 mg BID
- CTP-543 12 mg BID
- CTP-543 8 mg BID to CTP-543 12 mg BID
- CTP-543 12 mg BID to CTP-543 8 mg BID
- Total CTP-543

For analyses of laboratory evaluations, vital signs, and ECGs, the treatment groups CTP-543 8 mg BID and CTP-543 12 mg BID refer to subjects who initially received CTP-543 8 mg BID or CTP-543 12 mg BID, respectively, during CP543.5002 and received no qualifying dose changes. For clarity, for purposes of identifying treatment groups for these analyses, the initial dose will be the first dose that was dispensed for at least 2 visits; if no dose meets that criteria, then the initial dose is the first dose actually received in CP543.5002. A qualifying dose change is any dose change from the initial dose that spans more than one planned visit in CP543.5002 (i.e., the altered dose was dispensed at two or more consecutive visits). The treatment group CTP-543 8 mg BID to CTP-543 12 mg BID refers to subjects who received a qualifying dose change from 8 mg BID to 12 mg BID during CP543.5002. In the event of more than one qualifying dose change, only the first qualifying dose change will be considered. The treatment group CTP-543 12 mg BID to CTP-543 8 mg BID is defined similarly for qualifying dose changes from 12 mg BID to 8 mg BID.

If there are no subjects with dose adjustments meeting the criteria defined above, the CTP-543 8 mg BID to CTP-543 12 mg BID and CTP-543 12 mg BID to CTP-543 8 mg BID columns may be excluded from summaries which utilize the Safety population.

For analyses of efficacy, subjects will be classified in the same treatment groups as above for laboratory evaluations, vital signs and ECGs:

- CTP-543 8 mg BID

- CTP-543 12 mg BID
- CTP-543 8 mg BID to CTP-543 12 mg BID
- CTP-543 12 mg BID to CTP-543 8 mg BID
- Total CTP-543

Subjects will further be categorized into "analysis cohorts" based on their prior treatment in the qualifying study (CTP-543 8 mg BID, CTP-543 12 mg BID, or Placebo). Unless otherwise specified in this SAP, efficacy tables will be presented separately by analysis cohort and overall, with treatment groups as columns. If <5 subjects fall under a treatment group for a given analysis cohort, that column will be dropped. All subjects will still be included in the overall column.

Summary tables for exposure, and AEs will include the following treatment columns:

- CTP-543 8 mg BID
- CTP-543 12 mg BID
- Total CTP-543

For analyses of exposure, a subject with a qualifying dose change will be treated as if the subject changed dose from one study to another and will be included under more than one treatment column. For analyses of AEs, AEs will be considered treatment-emergent with respect to the most recent dose taken prior to the start of the adverse event. Subjects may be included in more than one treatment column due to dose changes.

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 23.1. Concomitant medications will be coded in World Health Organization (WHO) Drug Global Version 2020-SEP and Anatomical-Therapeutic-Chemical (ATC) classification and preferred term.

4.2. Assessment Time Windows

The visit schedule for all study assessments is provided in Appendix 14.1.

For scheduled visits, there will be no reassignment of the analysis visit based on date, and all scheduled visit data will appear in summary tables based on the nominal timepoint as recorded in the electronic case report form (eCRF).

Unscheduled visits and early termination visits will be reassigned based on the analysis windows in Table 2 and the schedule of events. Assessments may only be re-assigned to visits where they were to be collected per the schedule of events. Unless otherwise specified, early termination visit and unscheduled visit data will be included in tables and figures if no scheduled visit data is available for the nominal eCRF recorded visit. If more than one unscheduled assessment (early termination or unscheduled) is performed within an analysis window, the assessment performed closest to the target day will be used. If more than one assessment is equally close to the target day, the latest assessment in a window will be selected as the visit used in summaries. All visits will be included in by-subject data listings.

Table 2: Analysis Windows for Unscheduled and Early Termination Visits

	Safety Analyses			Efficacy Analyses		
Nominal Visit	**Lower**	**Target**	**Upper**	**Lower**	**Target**	**Upper**
Visit 1-Baseline	1	1	1	1	1	1
Visit 2-Week 4	2	29	43	22	29	36
Visit 3-Week 8	44	57	71	50	57	64
Visit 4-Week 12	72	85	113	78	85	92
Visit 5-Week 20	114	141	169	127	141	155
Visit 6-Week 28	170	197	225	183	197	211
Visit 7-Week 36	226	253	281	239	253	267
Visit 8-Week 44	282	309	337	295	309	323
Visit 9-Week 52	338	365	393	351	365	379 [1]
Visit 10-Week 60	394	421	449	407	421	435
Visit 11-Week 68	450	477	505	463	477	491
Visit 12-Week 76	506	533	561	519	533	547
Visit 13-Week 84	562	589	617	575	589	603
Visit 14-Week 92	618	645	673	631	645	659
Visit 15-Week 100	674	701	729	687	701	715
Visit 16-Week 108	730	757	785	743	757	760

[1] For efficacy analyses, the upper bound at Week 52 will be 368 for non-responders and any subjects who respond but discontinue the study at the Week 52 visit, and 379 for responders who continue the study past Week 52. Subjects will be classified as responders or non-responders at Week 52 based on their Week 52 SALT assessment.

5. ANALYSIS SAMPLES

The All Enrolled Population will be defined as all subjects who signed informed consent.

The Safety Population will be defined as all subjects who received at least 1 dose of CTP-543 in this study.

The Efficacy Population will be defined as all subjects who received at least 1 dose of CTP-543 in this study and have at least 1 post-baseline SALT assessment in this study.

Subjects will be analyzed under treatment groups as specified in Section 4.1.

6. STUDY SUBJECTS

6.1. Disposition of Subjects

The following disposition information will be summarized (percentages based on the number enrolled, with the exception of the reasons for discontinuation):

- The number of subjects enrolled (defined as the number of subjects who have signed informed consent).
- The number and percentage of subjects enrolled from each qualifying study.
- The number and percentage of subjects within the Safety and Efficacy Populations.
- The number and percentage of subjects who completed the study, defined as subjects with "Complete" noted for the question "Subject Status" on the *Study Discontinuation/Completion* electronic case report form (eCRF) page.
- The number and percentage of subjects who prematurely discontinued the study, and the frequency and percentage of each discontinuation reason. The denominator for the percentage of each discontinuation reason will be the Safety population.
- The time to study discontinuation in weeks (Safety Population).
- The number and percentage of subjects who prematurely discontinued the study due to the COVID-19 pandemic and the frequency and percentage of each discontinuation reason. The denominator for percentage of subjects who prematurely discontinued the study due to COVID-19 will be the number of subjects who discontinued the study. The denominator for the percentage of each COVID-19 discontinuation reason will be the number of subjects who discontinued the study due to the COVID-19 pandemic.

Disposition will also be presented in by-subject data listings. Patient data listings will list, age, sex, race, date of informed consent, date of first/last treatment in the 5002 study, date of end of study/early study termination, reasons for study discontinuation, and whether or not the reason was related to the COVID-19 pandemic, along with the specific reason. Should a higher than expected rate of treatment termination be observed in the OLE study relative to the qualifying studies, exploratory figures and analyses may be performed. A listing of all visits for each subject will be presented in a separate listing.

6.2. Demographic and Other Baseline Characteristics

Demographic characteristics (i.e. sex, ethnic origin, race, and age) will be collected at the Day 1 visit, which will occur on the same day as their last visit in the preceding clinical trial, and detailed on the eCRF. Age will be reported as collected in the eCRF for the CP543.5002 study. Baseline body mass index (BMI) will be calculated based on data from the preceding clinical trial, using the weight from the last visit and the height. Demographic characteristics will be summarized using descriptive statistics for all subjects in the Enrolled Population, and separately for all subjects in the Safety Population.

Baseline characteristics will be summarized for both the "pre-zero" baseline and the CP543.5002 study baseline using descriptive statistics for the Safety Population by treatment group and overall and will include the following:

- baseline total SALT score
- baseline alopecia areata classification: scalp hair loss (SALT <50); partial scalp hair loss (SALT ≥ 50 and < 95); complete or near-complete scalp hair loss (SALT ≥ 95)
- whether the subject has experienced any past and/or concomitant diseases, conditions, exposures to serious infections, or past surgeries (as collected in CP543.3001 and CP543.3002)

The "pre-zero" baseline is defined as the last observation obtained prior to first dose of active drug in either CP543.5002 or the qualifying study. "CP543.5002 study baseline" is defined as the last observation prior to first dose in CP543.5002.

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

All demographics characteristics will be listed within a by-subject data listing for all enrolled subjects.

6.3. Concomitant Medications

Concomitant medications will be recorded in the eCRF from Day 1 through the Final Study Visit or the Early Termination Visit, whichever occurs first. All medications, including over the counter therapies, taken at Day 1 through the last study visit will be documented in the eCRF. Additionally, any medications given in the treatment of an adverse event (AE) will be recorded as a Concomitant Medication in the eCRF. All medications will be coded using the WHO Drug Dictionary Global Version 2020.09.

Medications are classified as concomitant if used on or after the first dose date of study treatment in CP543.5002. Note: All ongoing concomitant medications will be copied over by the study sites from CP543.3001 and CP543.3002 for subjects enrolled in CP543.5002.

Concomitant medications will be summarized with counts and percentages separately for the Safety Population by treatment group and overall, WHO Drug ATC classification level 2 and preferred term. For each summary, a subject will be counted only once for each medication.

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 9.3 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 first dose of study treatment in CP543.5002 unless the stop date is prior to the date of first dose of study treatment in CP543.5002, 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.

Concomitant medications will also be listed by-subject. Medications related to COVID-19 will be flagged.

6.4. Medical History

Medical history and AE data from CP543.3001 and CP543.3002 may be recorded on the medical history eCRF CP543.5002. Newly discovered medical history and worsening AEs prior to first dose will also be collected in the eCRF for CP543.5002. Medical history will be coded with the MedDRA terminology Version 23.1 and summarized as counts and percentages for the Safety Population by treatment group and overall, system organ class, and preferred term. A subject will be counted only once for each condition. Conditions will be presented in by-subject listings, including the verbatim investigator description of the relevant medical condition, the coded terms (system organ class, preferred term), start date, end date, and whether or not the condition is ongoing.

7. STUDY OPERATIONS

7.1. Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. Protocol deviations will be recorded on the source documents and with an explanation for the deviation. All protocol deviations will also be recorded as specified in the monitoring plan.

Protocol deviations will be identified by site staff, through medical reviews, and by clinical research associates during site monitoring. 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 as counts and percentages by treatment group and overall, deviation severity, and category for all enrolled subjects. Subjects will be counted once for each category within each level of severity. Deviations will also be presented by subject in a data listing for all enrolled subjects. Any prohibited medications will be identified as a protocol deviation and will be listed.

7.2. Randomization, Dose Assignment and Dose Changes

Placebo subjects from CP543.3001 and CP543.3002 are expected to enroll in the CP543.5002 extension study. These subjects will be randomized in a 1:1 ratio to each of the two study arms:

- CTP-543 12 mg BID
- CTP-543 8 mg BID

Subjects enrolling from CP543.3001 and CP543.3002 who were previously randomized to receive active treatment are initially assigned the same dose of CTP-543 in CP543.5002.

Although CP543.5002 is an open-label study and the assigned treatment for subjects will be known by both study personnel and subjects at the time of treatment, the strata associated with individual subjects corresponds to the subjects' treatment assignments from the blinded qualifying studies. As such, the assigned treatment in CP543.5002 will not be blinded to study personnel or participants, but the stratification values (previous assigned treatment in the qualifying study) will remain blinded to subjects for the duration of the study. Tablets and packaging of each CTP-543 dosage will be identical in appearance, but the labels will specify 8 mg or 12 mg.

Dose changes (8 mg BID to 12 mg BID or 12 mg BID to 8 mg BID) are permitted during the study at the investigator's discretion. See Section 4 for how dose changes are addressed in the analyses.

The number of enrolled subjects by country and site will be summarized. A by-subject listing of randomized treatment group and randomization number will be presented for the placebo subjects from the qualifying studies.

7.3. Measures of Treatment Compliance

Subjects will strive for 100% compliance with the daily dosing schedule. Treatment compliance will be summarized overall as percent of planned dose received, regardless of the dosing regimen or dose changes. Percent of planned dose received will be calculated for the entire treatment period as follows:

100*(Tablets Dispensed-Tablets Returned)/(Tablets Expected)

Tablets Expected will be defined as the time on study multiplied by the expected number of pills taken daily (x2 for the 12 mg BID group; x2 for the 8 mg BID group), where time on study is defined as treatment end date – treatment start date + 1. Dose interruptions will be ignored in this calculation. Time on treatment will be defined as the number of weeks in which study drug was at least partially administered. Dose interruptions are excluded from the time on treatment calculation. Time on study (weeks), time on treatment (weeks) and percent of planned dose received will be summarized by treatment group. Derived subject compliance, derived subject compliance category (80% or higher versus less than 80%), and dosing exceptions will be listed in by-subject data listings.

If the last dose of study drug in CP543.3001 or CP543.3002 occurred on the same day as the first dose of study drug in CP543.5002, it will be assumed that only 1 dose of study drug is expected in CP543.5002 on the treatment start date. Otherwise, if the last dose of study drug in CP543.3001 or CP543.3002 occurred prior to the day of the first dose of study drug in CP543.5002, it will be assumed that 2 doses of study drug are expected in CP543.5002 on the treatment start date. It will be assumed that 2 doses of study drug will be administered on the date of the last dose of study drug unless the last dose occurs on the same day as their final study visit, where drug was not dispensed, in which case it will be assumed that only 1 dose of study drug will be administered on that date.

8. EFFICACY ENDPOINT EVALUATION

8.1. Overview of Efficacy Analysis Methods

8.1.1. Multicenter Studies

Subjects will be enrolled at approximately 50 sites; site identifiers will be included on by-subject listings.

8.1.2. Timing of Analyses

An interim analysis requiring a data freeze in late 2022 will be performed for a New Drug Application (NDA) submission as described in Section 11.

All final, planned analyses will be performed after the last subject has completed all study assessments, all relevant study data have been processed and integrated into the analysis database, and the database has been locked.

Any post hoc, exploratory analyses completed to support planned study analysis, which were not identified in this SAP, will be documented and reported in appendices to the CSR. Any results from these unplanned analyses (post hoc) will also be clearly identified in the text of the CSR.

8.2. Efficacy Endpoint

The efficacy endpoint is the relative change in SALT score over time from baseline. Both the change from the "pre-zero" baseline and the change from the CP543.5002 study baseline will be assessed (see Section 6.2).

8.2.1. Computation of the Efficacy Endpoint

The SALT assessment is a measure of hair loss 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. The total score is calculated as [(left quadrant raw score × 0.18) + (right quadrant raw score × 0.18) + (top quadrant raw score × 0.40) + (back quadrant raw score × 0.24)]. An example of the SALT assessment can be found in Appendix 16.1 of the study protocol.

Absolute change in SALT score is derived as the follow-up SALT score minus the baseline SALT score. Relative change in SALT score is derived as 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). Absolute change and relative change from baseline will be computed for both the "pre-zero" baseline and the CP543.5002 study baseline.

Absolute change in SALT score should be rounded to the nearest whole number following its derivation. Relative change in SALT score should be rounded to one decimal place following its derivation.

No imputation will be conducted for missing SALT scores.

8.2.2. Primary Analysis of the Efficacy Endpoint

All efficacy summaries will be descriptive with no statistical hypothesis testing and based on the Efficacy Population.

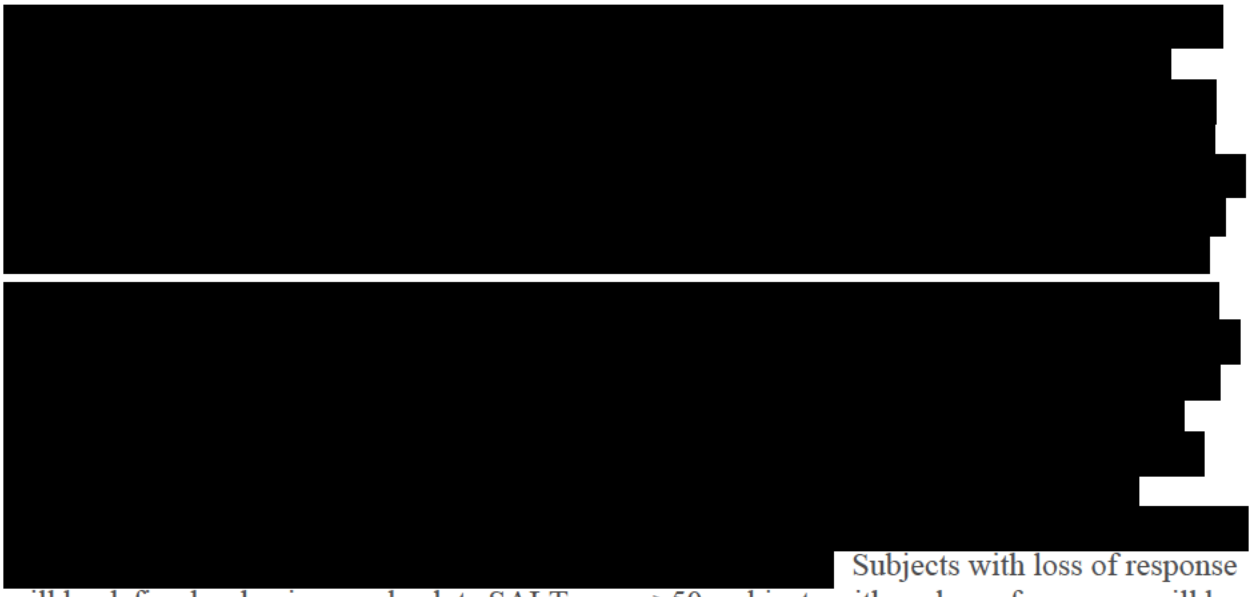
The observed, absolute change, and relative change from baseline in SALT score will be reported by treatment group and overall, as specified in Section 4. Change from baseline will be presented separately for the "pre-zero" baseline and the CP543.5002 study baseline. The results may also be displayed graphically. By-subject listings for SALT will also be presented.

8.2.3. Supportive Analyses of the Efficacy Endpoint

The number and percentage of subjects with an absolute SALT score ≤ 20 will be reported by study visit and treatment group.

A shift table comparing treatment response (responder, non-responder) at baseline to treatment response (responder, non-responder) post-baseline will be produced by visit and treatment group, separately for the "pre-zero" baseline and the CP543.5002 study baseline. Responders will be defined as having an absolute SALT score ≤ 20; non-responders will be defined as having an absolute SALT score > 20.

8.2.3.1. Analysis of the Efficacy Endpoint Post-Dose Reduction



Subjects with loss of response will be defined as having an absolute SALT score >50; subjects with no loss of response will be defined as having an absolute SALT score <=50. Responders at pre-dose reduction baseline will be defined as having an absolute SALT score ≤ 20 at pre-dose reduction baseline; non-responders will be defined as having an absolute SALT score > 20. A line graph of the absolute change from pre-dose reduction baseline SALT score vs. visits since dose reduction will also be produced for subjects who had a dose reduction from CTP-543 12 mg to 8 mg on or after 28 Apr 2023 due to the urgent safety measures.

8.3. Other Efficacy Endpoints

No other efficacy endpoints are specified.

8.4. Examination of Subgroups

No subgroup analyses are planned.

9. SAFETY EVALUATION

9.1. Overview of Safety Analysis Methods

All safety summaries will be descriptive with no statistical hypothesis testing and based on the Safety Population. Safety assessments will be summarized by treatment group and overall, as specified in Section 4. All safety endpoints will be listed in by-subject data listings.

9.2. Extent of Exposure

Study drug exposure will be summarized for the CTP-543 8 mg BID and CTP-543 12 mg BID treatment groups and overall. Duration of exposure in weeks will be calculated as (date of last dose of study drug minus the date of first dose of study drug + 1 day)/7. Study drug exposure will be summarized categorically by duration of treatment in weeks (≥4, ≥8, ≥12, ≥16, ≥20, ≥24, ≥28, ≥36, ≥44, ≥52, ≥60, ≥68, ≥76, ≥84, ≥92, ≥100, and ≥108) and will include a summary of subjects receiving ≥1 dose. Dose interruptions, missed doses, and partial doses will be ignored. Subjects who are lost to follow-up and were on treatment as of their last visit will be counted as receiving their last dose on the date of the last visit completed. Duration of study drug exposure in weeks as a continuous variable will also be summarized.

All summaries of exposure will be limited to exposure in CP543.5002.

Duration of cumulative study drug exposure in weeks for subjects who entered the OLE will be calculated as (OLE treatment end date – OLE treatment start date – the number of days of missed dose + 1)/7. Duration of cumulative study drug exposure will be summarized and calculated in the same manner as study drug exposure, except that any period of dose interruptions or missed doses will be subtracted. If the reason not dosed is “dose interruption", it will be counted as a missed dose regardless of the actual number of tablets taken. If the reason not dosed is “missed dose” or “partial dose” and no tablets were taken, it will be treated as a missed dose; if the reason not dosed is “missed dose” but 1 tablet was taken, it will be treated as a partial dose.

Duration of exposure up to a qualifying dose change in CP543.5002 will be summarized as a categorical measure based on treatment sequence between the qualifying study and initial dosing in CP543.5002, as follows: Placebo to 8 mg BID, Placebo to 12 mg BID, 8 mg BID to 8 mg BID, and 12 mg BID to 12 mg BID. Duration of exposure up to a qualifying dose change for subjects previously on placebo will be separately tabulated from that of subjects previously on active drug in the qualifying study. For purposes of these tabulations, if a subject experiences a qualifying dose change, duration of exposure will be counted up to the qualifying dose change. Dose interruptions, missed doses, and partial doses will be ignored.

Duration of exposure after a qualifying dose change in the OLE study will be summarized as a categorical measure based on treatment sequence for subjects with any qualifying dose change in CP543.5002. The following treatment sequences will be used (based on treatment sequence within CP543.5002): 12 mg BID to 8 mg BID and 8 mg BID to 12 mg BID. For purposes of this tabulation, the relevant duration of exposure will be the last dose of study drug in CP543.5002 minus the date of the first qualifying dose change + 1 day. Therefore, if a subject experiences

more than one qualifying dose change, the subject will be classified according to the first qualifying dose change. Dose interruptions, missed doses, and partial doses will be ignored.

9.3. Adverse Events

An AE is any untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values, regardless of etiology. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the eCRF rather than the individual signs or symptoms of the diagnosis or syndrome. A worsening of the condition under study, alopecia areata, will not be reported as an AE.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of the following parameters: the subject's clinical symptoms, laboratory, physical examination findings, or findings from other tests and/or procedures.

AEs will be coded using MedDRA version 23.1 and summarized by treatment group, system organ class, and preferred term.

An AE with a start date before the date of the first dose of study drug in CP543.5002 (i.e., generally Day 1), will be considered a pre-treatment AE. TEAEs will be defined as any AE that occurs on or after the day of administration of the first dose of study drug. Non-serious AEs are collected until completion of the study or the Early Termination Visit. Serious adverse events are reported through 30 days beyond the last dose of study drug. The number and percentage of subjects who report TEAEs will be summarized by treatment group, system organ class, and preferred term.

If a subject changes dose during the study, AEs will be considered treatment-emergent with respect to the most recent dose taken prior the start of the AE and will be tabulated under that treatment column. This may result in some subjects being included in more than one treatment column.

TEAEs 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 visit date for the subject, in which case the end day will be set to that of the subject's last visit date.
- For a missing end day and month where the year is present, the end day and month will be set to the subject's last visit date, unless the year of the subject's last visit 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 start date, the adverse event will be deemed treatment emergent unless the end date is before the first date of administration or, in the case of a partial end date, it is clear from the available date parts that the end date is prior to the date of administration.

Subjects 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 subject reports multiple preferred terms for a system organ class, the subject will be counted only once for that system organ class.

An overall TEAE summary table by treatment group and overall with the total number of TEAEs and the number and percentage of subjects with at least one of the following will be presented: TEAE, serious TEAE, serious related TEAE, TEAE leading to study drug interruption, TEAE leading to dose reduction, TEAE leading to study discontinuation, TEAE leading to death, mild TEAE (CTCAE grade 1), moderate TEAE (CTCAE grade 2), severe TEAE (CTCAE grade 3 or above), mild related TEAE (CTCAE grade 1), moderate related TEAE (CTCAE grade 2), severe related TEAE (CTCAE grade 3 or above), related TEAE, possibly related TEAE, probably related TEAE, definitely related TEAE, not related TEAE, unlikely related TEAE, related serious TEAE, possibly related serious TEAE, probably related serious TEAE, definitely related serious TEAE, not related serious TEAE, unlikely related serious TEAE. “Related” TEAEs will be defined as TEAEs which the study investigator has categorized as possibly, probably, or definitely related to study drug. “Not related” TEAEs will be defined as TEAEs which the study investigator has categorized as unlikely or not related to study drug. “Related” serious TEAEs and “not related” serious TEAEs will be defined analogously for serious TEAEs. For each severity category, the subject will be counted once at the subject’s maximum level of severity. For each relatedness category, subjects will be counted once at the subject's maximum level of relatedness.

The number and percentage of subjects who experience TEAEs and the total number of TEAEs will be summarized by treatment group and overall for the following:

- By system organ class and preferred term
- By severity/intensity (mild [CTCAE grade 1], moderate [CTCAE grade 2], or severe [CTCAE grade 3 or above]), system organ class, and preferred term
- By maximum severity/intensity (mild [CTCAE grade 1], moderate [CTCAE grade 2], or severe [CTCAE grade 3 or above]), system organ class, and preferred term
- By relationship to study drug, system organ class, and preferred term

- By maximum relationship to study drug, system organ class, and preferred term
- Serious TEAEs by system organ class and preferred term
- Serious TEAEs by relationship to study drug, system organ class, and preferred term
- Serious TEAEs by maximum relationship to study drug, system organ class, and preferred term
- TEAEs resulting in study discontinuation by system organ class and preferred term
- TEAEs that result in study drug dose interruption by system organ class and preferred term
- TEAEs that result in study drug dose reduction by system organ class and preferred term

By-subject listings will include all AEs. TEAEs will be flagged.

9.4. Deaths, Serious Adverse Events, and Other Significant Adverse Events

A serious adverse event is an AE that fulfills the following criteria:

- Is fatal (results in death);
- Is life-threatening (Note: the term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that could hypothetically have caused death had it been more severe);
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect; or
- Constitutes an important medical event that may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed above.

Serious adverse events will be summarized according to Section 9.3.

By-subject listings will be provided for any deaths, serious adverse events, and AEs leading to discontinuation of treatment. TEAEs that result in dose interruption or reduction will also be identified.

9.5. Clinical Laboratory Evaluation

Clinical laboratory samples should be collected at the beginning of each clinic visit and just prior to a dose on all Study Visit Days and will be processed by a central laboratory. In the event a subject is unable to attend an in-clinic visit due to COVID-19, clinical laboratory blood draws may be performed by a Home Health Care agency or a local laboratory.

Clinical laboratory variables will be presented in 3 ways. First, the mean change from baseline to each scheduled assessment will be summarized descriptively by dosing regimen for each

clinical laboratory variable specified in this protocol. Change from baseline will be summarized separately for the "pre-zero" baseline and the CP543.5002 study baseline (see Section 6.2). Values will only be included if the subject had both a baseline and post-baseline value for that parameter.

Second, treatment-emergent potentially clinically significant (PCS) laboratory values will be identified. Potentially clinically significant values are defined as those that meet Grade 3 or Grade 4 toxicity criteria from the common terminology criteria for adverse events (CTCAE) criteria (or Grade 2 or higher for platelets). Laboratory values will be graded using CTCAE version 5.0, for those values included. CTCAE grades will be based solely on numeric results and without regard to other symptoms based on clinical judgment. For laboratory parameters whose CTCAE grading is independent of baseline criteria, treatment-emergent PCS laboratory values are those in which the CP543.5002 study baseline value is not PCS and the post-baseline value is PCS. For laboratory parameters whose CTCAE grading is dependent upon baseline criteria, any post-baseline grading of Grade 3 or Grade 4 (or 2 or higher in the case of platelets) will be considered treatment-emergent, and values will only be included if the subject had both a baseline and post-baseline value for that parameter. The number and percentage of subjects with treatment-emergent PCS laboratory values will be summarized by treatment group and overall for each clinical laboratory variable, separately for the "pre-dose" baseline and the CP543.5002 study baseline. Results will be presented by post-baseline visit and overall; for this analysis, the visit with the highest CTCAE grade value within an analysis window will be selected.

Third, laboratory values which are TEAEs that result in dose interruption will be recorded as TEAEs. These analyses are described in Section 9.3.

These analyses will be performed for serum chemistry results, hematology results, and lipid results (where lipid tests include total cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides). Laboratory results will also be listed. Central laboratory reference ranges for each clinical laboratory parameter will also be summarized in a data listing.

Pregnancy test results will be listed only.

Laboratory results for subjects who experience the hematologic thresholds in Table 3 will also be listed.

Table 3: Selected Hematologic Thresholds for Dose Interruption

Neutrophil Count	$< 0.5 \times 10^9$/L
	$\geq 0.5 \times 10^9$/L and $< 1 \times 10^9$/L
Hemoglobin Level	Female: < 10 g/dL
	Male: < 11.5 g/dL
Platelet Count	$< 75 \times 10^9$/L
	$> 750 \times 10^9$/L

The mean and standard error for key hematology parameters (Alanine aminotransferase [ALT], neutrophils, platelets, and hemoglobin) and other laboratory parameters (lymphocyte count, reticulocyte count, cholesterol, HDL, LDL, creatinine, creatine kinase, aspartate aminotransferase [AST], alkaline phosphatase, amylase, lipase, and triglycerides) may be summarized graphically by visit and treatment group.

Box Plots

Box plots for hemoglobin, platelets, neutrophils, lipase, triglycerides, and CPK may be produced visit and treatment group as a means of identifying outliers. The median will be presented as a line within the box, with the 25th and 75th percentiles defining the edges of the box. The mean will be plotted as a circle. The interquartile range (IQR) will be defined as the difference between the 25th and 75th percentile. The whiskers will extend 1.5 times the IQR from the top and bottom of the box. If the data do not extend to the end of the whiskers, then the whiskers will extend to the minimum and maximum data values. If there are values which fall above or below the end of the whiskers, they will be plotted as dots.

Potential Hy's Law

The number and percentages of subjects with at least 1 post-baseline value of ALP, ALT, AST and/or total bilirubin will be tabulated, based on the cut-offs provided in Table 4 below.

Table 4: Elevated Liver Chemistry Criteria

Clinical Laboratory Parameter	Category
ALT	≥3 × ULN; ≥5 × ULN
AST	≥3 × ULN; ≥5 × ULN
ALT or AST	≥3 × ULN; ≥5 × ULN
ALP	≥1.5 × ULN; ≥2 × ULN
Total bilirubin	≥1.5 × ULN; ≥2 × ULN; ≥3 × ULN
Concurrent total bilirubin elevation with ALT elevation [1]	(ALT ≥3 × ULN) and (total bilirubin ≥2 × ULN)
Concurrent total bilirubin elevation with ALT or AST elevation [1]	(ALT or AST ≥3 × ULN) and (total bilirubin ≥2 × ULN)
Concurrent total bilirubin elevation with ALT or AST elevation and ALP <2 × ULN [1] ("potential Hy's law cases")	(ALT or AST ≥ 3 × ULN) and ALP <2 × ULN and (total bilirubin ≥2 × ULN)

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal
[1] Concurrent means on the same date.

Potential Hy's law cases (based on the recommendation in "Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation") will be identified as subjects with ALT or AST

≥3 x upper limit of normal (ULN) , ALP < 2 x ULN, and total bilirubin ≥2 x ULN on the same date, as noted above.

To assess cases potentially meeting requirements for Hy's Law, an evaluation of drug-induced serious hepatotoxicity (eDISH) plots of bilirubin against peak ALT will be generated by treatment group, as described by Watkins et al (2008). This plot will be reproduced for peak AST vs. peak total bilirubin, as well as for the greater of peak AST and peak ALT vs. peak total bilirubin.

Potential drug-induced liver injuries will also be presented in a listing, including all relevant laboratory measurements displayed by visit. One listing will show all subjects with ALT or AST ≥3 x ULN and total bilirubin ≥ 2 x ULN at the same visit. A second listing will show all subjects with ALT or AST ≥5 x ULN.

Graphical representations of the liver function tests (ALP, ALT, AST and total bilirubin) over time, including drug exposure times, will be produced for subjects with possible drug induced liver injury.

Additional exploratory analyses of laboratory evaluations may be conducted based on data reviews.

9.6. Vital Signs, Physical Findings, and Other Observations Related to Safety

9.6.1. Vital Signs

Vital signs will include blood pressure, pulse rate, respiratory rate, and temperature.

Height will only be measured at the Screening Visit for CP543.3001 and CP543.3002. Weight and vital signs will be measured according to the Schedule of Assessments (Appendix 14.1) during each physical examination. Weight and height will be used to calculate the subject's baseline BMI.

The mean and mean change from baseline to each scheduled assessment will be summarized descriptively by treatment group and overall for each vital sign variable specified in the protocol. Change from baseline will be summarized separately for the "pre-zero" baseline and the CP543.5002 study baseline (see Section 6.2).

A listing of vital signs by subject will also be provided.

Vital signs (systolic blood pressure, diastolic blood pressure, and weight) will be assigned the grades (severities) based on CTCAE criteria. Values will be graded using CTCAE version 5.0, for those values and directions included. For systolic blood pressure and diastolic blood pressure, shift tables using CTCAE grades to compare baseline to the worst post-baseline CTCAE grade by vital sign parameters and treatment group will be produced for applicable parameters, separately for each baseline type. For weight, the frequency of worst CTCAE grades will be produced, separately for each baseline type. Values will only be included if the subject had both a baseline and post-baseline value for that parameter.

Clinically notable vital signs will be identified based on the criteria below for heart rate. The number and percentage of subjects with at least 1 treatment-emergent notable value will be tabulated by treatment group, using the worst post-baseline value in either direction.

Vital Sign Parameter	Value
Heart rate	>100 bpm with increase from baseline* of ≥20 bpm <60 bpm with decrease from baseline* of ≥15 bpm

bpm = beats per minute

*CP543.5002 study baseline

The mean and standard error for weight may be summarized graphically, visit and treatment group.

9.6.2. Physical Examinations

A complete physical examination will consist of vital signs, weight, an examination of all major organ systems, with an emphasis on assessing for active signs and symptoms of infection, exposure to tuberculosis, and skin examinations for non-melanoma skin cancers. Evaluation for progressive multifocal leukoencephalopathy (PML) symptoms such as facial droop, general weakness, clumsiness, trouble speaking, personality changes, memory problems, and vision changes will be assessed.

Brief physical examinations will focus on an evaluation of safety and include vital signs, weight, abdominal palpation, and head, eyes, ears, nose and throat assessment, assessing for active signs and symptoms of infection, exposure to tuberculosis (TB), inquiry on changes to skin lesions and/or moles indicative of skin cancers, and an evaluation for PML as noted above. Physical examinations will be performed according the Schedule of Events (Appendix 14.1). A listing of the date and type of physical examinations performed will be provided. Deteriorations from baseline on physical examination should be reported as AEs and summarized as such.

9.6.3. Other Safety Measures

9.6.3.1. 12-Lead Electrocardiogram

Twelve-lead ECGs will be performed at Week 52, Week 108 (for responders only), and/or the Early Termination Visit. Individual parameters including heart rate, PR, QT, QTcF (Frederica's correction), QRS, RR intervals will be collected. If a subject is unable to attend an in-person clinic visit due to COVID-19, a 12-lead ECG may not be performed. Missed assessments will be recorded in the eCRF as due to COVID-19.

The mean and mean change from baseline to each scheduled assessment will be summarized descriptively by treatment group and overall for each 12-lead ECG variable specified in the protocol. Change from baseline will be summarized separately for the "pre-zero" baseline and the CP543.5002 study baseline (see Section 6.2); only subjects who have both a baseline and at least 1 post-baseline assessment will be included. Clinically significant ECG results will be identified based on the criteria in Table 5, and will be summarized descriptively by treatment group and overall, separately for each baseline definition. Clinically significant ECG results will

be identified based on the criteria below. For each ECG parameter, the number and percentage of subjects with at least 1 treatment-emergent notable value will be tabulated overall, using the worst post-baseline value. The number and percentage will be summarized separately for the "pre-zero" baseline and the CP543.5002 study baseline (see Section 6.2). To be defined as treatment-emergent, the criteria should be met after first dose of study drug (as applicable to each baseline definition) and not met at baseline. Clinically significant ECG results for subjects who meet the criteria after first dose of study drug and are missing their baseline value will conservatively be counted as treatment-emergent.

Table 5: Clinically Significant ECG Criteria

ECG Parameter	Criteria
QTcF	Post-baseline >450 msec Post-baseline >480 msec Post-baseline ≥500 msec Post-baseline >450 msec and ≤480 msec Post-baseline >480 msec and ≤500 msec Post-baseline increase >30 msec Post-baseline increase >60 msec Post-baseline increase >30 msec resulting in a post-baseline >450 msec Post-baseline increase >30 msec resulting in a post-baseline >480 msec Post-baseline increase >30 msec resulting in a post-baseline ≥500 msec
QRS	Post-baseline ≥120 msec and ≥20% increase from baseline
PR	Post-baseline ≥220 msec and ≥20% increase from baseline
Heart rate	Post-baseline ≤50 bpm and ≥20% decrease from baseline

bpm = beats per minute; ECG = electrocardiogram; msec = millisecond; QTcF = QT corrected for heart rate using Fridericia's method

A listing of electrocardiogram results will be provided. A listing of abnormal ECG findings will also be provided.

10. OTHER ANALYSES

In light of the COVID-19 pandemic, listings of the missed visits or assessments specifically due to COVID-19 will be provided.

11. INTERIM ANALYSES AND DATA MONITORING

An interim analysis will be performed for an integrated summary of safety (ISS) and integrated summary of efficacy (ISE) to evaluate the safety and efficacy across the study program for a NDA submission. These analyses are described in separate ISS and ISE SAPs.

12. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

The following changes to the protocol were made:

Protocol Section 11.2.3.2 states “The number and percentage of subjects with Abnormal, clinically significant laboratory values (per Investigator judgement) and the number and percentage of subjects with treatment-emergent PCS laboratory values will be summarized by dosing regimen for each clinical laboratory variable.” The SAP removes this analysis because it is not feasible given the CRF design.

13. REFERENCES

Not applicable.

14. APPENDIX

14.1. Schedule of Events

All Enrolled Subjects (Visit 1-9)

Event	Baseline[1,2] (Visit 1)	Visit 2 (Week 4)[3] Visit 3 (Week 8) Visit 4 (Week 12) Visit 5 (Week 20)[4] Visit 6 (Week 28) Visit 7 (Week 36) Visit 8 (Week 44)	Home Urine Pregnancy Testing Week 16 Week 24 Week 32 Week 40 Week 48 4-Week Post Final Study visit	Visit 9 (Week 52) Early Termination Visit
Informed consent	X			
Eligibility assessment	X			
Complete physical examination				X
Brief physical examination		X		
Pregnancy test[5]		X	X[6]	X
Clinical laboratory testing[7,8]		X		X
12-lead electrocardiogram				X
Severity of Alopecia Tool assessment		X		X[9]
Dispense study drug	X	X		X[10]
Adverse events	Continuous			
Concomitant medications	Continuous			

[1]All subsequent visits should be based on the date of the Day 1 visit.
[2]As subjects will be rolling into this study from a previous qualifying CTP-543 clinical trial (refer to Protocol Section 6.1), and baseline of this study will occur on the same day as their last visit in the preceding clinical trial. Assessments for physical exams, clinical laboratory tests, 12-lead ECGs, and SALT will not be repeated. These assessments will be carried over from the preceding clinical trial database into this study database and count as their baseline assessment.
[3]Visit window is ± 2 days for Visits 2-4.
[4]Visit window is ± 3 days for Visits 5-9.
[5]Pregnancy testing will be performed every 4-weeks throughout study enrollment. As in-clinic visits are performed bi-monthly following Visit 4 (Week 12), subjects will perform in-home urine pregnancy tests at Week 16, Week 24, Week 32, Week 40, Week 48, and 4-weeks post the final study visit. The test date and result will be documented.
[6]In-home pregnancy testing window is ± 3 days.
[7]Collected pre-dose, when possible.
[8]Includes fasted hematology, serum chemistry, SARS-CoV-2 testing, and lipids performed by the central lab.
[9]At the Week 52 visit, patients will be assessed via SALT for treatment success (Responder) defined as having an absolute SALT score of ≤20 at Week 52. These responders will be eligible to continue in the OLE extension for up to a maximum of one additional year.
[10]Study drug dispensation will occur at Visit 9 (Week 52) for RESPONDERS ONLY (defined as having a SALT score ≤20).

Schedule of Events – Responders (Visit 10-16)

Event	Visit 10 (Week 60)[1] Visit 11 (Week 68) Visit 12 (Week 76) Visit 13 (Week 84) Visit 14 (Week 92) Visit 15 (Week 100)	Home Urine Pregnancy Testing Week 56 Week 64 Week 72 Week 80 Week 88 Week 96 Week 104 4-Week Post Final Study visit	Visit 16 (Week 108; Final Study Visit) Early Termination Visit
Informed consent			
Eligibility assessment			
Complete physical examination			X
Brief physical examination	X		
Pregnancy test[2]	X	X[3]	X
Clinical laboratory testing[4] [5]	X		X
12-lead electrocardiogram			X
Severity of Alopecia Tool assessment	X		X
Dispense study drug	X		
Adverse events	Continuous		
Concomitant medications	Continuous		

[1]Visit window is ± 3 days for Visits 10-16.

[2]Pregnancy testing will be performed every 4-weeks throughout study enrollment. As in-clinic visits are performed bi-monthly, subjects will perform in-home urine pregnancy tests at Week 56, 64, 72, 80, 88, 96, 104 and 4-weeks post the final study visit. The test date and result will be documented.

[3]In-home pregnancy testing window is ± 3 days

4Collected pre-dose, when possible.

[5]Includes fasted hematology, serum chemistry, SARS-CoV-2 testing, and lipids performed by the central lab.

[redacted]

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To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an email to [redacted] and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

Required hardware and software

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: https://support.docusign.com/guides/signer-guide-signing-system-requirements.

Acknowledging your access and consent to receive and sign documents electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

By selecting the check-box next to 'I agree to use electronic records and signatures', you confirm that:

- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- Until or unless you notify [redacted] as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by [redacted] during the course of your relationship with [redacted]