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:	Protocol Version 5: 21 January 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

INVESTIGATIONAL PRODUCT:	CTP-543
PROTOCOL NUMBER:	CP543.2001
AMENDMENT 5 DATE:	**21 January 2019**
AMENDMENT 4 DATE:	17 August 2018
AMENDMENT 3 DATE:	25 September 2017
AMENDMENT 2 DATE:	05 July 2017
AMENDMENT 1 DATE:	14 February 2017
ORIGINAL PROTOCOL:	14 November 2016
EudraCT NUMBER:	Not Applicable
IND NUMBER:	131,423
SPONSOR NAME / ADDRESS:	Concert Pharmaceuticals, Inc. 99 Hayden Avenue, Suite 500 Lexington, MA 02421

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CONCERT SIGNATURE PAGE

PROTOCOL TITLE: 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

[redacted]

Sponsor Representative Signature [redacted] **dd mmm yyyy**

[redacted]

Printed Name of Sponsor Representative

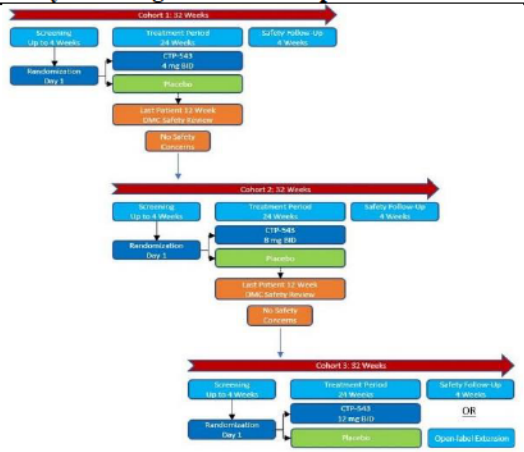
By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Protocol Number: CP543.2001

Signature of Site Principal Investigator	**dd mmm yyyy**
Printed Name of Site Principal Investigator **Institution Name:**	
By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Investigational Review Board procedures, instructions from Concert representatives, the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

Summary of Changes

Section	Previous Text	New Text	Reason for Revision
Synopsis/Methodology **Section 7.1/Study Design**	A cohort within the study is divided into 3 periods: Screening, Treatment, and Post-Treatment Safety Follow-Up. The Screening Period may last up to 28 days prior to initiation of study drug. The Treatment Period is a 24-week, double-blind, placebo-controlled period to define efficacy and safety for the study. The Post-Treatment Safety Follow-up Period is the final 4 weeks of each cohort to assess safety following treatment completion.	The Screening Period may last up to 28 days prior to initiation of study drug. The Treatment Period is a 24-week, double-blind, placebo-controlled period to define efficacy and safety for the study. 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.**	
Synopsis/Study Design **Section 7.1/Study Design**			Added OLE option to Cohort 3 Study Design schematic
Synopsis/Study Design **Section 7.1/Study Design**	Upon completion of treatment at Week 24, patients will stop taking study medication and enter a 4 week Post-Treatment Safety Follow-Up Period. Patients will be assessed for safety through Week 28.	**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 be eligible to either complete treatment at Week 24 and exit the study at Week 28 following the Safety Follow-up visit, or roll-over into a Long-term Open-label Extension study at Week 24.**	

Section	Previous Text	New Text	Reason for Revision
Section 7.1/Study Design	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 Post-Treatment Safety Follow-Up Period. Lipid levels will be assessed every 12 weeks throughout the Treatment Period and at the Post-Treatment Safety Follow-Up Visit.	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**.	
Synopsis/Duration of Study Participation	Subjects will participate in the study for approximately 32 weeks, including Screening and Follow-Up.	**Patients** will participate in the study for up to approximately 32 weeks **if exiting the study after the 4-week Safety Follow-up (4-week Screening, 24-week Treatment, 4-week Safety Follow-up). For Cohort 3, upon completion of the 24-week Treatment Period, patients will be eligible to either complete treatment and exit the study following the 4-week Safety Follow-up visit, or roll-over into a Long-term Open-label Extension study.**	Changes subjects to patients for consistency;
Schedule of Assessment	NA	**[13] The Safety Follow-Up Visit is intended for those patients who do not roll over into the open-label extension (Cohort 3) and for patients who have been discontinued from the study and completed the Early Termination Visit (Week 24).**	Footnote added

1. SYNOPSIS

Name of Sponsor/Company:
Concert Pharmaceuticals

Name of Investigational Product:
CTP-543

Name of Active Ingredient:
D8- ruxolitinib; 1*H*-Pyrazole-1-propanenitrile, β-(cyclopentyl-*2,2,3,3,4,4,5,5-d*$_8$)-4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-, (βR)-, phosphate

Title of Study:
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

Study center(s): Multicenter study; up 14 sites

Studied period (years):	**Phase of development:** 2
Estimated date first patient enrolled: August 2017 Estimated date last patient completed: July 2019	

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.

The primary objectives are:

- 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.

The exploratory objectives are:

- 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 change in Clinical Global Impression of Improvement (CGI-I) from baseline;
- To assess the change in alopecia areata severity as measured by the patient VAS-S from baseline;
- To assess the change in Patient Global Impression of Improvement (PGI-I) from baseline;
- To assess the change in patient reported outcomes as measured by the Alopecia Areata Symptom Impact Scale (AASIS) and exploratory questions from baseline;
- To evaluate the plasma concentrations of CTP-543 in adult patients with chronic, moderate to severe alopecia areata.

Methodology:
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

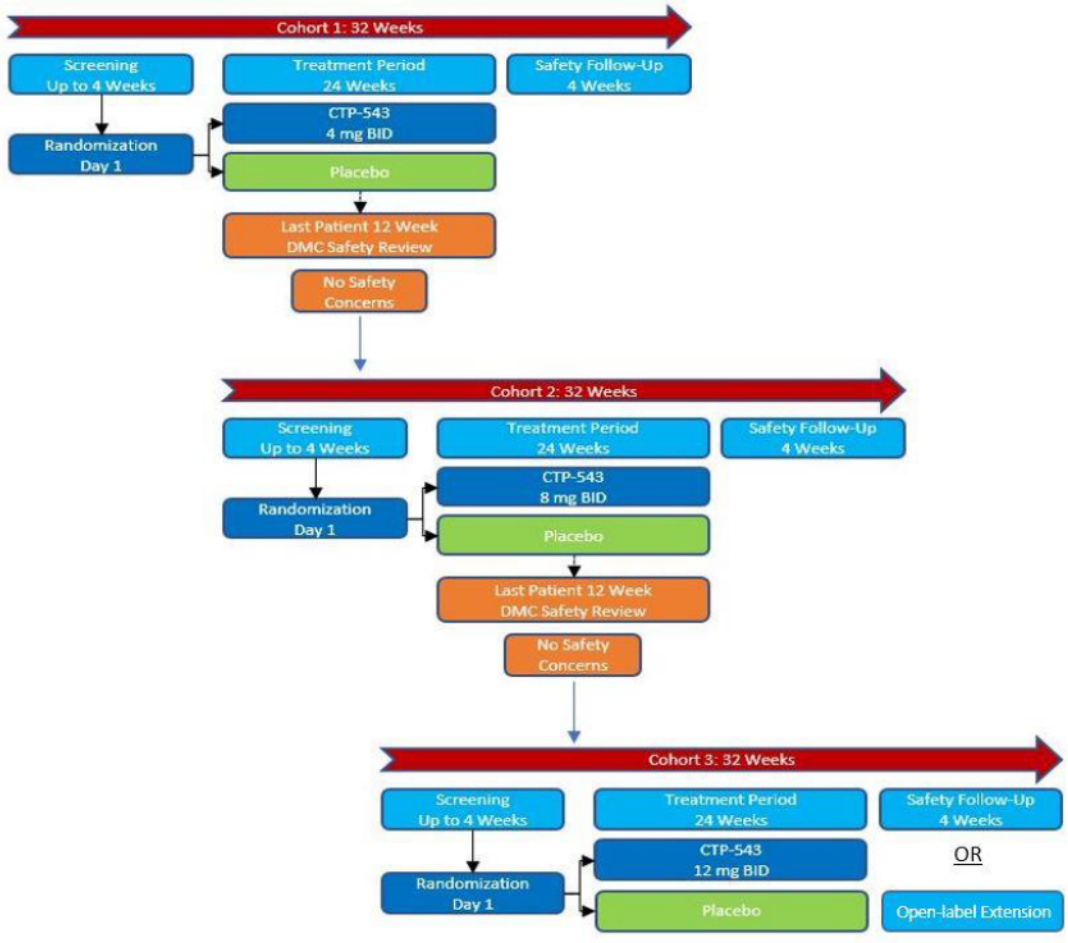
Screening and Baseline, and are not concurrently being treated for alopecia areata or with other treatments that might affect hair regrowth or immune response. Approximately 50% of alopecia areata patients with alopecia totalis or universalis, and approximately 10% with only alopecia ophiasis will be 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 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 initiation of study drug. The Treatment Period is a 24-week, double-blind, placebo-controlled period to define efficacy and safety for the study. The Post-Treatment Safety Follow-up Period is the final 4 weeks of each cohort to assess safety following treatment completion. Subjects 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 subjects 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, 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.

Study Design



Patients will provide appropriately obtained informed consent prior to completing any screening procedures. Patients meeting initial screening criteria will be eligible to continue to the cohort Day 1 visit for review of eligibility and baseline assessments, including SALT assessment, physical examination, clinical laboratory assessments, vital signs, and electrocardiogram. 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 the CTP-543 and placebo (pooled) groups. 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. An interim analysis of safety and efficacy will be performed when all patients in the 4 mg and the 8 mg cohorts have completed Week 24. 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 be eligible to either complete treatment at Week 24 and exit the study at Week 28 following the Safety Follow-up visit, or roll-over into a Long-Term Open-label Extension study at Week 24.

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 should 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 severity through dose interruption or discontinuation, and signs and symptoms of infection will be closely monitored and treated promptly. Patients who experience intolerable symptoms during treatment may discontinue the study at the discretion of the Investigator. Patients may withdraw consent at any time.

Number of patients (planned):

Approximately 150 patients are planned to be enrolled in the study. 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 the CTP-543 and placebo (pooled) groups.

Diagnosis and main criteria for inclusion:

Patients eligible for enrollment in the study must meet all of the following inclusion criteria and none of the exclusion criteria.

Inclusion Criteria:

1. Written informed consent, and authorization for release and use of protected health information.
2. Between 18 and 65 years of age, inclusive, at the time of informed consent.

3. Definitive 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.
4. At least 50% scalp hair loss, as defined by a SALT score ≥50, at Screening and Baseline.
5. If of reproductive age, willing and able to use a medically highly effective form of birth control during the study and for 30 days following last dose of study medication. Examples of medically highly effective forms of birth control are:
    a. Surgical sterility (via vasectomy, hysterectomy or bilateral ligation) or post-menopausal females
    b. Sexual partner is sterile, or of the same sex
    c. Implants of levonorgestrel in females
    d. Oral contraceptive (combined or progesterone only) in females
    e. Double-barrier method (any combination of physical and chemical methods)
    f. Intrauterine device in females, or other method with published data showing that the lowest expected failure rate is less than 1% per year
6. Willing to comply with the study visits and requirements of the study protocol.

Exclusion Criteria:

1. History or presence of hair transplants.
2. Treatment with other medications or agents within 1 month of Screening or during the study that may affect hair regrowth or immune response, including but not limited to: corticosteroids administered orally, by injection, or applied to areas of skin affected by alopecia; platelet-rich plasma injections; topical application to affected areas of anthralin, squaric acid, diphenylcyclopropenone, or minoxidil.
3. Treatment with systemic immunosuppressive medications including but not limited to methotrexate, cyclosporine, and azathioprine; chloroquine derivatives; Janus kinase inhibitors (ruxolitinib, tofacitinib, etc) or etanercept within 3 months of Screening or during the study; or biologics (adalimumab, atlizumab, canakinumab, certolizumab, fontolizumab, golimumab, infliximab, mepolizumab, rituximab, secukinumab, tocilizumab, ustekinumab) within 6 months of Screening or during the study.
4. Active scalp inflammation, psoriasis, or seborrheic dermatitis requiring topical treatment to the scalp, significant trauma to the scalp, or untreated actinic keratosis anywhere on the body at Screening and/or Baseline.
5. Known history of moderate to severe androgenic alopecia or female pattern hair loss prior to alopecia areata.
6. Unwilling to maintain a consistent hair style, including shampoo and hair products (including hair dye, process, and timing to hair appointments), and to refrain from weaves or extensions throughout the course of the study, or shaving of scalp hair for 2 weeks preceding a SALT assessment.
7. Use of adhesive wigs, other than banded perimeter wigs, during the study.
8. History of a lymphoproliferative disease or malignancy, other than non-melanoma skin cancer or cervical carcinoma. Patients with 3 or more basal or squamous cell carcinomas diagnosed in the past 2 years are excluded.
9. Atypical nevi or cutaneous lesions that are suspicious for malignancy.
10. History of solid organ or hematological transplantation.
11. Fever or infection within 2 weeks prior to first dose of study drug.

12. Abnormal levels of thyroid stimulating hormone at Screening, defined as <0.9 x the lower limit of normal (LLN) and >1.2 x the upper limit of normal (ULN) and, if taking thyroid medication, an inability to maintain levels within the normal range for 6 months prior to Screening or during the study.
13. Screening labs outside the normal range for parameters associated with potential risk for treatment under investigation. This will include but is not limited to:
    a. Platelets $\leq 120 \times 10^9$/L
    b. Absolute neutrophil count $\leq 1.5 \times 10^9$/L
    c. Hemoglobin levels ≤11 g/dL for females, or hemoglobin levels ≤12. 5 g/dL for males
14. Screening blood glucose levels of hemoglobin A1c ≥6.5% (48 mmol/mol).
15. Abnormal liver function at Screening, defined as ≥1.5 × ULN of serum alanine transaminase, serum aspartate transaminase, serum alkaline phosphatase, or total bilirubin (unless isolated Gilbert's syndrome).
16. Abnormal renal function (estimated glomerular filtration rate <60 mL/min/1.73 m^2 using the MDRD equation) at Screening.
17. Any active infection at Screening, active or previous Hepatitis B or C infection, or known human immunodeficiency virus infection.
18. Vaccination with herpes zoster vaccine or any live virus vaccine within 6 weeks before Screening or during the study.
19. Positive purified protein derivative test for non-bacillus Calmette-Guérin-vaccinated patients, positive QuantiFERON®-TB Gold test, or history of incompletely treated or untreated tuberculosis.
20. History of prolonged QT syndrome or a Screening QTc interval with Fridericia's correction (QTcF) > 450 msec for males or QTcF > 470 msec for females.
21. History of alcohol, medication, or illicit drug abuse within 1 year before the first dose of study drug.
22. Females who are nursing, pregnant, or planning to become pregnant while in the study, and for 30 days after last dose of study medication.
23. Participation in another investigational study within the greater of 4 weeks or 5 half-lives of an investigational medication prior to screening or during the study.
24. Use of strong cytochrome P450 3A4 (CYP3A4) inhibitors (such as, but not limited to clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, saquinavir, telaprevir, telithromycin, voriconazole, or fluconazole) dosed for systemic exposure.
25. Use of strong CYP3A4 inducers (such as, but not limited to barbiturates, carbamazepine, efavirenz, glucocorticoids, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's Wort, or troglitazone) dosed for systemic exposure.
26. Donation of blood within a month of first dose of study drug or at any point throughout the study and for 30 days after last dose of study medication.
27. Clinically significant medical condition, psychiatric disease, or social condition, as determined by the Investigator, that may unfavorably alter the risk-benefit of study participation, adversely affect study compliance, or confound interpretation of study results.

Investigational product, dosage and mode of administration:

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.

Reference therapy, dosage and mode of administration:

Matching placebo

Duration of treatment:

Patients will receive up to 24 weeks of study drug.

Duration of study participation:

Patients will participate in the study for up to approximately 32 weeks if exiting the study after the 4-week Safety Follow-up (4-week Screening, 24-week Treatment, 4-week Safety Follow-up). For Cohort 3, upon completion of the 24-week Treatment Period, patients will be eligible to either complete treatment and exit the study following the 4-week Safety Follow-up visit, or roll-over into a Long-term Open-label Extension study.

Criteria for evaluation:

Efficacy:

The primary efficacy endpoint will be the proportion of patients achieving at least a 50% relative reduction in SALT score from baseline at Week 24.

Exploratory efficacy endpoints include:

- Relative change in SALT scores from baseline (mean and percent) at Weeks:
  - 4, 8, 12, 16, 20, and 24 in the Blinded Treatment Period
- Relative change in alopecia areata severity from baseline as measured by the clinician's VAS-S at Weeks 12 and 24;
- Changes in alopecia areata from baseline using the clinician rated 7-point Likert scale CGI-I at Weeks 12 and 24;
- Relative change in alopecia areata severity from baseline as measured by the patient's VAS-S at Weeks 12 and 24;
- Changes in alopecia areata from baseline using the patient rated 7-point Likert scale PGI-I at Weeks 12 and 24;
- Patient-reported outcomes: Changes in symptoms from baseline as measured by AASIS and exploratory questions at Week 24

Pharmacokinetics:

Pharmacokinetic samples will be collected at the following time points to evaluate plasma concentrations of CTP-543 and metabolites.

- Day 1 and Week 4: 2 samples at each visit; 1 sample pre-dose, and 1 sample post-dose at the end of the visit
- Week 2: 1 sample pre-dose with the safety lab draw
- Weeks 8, 24: 1 sample at post-dose at the end of the visit

Safety:

Safety and tolerability of CTP-543 will be assessed by evaluating adverse events, vital signs, concomitant medications, clinical laboratory, and electrocardiogram results, as well as physical examinations.

Statistical methods:

Sample Size:

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 variance around these measures, in patients with alopecia areata. 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-square test. Approximately 150 patients will be randomized in order to provide 120 patients who complete treatment.

Efficacy Analyses:

The Efficacy Population will include all patients who receive study drug and have at least 1 post-treatment SALT assessment. The primary efficacy endpoint will be the proportion of patients with at least a 50% relative reduction in SALT score from baseline at Week 24. The placebo patients from the 3 cohorts will be combined for statistical comparisons to each active treatment group.

Data will be summarized by active treatment by dose level versus placebo-treated patients (i.e., by treatment group). Continuous measures will be summarized descriptively (mean, standard deviation, median, minimum value, and maximum value) and categorical measures will be presented as number and percentage.

All statistical tests will be 2-sided with a significance value of 0.05. There will be no adjustments for multiple comparisons.

An interim analysis of safety and efficacy will be performed when all patients in the 4 mg and the 8 mg cohorts have completed Week 24. The final efficacy analysis will be conducted when all patients in the 12 mg cohort have completed Week 24. Additional details for statistical methods will be provided in the Statistical Analysis Plan.

Pharmacokinetic Analyses:

The Pharmacokinetic Population will include all patients who receive study drug and have at least 1 pharmacokinetic sample taken. Plasma concentrations will be summarized by descriptive statistics as appropriate and will be listed by patient.

Safety Analyses:

The Safety Population will include all patients who receive study drug in the Treatment Period. Adverse events will be coded by system organ class and preferred term with the Medical Dictionary for Regulatory Activities. Concomitant medications will be summarized by World Health Organization Drug Dictionary Anatomical-Therapeutic-Chemical classification and preferred term. Adverse events, vital sign measurements, physical examination findings, electrocardiogram, clinical laboratory information, and concomitant medications will be tabulated and summarized by treatment and dose level. By-patient listings will be provided for any deaths, serious adverse events, and adverse events leading to discontinuation of treatment.

Table 1: Schedule of Events for each Cohort

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.

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

LIST OF TABLES

LIST OF FIGURES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 2: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AASIS	Alopecia Areata Symptom Impact Scale
BID	Twice daily dosing
CFR	Code of Federal Regulations
CGI-I	Clinical Global Impression of Improvement
CTCAE	Common terminology criteria for adverse events
CYP3A4	Cytochrome P450 3A4
DMC	Data monitoring committee
DMP	Data Management Plan
eCRF	Electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
ICF	Informed consent form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
JAK	Janus kinase
LLN	Lower Limit of Normal
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
PCS	Potentially clinically significant
PGI-I	Patient Global Impression of Improvement
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate (Fridericia's method)
SALT	Severity of Alopecia Tool
STAT	Signal transducers and activators of transcription
TEAE	Treatment-emergent adverse events
ULN	Upper Limit of Normal
VAS-S	Visual Analog Scale of Severity

4. INTRODUCTION

4.1. Overview of Alopecia Areata

Alopecia areata is an autoimmune disorder characterized by patches of non-scarring alopecia affecting scalp and body hair. Alopecia areata is clinically heterogeneous, affects men and women, and has a prevalence rate of 0.1% to 0.2% of the United States population [Safavi, 1992]. There is no preventative therapy or cure. Alopecia areata often presents as a cyclical disorder marked by unpredictable periods of hair loss and spontaneous regrowth, and variation in the degree or pattern of hair loss gives rise to different subtypes of alopecia areata, such as patchy, ophiasis, totalis, or universalis. Approximately 7% of patients have severe disease with almost complete hair loss and little or no regrowth [Villasante Fricke, 2015]. Onset can occur at any age and affects both men and women over the course of their lifetime. Approximately 80% of alopecia areata patients experience the first episode of hair loss by 40 years of age and 40% by 20 years of age [Villasante Fricke, 2015]. Alopecia areata can have a psychological impact with high rates of depression [Sellami, 2014] and anxiety reported, particularly in children and adolescents [Bilgic, 2013], and therefore, psychological counseling is often recommended as part of the standard of care [Al-Mutairi, 2011].

A cause for alopecia areata has not yet been identified, though as in other autoimmune disorders, genetic susceptibility and a wide array of environmental triggers are thought to be involved. Presently, treatments for alopecia areata include moderately effective intralesional corticosteroid injections or topicals, or aesthetic disguises such as makeup and wigs. Other treatments include off-label use of topical clobetasol propionate (Clobex®), approved for psoriasis (NDA 021535), or pimecrolimus (Elidel® cream 1%), approved for atopic dermatitis (NDA 021302); however, each has significant adverse reactions associated with its use, such as Cushing's syndrome, hyperglycemia, and diabetes mellitus for Clobex, and a black box warning of rare malignancies for Elidel. Currently, no existing therapies for alopecia areata have been approved by the United States Food and Drug Administration (FDA), indicating a significant unmet medical need.

4.2. Scientific Rationale for the Study

Concert has applied its deuterium chemical entity platform to ruxolitinib (Jakafi®), a selective Janus Kinase (JAK) inhibitor that modulates immune response through reduced intracellular JAK1 and JAK2 signaling. CTP-543 is structurally similar to ruxolitinib with the exception of eight deuterium atoms substituted in place of hydrogen. CTP-543 is being developed as a potential oral treatment for alopecia areata.

The mechanism of hair loss in alopecia areata appears to be mediated by cytotoxic T cell attack of the hair follicle after loss of immune privilege, regulated by upstream JAK signaling [Xing, 2014]. Therefore, directed JAK inhibition may represent a viable therapeutic approach to treating alopecia areata.

The JAKs are intracellular tyrosine kinases that play a central role in the signaling of cytokine and growth factor receptors [Ghoreschi, 2009]. Cytokine-induced receptor conformation changes activate the JAKs and trigger phosphorylation of the 6-member signal transducers and activators of transcription (STAT) protein transcription factor family. Upon phosphorylation, STATs dimerize and translocate to the nucleus to regulate gene transcription. Therapies that inhibit cytokine signaling or downstream JAK signaling have demonstrated efficacy in autoimmune disorders such as psoriasis, psoriatic arthritis, and rheumatoid arthritis, and multiple

JAK inhibitors are in development for autoimmune disorders such as atopic dermatitis, systemic lupus erythematosus and others.

Ruxolitinib (Jakafi®) is a selective JAK inhibitor that was launched in the United States by Incyte Corporation in 2011 as the first therapeutic agent to decrease splenomegaly and ameliorate symptoms in primary or secondary myelofibrosis, and was most recently approved in the United States in 2014 for the treatment of polycythemia vera. Ruxolitinib is currently under development by Incyte Corporation for additional hematological malignancies as well as essential thrombocythemia, graft-versus-host disease, and as a topical formulation for atopic dermatitis and vitiligo.

A pilot study (NCT01950780) conducted by Columbia University demonstrated clinical evidence for efficacy of oral ruxolitinib dosed at 20 mg BID (the approved dose for myelofibrosis) in patients with moderate to severe alopecia areata [Xing, 2014]. The majority of these patients (9 out of 12) exhibited extensive hair regrowth within 3 to 6 months of treatment initiation, averaging a 92% reduction in hair loss from baseline [Mackay-Wiggan, 2016]. In this population, ruxolitinib was considered well tolerated. In addition, there are three other case studies and one academic clinical trial (NCT02197455 and NCT02312882) that have successfully treated patients with alopecia areata using JAK inhibitors [Craiglow and King, 2014; Jabbari et al, 2015; Harris, 2016; Crispin, 2016].

4.3. Preclinical Information for CTP-543

[redacted] The CTP-543 Investigator's Brochure should be consulted for more detailed technical information, current discussion of nonclinical evaluations, and relevant information regarding the known safety profile of CTP-543 to date, and potential safety concerns based on known effects of ruxolitinib.

4.4. Clinical Information

4.4.1. Pharmacokinetics and Clinical Safety of Ruxolitinib

The oral dose pharmacokinetics, pharmacodynamics, and safety and tolerability of ruxolitinib were evaluated in 2 double-blind, randomized, placebo-controlled studies in healthy volunteers. The first study evaluated single ascending doses from 5 mg up to 200 mg, and the second study evaluated multiple ascending doses, including both once daily and twice daily administration for 10 days, up to a total daily dose of 100 mg. In both studies, ruxolitinib was generally safe and well tolerated, with 100 mg once daily and 25 mg twice daily established as the maximum tolerated doses, respectively. The dose-limiting toxicity in the multiple ascending dose study was Grade 4 neutropenia [Shi, 2011].

Ruxolitinib demonstrated dose-linear pharmacokinetic parameters, steady-state achievement within 24 hours consistent with a short half-life of approximately 3 hours, and insignificant accumulation upon repeat dosing.

The pharmacodynamics of ruxolitinib, evaluated by the inhibition of phosphorylated STAT3, showed good correlation with ruxolitinib plasma concentrations.

Ruxolitinib was subsequently evaluated in 2 double-blind, randomized, placebo-controlled clinical trials in patients with myelofibrosis and 1 open-label, active-controlled clinical trial in

patients with polycythemia vera. The warnings and precautions section of the prescribing information for Jakafi, most recently updated in December 2017, includes thrombocytopenia, anemia and neutropenia; risk of infection; non-melanoma skin cancer; lipid elevations; and symptom exacerbation following interruption or discontinuation [Jakafi, 2017].

Recommendations for management of cytopenias include dose reduction or interruption, and monitoring of complete blood counts every 2 to 4 weeks until stabilized, and as clinically indicated thereafter. Serious infections reported include tuberculosis, progressive multifocal leukoencephalopathy, herpes zoster, and hepatitis B; all signs and symptoms of infection should be managed promptly. Periodic skin examinations are recommended to detect non-melanoma skin cancers including basal cell, squamous cell and Merkel cell carcinoma. Lipid elevations including total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglycerides should be assessed every 8 to 12 weeks for monitoring and treatment of hyperlipidemia.

4.4.2. Clinical Studies of CTP-543

Two clinical studies with CTP-543 in healthy volunteers have been completed. Study CP543.1001 was a pharmacokinetic/pharmacodynamic study consisting of a first-in-human single ascending dose study and a sequential multiple ascending dose study. The objective of the study was to assess safety, tolerability, pharmacokinetics, and pharmacodynamics of CTP-543 in healthy volunteers. A total of 82 subjects were planned for the study; 32 subjects in 4 cohorts randomized at a ratio of 3:1 CTP-543 to placebo for the single ascending dose part (Part A), and thereafter, 50 subjects in 5 cohorts randomized at a ratio of 4:1 CTP-543 to placebo for the multiple ascending dose part (Part B). The doses studied in the single ascending dose study were 8 mg, 16 mg, 32 mg, and 48 mg. The doses studied in the multiple ascending dose study were 8 mg once daily, 8 mg twice daily, 24 mg once daily, 32 mg once daily, and 16 mg twice daily, dosed for 7 consecutive days.

The second clinical study CP543.1002, also performed in healthy volunteers was a single dose cross-over study to assess safety and tolerability and to compare the metabolite and pharmacokinetic profiles of CTP-543 versus ruxolitinib. A total of 12 subjects were enrolled in the study; 2 groups of 6 subjects each were dosed with either 15 mg of ruxolitinib (1 x 15 mg tablet) or 16 mg of CTP-543 (2 x 8 mg tablets) in period 1 who then crossed over to the alternate treatment for period 2. A washout period of 3 days occurred between treatments.

To date, CTP-543 has been generally well tolerated. No deaths or serious adverse events have occurred following dosing with CTP-543.

5. ETHICS

The procedures set out in this study protocol, pertaining to the conduct, evaluation and documentation of this study, are designed to ensure that the Sponsor and the Investigator abide by Good Clinical Practice (GCP), including but not limited to Title 21 Code of Federal Regulations (CFR) Parts 50, 56, and 312, and the International Conference on Harmonisation (ICH) guidelines and directives. Compliance with these regulations also constitutes compliance with the ethical principles described in the current revision of the Declaration of Helsinki and applicable local regulatory requirements and law.

The Investigator is responsible for protecting the rights, safety, and welfare of patients under his/her care, and for the control of the medications under investigation. All ethical, regulatory, and legal requirements must be met before the first patient is enrolled in the study.

5.1. Institutional Review Board (IRB)

The Institutional Review Board (IRB) will meet all FDA requirements governing IRBs according to CFR, Title 21, Part 56. The Investigator (or designee) must submit this study protocol and any amendments, the Sponsor's approved informed consent form(s) (ICF), patient information sheets, patient recruitment materials, and other appropriate documents to the IRB for review and approval. Following review of the submitted materials a copy of the written and dated approval/favorable opinion will be forwarded to the Sponsor (or designee).

Any advertisements used to recruit patients for the study will be reviewed by the Sponsor and the IRB prior to use.

5.2. Written Informed Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the patient.

The ICF, as specified by the clinical site's IRB, must follow the Protection of Human Subjects regulations listed in the Code of Federal Regulations, Title 21, Part 50. The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary must be explained to the patient. The patient must be given sufficient time to consider whether to participate in the study.

A copy of the ICF, signed and dated by the patient, must be given to the patient. Confirmation of a patient's informed consent must also be documented in the patient's source documentation prior to any testing under this protocol, including screening tests and assessments. The original signed consent form will be retained with the study records.

All ICFs used in this study must be approved by the appropriate IRB and by the Sponsor. The ICF must not be altered without the prior agreement of the relevant IRB and the Sponsor.

6. 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.

6.1. Primary Objectives

The primary objectives are:

- To assess the efficacy of CTP-543 on 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.

6.2. Exploratory Objectives

The exploratory objectives are:

- To assess the change in patient alopecia areata severity as measured by the clinician Visual Analog Scale;
- To assess the change in Clinical Global Impression of Improvement (CGI-I) from baseline;
- To assess the change in alopecia areata severity as measured by the patient Visual Analog Scale from baseline;
- To assess the change in Patient Global Impression of Improvement (PGI-I) from baseline;
- To assess the change in patient reported outcomes as measured by the Alopecia Areata Symptom Impact Scale (AASIS) and exploratory questions from baseline;
- To evaluate the plasma concentrations of CTP-543 in adult patients with chronic, moderate to severe alopecia areata.

7. OVERALL STUDY DESIGN

7.1. 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 require a definitive diagnosis of alopecia areata by the Investigator based on clinical evaluation involving physical examination and medical history. 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.

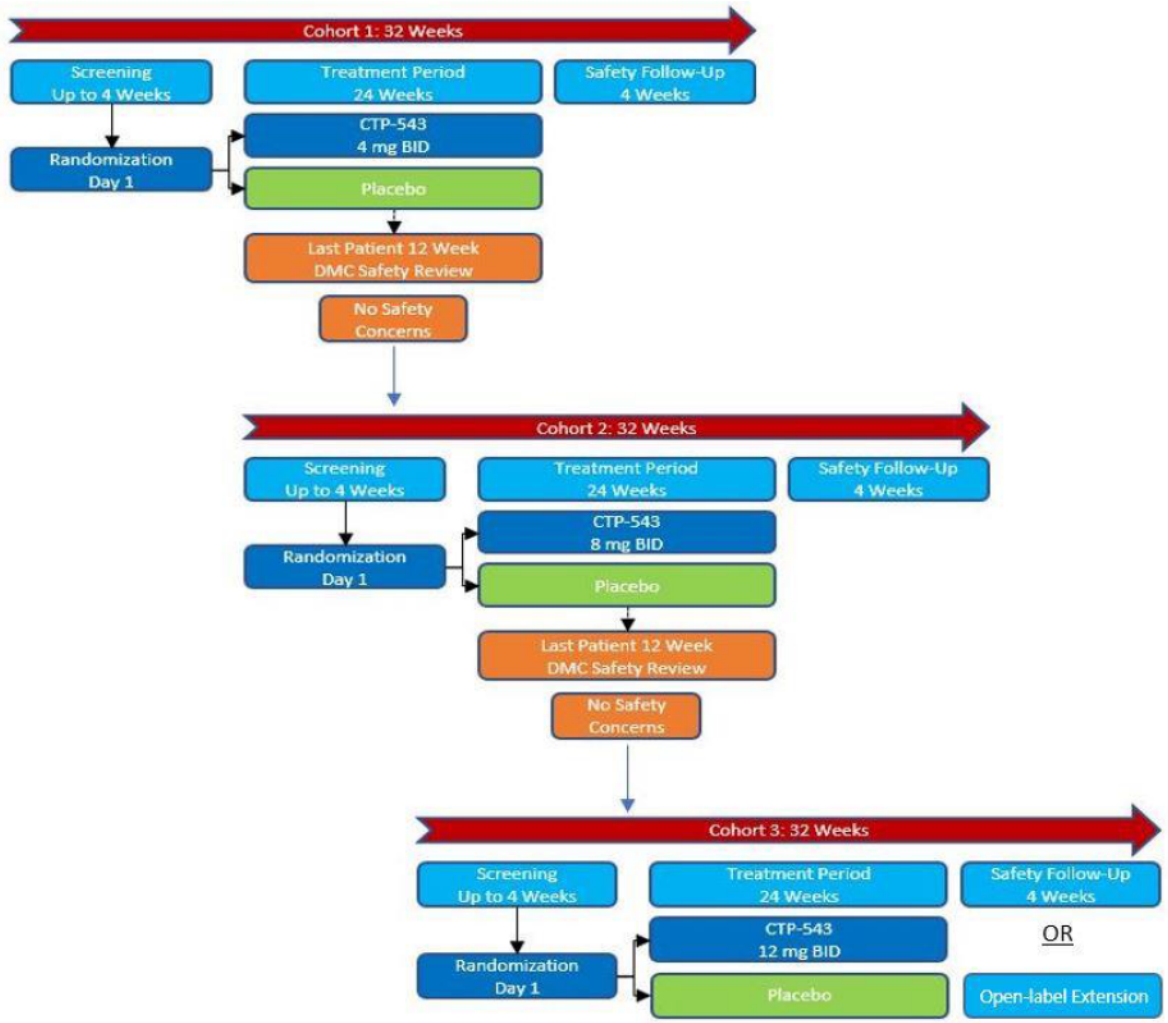
Patients will be between 18 and 65 years of age and experiencing a current episode of alopecia areata lasting at least 6 months and not exceeding 10 years. Total disease duration may exceed the duration of the current episode. Patients will require at least 50% hair loss as measured by the SALT assessment at Screening and Baseline, and should not be treated concurrently for alopecia areata or with other treatments that might affect hair regrowth. 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 dose cohort. Patients will not dose escalate within a cohort and may only participate in one cohort.

The Screening Period will last up to 28 days prior to initiation of study drug. The Treatment Period is the initial 24-week, double-blind, placebo-controlled period to define primary efficacy and safety for the study. The Post-Treatment Safety Follow-up Period is the final 4 weeks of each cohort to assess safety following treatment completion. Subjects 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 subjects 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 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. The DMC may advise treatment arm cessation due to intolerability at any time.

Figure 1: Study Design



Patients will provide appropriately obtained informed consent prior to completing any screening procedures. Patients meeting initial screening criteria will be eligible to continue to the cohort Day 1 visit for review of eligibility and baseline assessments, including SALT assessment, physical examination, clinical laboratory assessments, vital signs, and electrocardiogram. 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 the CTP-543 and pooled placebo arms. 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. All SALT assessments will be performed with a live physical examination of the patient by qualified, trained site personnel. Photographs of the scalp will be used to provide a visual record at the time of SALT assessment, and photographs of the hands and/or eyes will be taken to document nail or eyelash/eyebrow involvement in those patients for whom it applies. The

efficacy analysis will be conducted when all patients in the highest dose cohort have completed Week 24 of dosing.

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 (12 mg BID), patients will be eligible to either complete treatment at Week 24 and exit the study at Week 28 following the Safety Follow-up visit, or roll-over into a Long-term Extension study at Week 24.

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 with or without food, for the duration of the Treatment Period. Patients should 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 study by the Investigators, and supported by regular review by the Medical Monitor, and 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 severity through dose interruption or discontinuation, and signs and symptoms of infection will be closely monitored and treated promptly. Patients who experience intolerable symptoms during treatment may discontinue the study at the discretion of the Investigator. Patients may withdraw consent at any time.

7.2. Number of Patients and Sites

Approximately 150 patients are planned to be enrolled in the study at up to 14 sites. The first 2 cohorts will be randomized in a 2:1 ratio and the third cohort will be randomized in a 5:1 ratio in order to provide a similar number of patients across the CTP-543 and pooled placebo arms.

7.3. Method of Treatment Assignment and Blinding

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, and 3) alopecia ophiasis. Approximately 50% of alopecia areata subjects with alopecia totalis or universalis, and approximately 10% with only alopecia ophiasis, will be enrolled. The randomization schedule will be generated prior to study start.

All study participants will be blinded to study drug assignment for the duration of the study. Tablets and packaging of CTP-543 and placebo will be identical in appearance.

7.4. Rationale for Study Design

Double-blind, randomized, placebo-controlled studies are considered optimal for obtaining unbiased estimates of the efficacy and safety of investigational products. The 24-week duration of the Treatment Period is anticipated to allow sufficient time for initiation of hair growth with CTP-543. Assessment of treatment through 24 weeks will provide an initial assessment of the safety profile associated with CTP-543.

8. SELECTION AND WITHDRAWAL OF PATIENTS

Patients eligible for enrollment in the study must meet all of the following inclusion criteria and none of the exclusion criteria.

8.1. Patient Inclusion Criteria

1. Written informed consent, and authorization for release and use of protected health information.
2. Between 18 and 65 years of age, inclusive, at the time of informed consent.
3. Definitive diagnosis of alopecia areata with a current episode of at least 6 months and not exceeding 10 years at the time of Screening. Total disease duration greater than 10 years is permitted.
4. At least 50% scalp hair loss, as defined by a SALT score ≥50, at Screening and Baseline.
5. If of reproductive age, willing and able to use a medically highly effective form of birth control during the study and for 30 days following last dose of study medication. Examples of medically highly effective forms of birth control are:
    a. Surgical sterility (via vasectomy, hysterectomy or bilateral ligation) or post-menopausal females
    b. Sexual partner is sterile, or of the same sex
    c. Implants of levonorgestrel in females
    d. Oral contraceptive (combined or progesterone only) in females
    e. Double-barrier method (any combination of physical and chemical methods)
    f. Intrauterine device in females, or other method with published data showing that the lowest expected failure rate is less than 1% per year
6. Willing to comply with the study visits and requirements of the study protocol.

8.2. Patient Exclusion Criteria

1. History or presence of hair transplants.
2. Treatment with other medications or agents within 1 month of Screening or during the study that may affect hair regrowth or immune response, including, but not limited to: corticosteroids administered orally, by injection, or applied to areas of skin affected by alopecia; platelet-rich plasma injections; topical application to affected areas of anthralin, squaric acid, diphenylcyclopropenone, or minoxidil.
3. Treatment with systemic immunosuppressive medications including but not limited to methotrexate, cyclosporine, and azathioprine; chloroquine derivatives; JAK inhibitors (ruxolitinib, tofacitinib, etc) or etanercept within 3 months of Screening or during the study; or biologics (adalimumab, atlizumab, canakinumab, certolizumab, fontolizumab, golimumab, infliximab, mepolizumab, rituximab, secukinumab, tocilizumab, ustekinumab) within 6 months of Screening or during the study.
4. Active scalp inflammation, psoriasis, or seborrheic dermatitis requiring topical treatment to the scalp, significant trauma to the scalp, or untreated actinic keratosis anywhere on the body at Screening and/or Baseline.

5. Known history of moderate to severe androgenic alopecia or female pattern hair loss prior to alopecia areata.
6. Unwilling to maintain a consistent hair style, including shampoo and hair products (including hair dye, process, and timing to hair appointments), and to refrain from weaves or extensions throughout the course of the study, or shaving of scalp hair for at least 2 weeks prior to a SALT assessment.
7. Use of adhesive wigs, other than banded perimeter wigs, during the study.
8. History of a lymphoproliferative disease or malignancy, other than non-melanoma skin cancer or cervical carcinoma. Patients with 3 or more basal or squamous cell carcinomas diagnosed in the past 2 years are excluded.
9. Atypical nevi or cutaneous lesions that are suspicious for malignancy.
10. History of solid organ or hematological transplantation.
11. Fever or infection within 2 weeks prior to first dose of study drug.
12. Abnormal levels of thyroid stimulating hormone at Screening, defined as <0.9 x the lower limit of normal (LLN) and >1.2 x the upper limit of normal (ULN) and, if taking thyroid medication, an inability to maintain levels within the normal range for 6 months prior to Screening or during the study.
13. Screening labs outside the normal range for parameters associated with potential risk for treatment under investigation. This will include but is not limited to:
    a. Platelets $\leq 120 \times 10^9$/L
    b. Absolute neutrophil count $\leq 1.5 \times 10^9$/L
    c. Hemoglobin levels ≤11 g/dL for females, or hemoglobin levels ≤12. 5 g/dL for males
14. Screening blood glucose levels of hemoglobin A1c ≥6.5% (48 mmol/mol).
15. Abnormal liver function at Screening, defined as ≥1.5 × ULN of serum alanine transaminase, serum aspartate transaminase, serum alkaline phosphatase, or total bilirubin (unless isolated Gilbert's syndrome).
16. Abnormal renal function (estimated glomerular filtration rate <60 mL/min/1.73 m^2 using the MDRD equation) at Screening.
17. Any active infection at Screening, active or previous Hepatitis B or C infection, or known human immunodeficiency virus infection.
18. Vaccination with herpes zoster vaccine or any live virus vaccine within 6 weeks before Screening or during the study.
19. Positive purified protein derivative test for non-bacillus Calmette-Guérin-vaccinated patients, positive QuantiFERON®-TB Gold test, or history of incompletely treated or untreated tuberculosis.
20. History of prolonged QT syndrome or a Screening QTc interval with Fridericia's correction (QTcF) > 450 msec for males or QTcF > 470 msec for females.
21. History of alcohol, medication, or illicit drug abuse within 1 year before the first dose of study drug.

22. Females who are nursing, pregnant, or planning to become pregnant while in the study, and for 30 days after last dose of study medication.
23. Participation in another investigational study within the greater of 4 weeks or 5 half-lives of an investigational medication prior to screening or during the study.
24. Use of strong CYP3A4 inhibitors (such as, but not limited to clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, saquinavir, telaprevir, telithromycin, voriconazole, or fluconazole) dosed for systemic exposure.
25. Use of strong CYP3A4 inducers (such as, but not limited to barbiturates, carbamazepine, efavirenz, glucocorticoids, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's Wort, or troglitazone) dosed for systemic exposure.
26. Donation of blood within a month of first dose of study drug or at any point throughout the study and for 30 days after last dose of study medication.
27. Clinically significant medical condition, psychiatric disease, or social conditions, as determined by the Investigator, that may unfavorably alter the risk-benefit of study participation, adversely affect study compliance, or confound interpretation of study results.

8.3. Patient Withdrawal Criteria

All patients are free to withdraw from participation in the study at any time, for any reason, and without prejudice. The Investigator must withdraw any patient from the study if the patient requests to stop participating in the study. The Investigator, Sponsor, or its designee may remove a patient from the study at any time and for any reason. In addition, patients should be withdrawn if they:

- Experience an intolerable adverse event, including but not limited to, an adverse event ≥ Grade 4, including bone marrow-related events, or a ≥ Grade 3 cardiac event, according to CTCAE v4.0 criteria
- Require a medication that is prohibited by the protocol
- Do not follow guidelines specified in the protocol (ie, is noncompliant with protocol procedures or study treatment administration)
- Any medically appropriate reason or significant protocol violation, in the opinion of the Investigator
- Are lost to follow up

Patients who withdraw or are withdrawn from the study will not be replaced.

8.3.1. Patient Withdrawal Procedures

A patient who prematurely discontinues study treatment/study participation should have all Week 24 assessments performed as an Early Termination Visit, and return for the Safety Follow-up Visit. The Safety Follow-Up Visit may be waived by the Sponsor in instances where patients have discontinued dosing prior to the Early Termination Visit on a case-by-case basis.

If a patient terminates early from the study, the Investigator will record the reason(s) for early termination on the relevant electronic case report form (eCRF). The specific reason for the withdrawal should be carefully documented on the eCRF.

Patients who require a dose interruption lasting more than 21 days should be discontinued from the study. Adverse events resulting in patient early termination will be followed to the satisfactory resolution and determination of outcome, as ascertained by the Investigator (and/or Sponsor, or its designee); See Section 11.1.2: Adverse Events. The data will be recorded on the appropriate eCRF.

8.4. Emergency Unblinding of Treatment Assignment

In the case of a medical requirement to break the blind to determine appropriate treatment for an adverse event, unblinding of a patient's treatment assignment can be achieved through the study-specific Interactive Web Response System. If possible, the Investigator should discuss the circumstances with the Medical Monitor prior to accessing unblinding information. In the event of a blind break, the Medical Monitor will be notified through the electronic data capture system. The patient for whom the blind is broken should be subsequently withdrawn from the study. The details regarding the process of breaking the blind are outlined in the Pharmacy Manual.

8.5. Criteria for Study Termination

If the DMC determines that treatment with CTP-543 poses an unjustified risk to patients, the study may be terminated. The Sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons.

The DMC will review collective safety data for each cohort at regular intervals throughout the study. Should safety signals arise that suggest treatment with CTP-543 poses an unjustified risk to patients, termination of the study or modification of dosing arms may occur upon Sponsor review of the DMC recommendation. The DMC may call for unscheduled data review meetings at any time to ensure appropriate safety monitoring.

Events that would trigger an unscheduled review may include, but are not limited to:

- High frequency of dose interruptions
- High frequency of, or a trend in, SAEs
- High frequency of Grade 3/4 adverse events
- Trend in organ system-specific moderate and/or severe adverse events
- High frequency of patient withdrawal due to adverse events

The Sponsor will notify Investigators of any recommendation of study termination by the DMC. The Sponsor will notify Investigators of recommendation for study modification as necessary to protect patient safety including appropriate instructions for removing patients from treatment, while maintaining the blind.

Any termination required by the Sponsor must be implemented by the Investigator, if instructed to do so, in a time frame that is compatible with the patient's well-being.

9. DESCRIPTION OF STUDY TREATMENTS

9.1. Description of Treatments

For each cohort, patients will be stratified by alopecia areata subtype and randomized to CTP-543 or placebo in a 2:1 ratio for Cohorts 1 and 2, and 5:1 ratio for Cohort 3.

Treatments arms for each cohort will include:

- Cohort 1
  - CTP-543 4 mg every 12 hours
  - Placebo every 12 hours

  If the DMC review of safety parameters for all patients in Cohort 1 (4 mg BID) through Week 12 indicates no safety concerns, Cohort 2 (8 mg BID) will be initiated.
- Cohort 2
  - CTP-543 8 mg every 12 hours
  - Placebo every 12 hours
- If the DMC review of safety parameters for all patients in Cohort 2 (8 mg BID) through Week 12 indicates no safety concerns, Cohort 3 (12 mg BID) will be initiated.
- Cohort 3
  - CTP-543 12 mg every 12 hours
  - Placebo every 12 hours

For each cohort, patients will take the first dose of study drug in the clinic on Day 1 of the Treatment Period and will be instructed to take study drug every 12 hours for the duration of the period. Patients should dose study drug in the clinic on all Study Visit Days after clinical laboratory blood draws are completed.

9.2. Dose-Adjustment Criteria

No individualized dose adjustment is allowed during the Treatment Period except in the event of intolerability, for which a dose interruption or study discontinuation may occur at the discretion of the Investigator (see Section 9.2.1 below for details).

The DMC will review collective safety data throughout the study in accordance with the DMC Charter. If the DMC determines a cohort's CTP-543 treatment arm should be stopped, patients receiving treatment at that dose will move to the next lower cohort's CTP-543 treatment arm in a blinded fashion at the patient's next visit, if a lower CTP-543 treatment is available. If a lower CTP-543 treatment arm is not available, the study will terminate. If an immediate hazard is suspected, patients without an imminent visit may have an Unscheduled Visit for potential dose adjustment to maintain the blind. In the event of CTP-543 treatment arm cessation and cohort dose adjustment to a lower CTP-543 treatment, the blind will be maintained and individual patient treatment modifications will not be disclosed.

9.2.1. Dose Interruption Safety Criteria and Management

Patients who experience hematologic adverse events as described in Table 3 or adverse events that may reflect an unfavorable risk-benefit profile may have their dose interrupted at the discretion of the Investigator. The Medical Monitor should be consulted whenever possible prior to decisions for dose interruption.

Patients who require a dose interruption lasting more than 21 days will be discontinued from the study.

Patients who are discontinued from the study should undergo an Early Termination Visit and subsequent Safety Follow-up Visit as appropriate per Section 8.3.1 Patient Withdrawal Procedures, and associated adverse events followed as described in Section 11 Adverse Events.

In each cohort, hematology parameters will be assessed every 2 weeks for the first 8 weeks of the Treatment Period, and every 4 weeks thereafter for the remainder of each Period. Prior to dose interruption, hematology parameters should be confirmed with repeat testing at an Unscheduled Visit within 72 hours, except in severe cases (i.e.: neutrophil counts below 0.5 x 10^9/L) where immediate interruption of dosing is necessary for the safety of the patient. **Blood draws confirming dose interruption criteria should occur prior to the first daily dose on the day of draw.**

Dose interruption requirements for hematologic abnormalities are provided below. However, less significant changes may warrant clinical intervention and the Investigator should use his/her best clinical judgment when considering a dose interruption whether for singular or aggregate hematology results above the limits provided in Table 3, or for other clinical signs, symptoms, or considerations that suggest dose interruption is in the best interest of the patient.

Table 3: Selected Hematologic Thresholds for Dose Interruption

Neutrophil Count	**Dose Adjustment**
Between 0.5 to 1 x 10^9/L (Grade 3)	Interrupt dose until recovered to greater than 1.5 x 10^9/L and resume dosing at previous dose
Less than 0.5 x 10^9/L (Grade 4)	Severe case: Interrupt dose immediately and repeat CBC with differential within 72 hours. Recommend hematology consult and contact medical monitor. Patient discontinuation from the study should occur upon repeat confirmation
Female Hemoglobin Level	**Dose Adjustment**
Less than 10 g/dL	Interrupt dose until recovered to greater than 11.0 g/dL and resume dosing at previous dose
Male Hemoglobin Level	**Dose Adjustment**
Less than 11.5 g/dL	Interrupt dose until recovered to greater than 12.5 g/dL and resume dosing at previous dose
Platelet Count	**Dose Adjustment**
Less than 75 x 10^9/L	Interrupt dose until recovered to greater than 120 x 10^9/L and resume dosing at previous dose

Upon dose interruption, the parameters that triggered the interruption should be monitored at least weekly until either: 1) recovery above the threshold for dosing resumption is achieved, or 2)

the allowable 21-day dose interruption period has elapsed. In the case of severe neutropenia (neutrophil counts less than 0.5 x 10^9/L) patients should discontinue the study and receive instructions to seek medical help if they develop fever or signs of infection. Patients who discontinue the study due to lack of acceptable recovery of parameters within the 21-day dose interruption period should continue to be monitored as appropriate through acceptable clinical resolution.

9.2.2. Pharmacokinetic Criteria for Stopping Doses

There are no pharmacokinetic criteria for stopping study drug doses.

9.3. Treatment Compliance

At each scheduled study visit after randomization, the Investigator or designee will interview the patient regarding treatment compliance and compare the number of dispensed versus returned study drug tablets. Patients should strive for 100% compliance with the daily dosing schedule. Retraining on treatment compliance should occur for patients with less than 80% compliance at any visit and the Sponsor should be notified.

9.4. Study Drug Materials and Management

Please consult the Pharmacy Manual for a complete description of the study drug and requirements for storage, handling, dispensing, accountability, returns and destruction.

9.4.1. Physical Description of Study Drug

Study drug will include CTP-543, a deuterated analog of ruxolitinib, and matching placebo. Details regarding formulation and dosage are presented in Table 4 .

Table 4: Investigational Product

	Investigational Product (CTP-543 or Placebo)
Product Name:	CTP-543 or Matching placebo
Dosage Form:	Tablet
Dosage Strength of CTP-543	4 mg, 8 mg, 12 mg
Route of Administration	Oral
Physical Description	White, capsule-shaped tablets

9.4.2. Study Drug Packaging, Labeling, and Storage

CTP-543 active and placebo tablets will be packaged and labeled by an appropriately qualified vendor. Each patient will receive a dosing card at each 4 week study visit. Details of the packaging, labeling and dispensing instructions can be found in the Pharmacy Manual.

The label(s) for the investigational product and placebo will include sponsor name, address and telephone number, the protocol number, investigational product name, dosage form, amount of investigational product per container, lot number, unique dosing card number, storage conditions, and required caution statements and/or regulatory statements, as applicable. Additional information may be included on the label as applicable per local regulations.

Adequate supplies of study drug will be provided to each site. Study drug should be stored in the original package between 15°C to 25°C (59°F to 77°F), as stated on the product label, in a secure, temperature-monitored, locked area, under the responsibility of the Investigator or other authorized individual until dispensed to the patients.

Study drug dispensed to patients should be stored in the original package at room temperature as stated on the package label. No special handling procedures are required.

9.4.3. Study Drug Preparation and Administration

No study drug preparation is required. Patients 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 should dose study drug in the clinic on all Study Visit Days after clinical laboratory blood draws are completed.

Study drug should be taken at approximately the same times each day, with water, and with or without meals. Patients should be instructed to take study drug as prescribed according to the Week, Day, and Time of day designations in the dosing card. If a dose is missed, the patient should skip the missed dose and resume dosing at the next scheduled dose. The patient should not take two doses at the same time. Deviations from prescribed dosing should be discussed at each visit for assessment of compliance and retraining when necessary.

9.4.4. Study Drug Return and Disposal

The Sponsor (or designee) will review with the Investigator and relevant site personnel the process for study treatment return, disposal, and/or destruction, including responsibilities for the site versus the Sponsor (or designee). Specific requirements for destruction or return are defined in the Pharmacy Manual.

9.4.5. Study Drug Accountability

To satisfy regulatory requirements regarding drug accountability, all study drug will be reconciled in full. The Investigator or designee must maintain accurate records of the receipt of study drug, including date received, lot number, amount received, condition of the package, and the disposition of study drug.

Current dispensing records will also be maintained, including the date and amount of medication dispensed to each individual patient. Returned study drug records will be maintained and final study drug reconciliation will also be recorded for each patient.

9.5. Concomitant Medications and Procedures

All medications, including over-the-counter therapies (e.g., vitamins, herbal, and nutritional supplements), taken at the time of the Screening Visit through the Follow-Up Visit will be recorded in the patient's source documentation and documented in the eCRF.

If taking thyroid medication, the patient must maintain thyroid stimulation hormone levels within the normal range for 6 months prior to Screening and throughout the study.

Any concomitant medication deemed necessary for the wellbeing of the subject may be given at the discretion of the Investigator. Use of medications that are prohibited per protocol will require patient withdrawal from the study.

The following treatments are not permitted during the study:

- Medications that may affect hair regrowth or immune response (such as: corticosteroids administered orally, by injection, or applied to areas of skin affected by alopecia; platelet-rich injections; topical application to affected areas of anthralin, squaric acid, diphenylcyclopropenone, or minoxidil;
- Treatment with systemic immunosuppressive medications including but not limited to methotrexate, cyclosporine, and azathioprine; chloroquine derivatives; Janus kinase inhibitors (ruxolitinib, tofacitinib, etc), etanercept; or biologics (adalimumab, atlizumab, canakinumab, certolizumab, fontolizumab, golimumab, infliximab, mepolizumab, rituximab, secukinumab, tocilizumab, ustekinumab);
- Use of strong CYP3A4 inhibitors (such as, but not limited to clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, saquinavir, telaprevir, telithromycin, voriconazole, or fluconazole) dosed for systemic exposure;
- Use of strong CYP3A4 inducers (such as, but not limited to barbiturates, carbamazepine, efavirenz, glucocorticoids, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's Wort, or troglitazone) dosed for systemic exposure.

10. STUDY ASSESSMENTS AND PROCEDURES

The schedule of assessments and procedures is presented in Table 1 and should be referenced for details regarding the collection of each assessment at each visit in the respective cohort periods.

10.1. Demographic Characteristics and Medical History

Demographic characteristics (i.e., sex, ethnic origin, 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.

Key criteria that distinguish alopecia areata from other forms of hair loss may include abrupt onset of disease, a history of recurrence and spontaneous remission, response to topical or intralesional steroid treatment, and distribution of hair loss pattern. Care must be taken during the evaluation to assess for other causes of hair loss such as trichotillomania, or scarring alopecia and other forms of non-scarring alopecia. Evidence of thinning hair should be distinguished from pattern hair loss or telogen effluvium and evidence of inflammation should be investigated to rule out infection, as appropriate.

Thorough medical history, including current medications, nail and facial hair involvement, co-morbidities, serious infection history and exposure risk, including HIV, as well as history or vaccination against herpes zoster will be collected at the Screening Visit, and at the Randomization Visit on Day 1 for each cohort.

Medical history should be thoroughly probed for potential exposure to serious infections such as HIV, history or vaccination against herpes zoster or other recent live virus vaccinations, as well as cancer risk due to the potential immunosuppressive properties of CTP-543 and known adverse events associated with JAK inhibitors.

10.2. Severity of Alopecia Tool (SALT)

The SALT score was introduced as part of investigative guidelines published by the National Alopecia Areata Foundation [Olsen, 2004]. 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. The SALT assessment will occur via live examination of the patient during clinic visits.

SALT will be used to determine efficacy for the study. To reduce variability, one rater should perform the SALT assessment for the patient for the duration of the study. All investigators using the SALT should be trained prior to use. Please consult the associated Site Operations Manual

for additional details regarding SALT scoring and training requirements for this study. An example of the SALT assessment tool is provided in Appendix 17.1.

10.3. Photographs

Photographs will be taken of each patient's scalp to provide visual support of Baseline assessment of SALT as well as potential changes in SALT scores throughout the study. No formal analyses of photographs will occur. Scalp photographs will correspond to the 4 defined quadrants of the SALT assessment and will be taken when SALT assessments are performed.

For those patients with eye and nail involvement in their alopecia areata phenotype, a photograph of the eyes and hands for eyelash/eyebrow and nail involvement, respectively, will be taken to document potential changes throughout the study compared to Baseline. No formal analyses of photographs will occur.

10.4. Global Impression Scales

The Global Impression Scales are measures commonly used in clinical trials to allow integration of several sources of information into a single rating of the patient's condition. The Global Impression Scales employ a 7-point Likert scale measuring either disease state severity or improvement after treatment. The alopecia areata assessments should consider the condition of the patient at the time of the assessment compared to Baseline.

In this study, the Global Impression Scale of Improvement will be performed by both the clinician and the patient at selected times during the study as indicated in Table 1.

10.4.1. 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 representing "Very Much Worse" to "Very Much Improved". To reduce variability, one rater should perform the CGI-I assessment for the patient for the duration of the study. An example of the CGI-I is provided in Appendix 17.2.1.

10.4.2. 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 representing "Very Much Worse" to "Very Much Improved". An example of the PGI-I is provided in Appendix 17.2.2.

10.5. 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. An example of the AASIS is provided in Appendix 17.3.1.

In addition to the AASIS, exploratory questions will be used to attempt to define clinically meaningful outcomes for patients with alopecia areata. The exploratory questions are provided in Appendix Section 17.3.2.

10.6. Visual Analog Scale (VAS)

The visual analog scale is a scale of continuous measure initially developed for pain that has been used in a variety of clinical settings where the endpoint of interest is based on a subjective perception. The visual analog scale 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.

10.6.1. 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. To reduce variability, one rater should perform the VAS-S assessment for the patient for the duration of the study. An example of the clinician VAS-S is provided in Appendix 17.4.1.

10.6.2. Patient VAS of Severity (VAS-S)

As specified in the Schedule of Events, 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. An example of the patient VAS-S is provided in Appendix 17.4.2.

10.7. Pharmacokinetic Assessments

Whole blood (4 mL each) will be collected in K_2EDTA vacutainer collection tubes at the following time points to evaluate plasma concentrations of CTP-543 and metabolites.

- Day 1 and Week 4: 2 samples at each visit; 1 sample pre-dose, and 1 sample post-dose at the end of the visit
- Week 2: 1 sample pre-dose with the safety lab draw
- Weeks 8, 24: 1 sample post-dose at the end of the visit

The exact time of blood collection as well as the exact time of the preceding dose will be recorded. The Week 4 pre-dose draw is the time point intended to examine steady-state trough levels of study drug, and therefore the preceding dose will not be observed in the clinic. To document the preceding dose time, patients should be instructed to record the last dosing time prior to the Week 4 Visit in their dosing card. All attempts to adhere to the pharmacokinetic schedule should be made. However, the inability to follow the schedule or to obtain/process a sample will not be considered a protocol deviation.

Instructions for harvesting and preparing plasma samples prior to freezing and additional procedures for blood sample collection will be provided in separate study laboratory manual.

10.8. Vital Signs, Weight, and Height

Vital signs will be measured after the patient has been in a supine or semi-supine position for at least 5 minutes and will include blood pressure, pulse rate, respiratory rate, and oral temperature.

Weight will be measured per institution standard of care. Patients should wear light clothing and remove his/her shoes before weight is measured. Height will be measured per institution standard of care, after the patient has removed his/her shoes. Height will only be measured at the Screening Visit. Weight and vital signs will be measured at each study visit according to the Schedule of Events. Weight and height will be used to calculate the patient's body mass index at Screening. Weight and height will be converted as needed to kilograms and centimeters, respectively, prior to statistical analyses.

10.9. Physical Examination

A complete physical examination will include an examination of all major organ systems, with an emphasis on assessing for active signs and symptoms of infection including tuberculosis, and will be performed as indicated in the Schedule of Events. Brief physical examinations including abdominal palpation, and head, eyes, ears, nose and throat assessment in addition to assessing for active signs and symptoms of infection, including tuberculosis, will be performed at all other intermediate visits as specified in Table 1. Patients should be instructed to notify the clinic of any signs of infection between visits for appropriate monitoring and follow-up.

10.10. Electrocardiogram

Twelve-lead electrocardiograms will be performed after the patient has rested in a supine or semi-supine position for at least 5 minutes. Individual parameters including heart rate, PR, QT, QTcF, QRS, and RR intervals will be collected. Repeat electrocardiograms (if deemed necessary) should be performed at least 5 minutes apart. The Investigator should indicate review of the electrocardiogram reports throughout the study by signing and dating each report.

10.11. Clinical Laboratory Assessments

Clinical laboratory assessments are presented in Table 5. Clinical laboratory samples should be collected at the beginning of each clinic visit and just prior to a dose on all Study Visit Days.

The results of clinical laboratory tests conducted at the Screening Visit (and prior to dosing) must be assessed by the Investigator to determine each patient's eligibility for participation in the study. The Investigator should indicate review of the laboratory reports throughout the study by signing and dating each report.

All clinical laboratory results that fall outside the reference range will be interpreted by the Investigator as Abnormal, not clinically significant, or Abnormal, clinically significant. Laboratory results deemed Abnormal, clinically significant will be recorded as an adverse event in the eCRF and should be fully investigated and repeated for verification. Clinically significant laboratory abnormalities indicative of hematologic or other effects requiring intervention should be discussed with the Medical Monitor. Additional tests and evaluations required to establish the significance or etiology of a clinically significant abnormal result or to monitor the course of an adverse event should be obtained when clinically indicated. Whenever possible, the etiology of the clinically significant abnormal findings will be documented on the eCRF.

Any significant laboratory abnormalities that are either serious or unexpected will be promptly reported to the Sponsor. Any additional relevant laboratory results obtained by the Investigator during the course of this study will be reported to the Sponsor or designee.

Table 5: Clinical Laboratory Assessments

Hematology	Chemistry	Serum Pregnancy
Complete blood count Absolute neutrophil count Absolute eosinophil count Platelet count White blood cell count with differential Absolute reticulocyte count Hemoglobin A1c	Alanine aminotransaminase Albumin Alkaline phosphatase Amylase Aspartate aminotransaminase Total bilirubin Direct bilirubin Indirect bilirubin Blood urea nitrogen Calcium Carbon dioxide Chloride Creatinine Creatine kinase Glucose Lipase Total protein Phosphorus Potassium Sodium Uric Acid	Human chorionic gonadotropin (females of childbearing potential only)
Serology	**Lipids**	**Other**
Hepatitis B virus Hepatitis C virus	Total cholesterol Low-density lipoprotein High-density lipoprotein Triglycerides	Tuberculosis Thyroid stimulating hormone

10.12. Pharmacodynamic Assessments

Blood samples will be collected for potential future exploration of the pharmacodynamic properties associated with CTP-543 dosing. Two milliliters of whole blood will be collected into a PAXgene® Blood RNA tube and 4 milliliters of whole blood will be collected in a K_2EDTA vacutainer collection tube. Pharmacodynamic samples will be collected at the following time points:

- Day 1: pre-dose
- Week 2: pre-dose with the safety lab draw
- Weeks 4, 8, 24: post-dose at the end of the visit

Collection of samples should be in conjunction with safety or pharmacokinetic blood draws when possible. All attempts to adhere to the pharmacodynamic schedule should be made. However, the inability to follow the schedule or to obtain/process a sample will not be considered a protocol deviation.

Instructions for harvesting and preparing samples prior to storing or freezing, and additional procedures for blood sample collection will be provided in a separate study laboratory manual.

Information obtained from these potential analyses would be limited to JAK-signaling related investigations only and would not be used for diagnostic purposes, generation of cell lines, or commercial uses, nor would results of individual patients be disclosed. However, results of the

blinded pharmacodynamic studies data may be presented or published in scientific or medical settings.

10.13. Unscheduled Visit

In addition to regularly scheduled protocol visits, an Unscheduled Visit may be conducted to ensure appropriate safety monitoring or follow-up of the patient, at the discretion of the Investigator. For example, an Unscheduled Visit may be scheduled to monitor potential or actual clinically meaningful safety laboratory results, for confirming hematology results to support dose interruption or resumption of dosing thereafter, for suspicion of tuberculosis, or for other clinical signs, symptoms, or considerations that warrant additional safety follow-up. Only those criteria requiring additional monitoring should be performed at an Unscheduled Visit. An Unscheduled Visit will not replace regularly scheduled protocol visits.

11. ADVERSE EVENTS

11.1.1. Definition of Adverse Event

An adverse event is any untoward medical occurrence that may appear or worsen in a patient 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 patient's health, including laboratory test values, regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an adverse event. A diagnosis or syndrome should be recorded on the adverse event 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 adverse event.

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

An adverse event reported after informed consent, but before the first dose of study drug (ie, Day 1), will be considered a pretreatment adverse event and will be captured on the eCRF. Adverse events will be considered treatment-emergent if the onset is after the first dose of study drug.

An abnormal laboratory value is considered to be an adverse event if the abnormality:

- results in discontinuation from the study;
- is judged by the Investigator to be of significant clinical importance requiring treatment, modification/interruption of investigational product dose, or any other therapeutic intervention

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the adverse event eCRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the adverse event. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (e.g., record thrombocytopenia rather than decreased platelets).

11.1.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all adverse events as to seriousness, severity/intensity, relationship to study drug, duration, action taken, and outcome.

11.1.2.1. Serious Adverse Event

A serious adverse event is an adverse event, as per Title 21 CFR 312.32 and ICH E2A.II.B 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 patient 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 patient's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect; or
- Constitutes an important medical event that may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed above.

Important medical events are defined as those occurrences that may not be immediately life-threatening or result in death, hospitalization, or disability, but may jeopardize the patient or require medical or surgical intervention to prevent one of the other outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization.

Events **not considered** to be serious adverse events are hospitalizations for:

- A procedure for protocol/disease-related investigations (e.g., sampling for laboratory, pharmacokinetic, and pharmacodynamic tests). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable serious adverse event.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an adverse event.
- A procedure that is planned (i.e., planned prior to the starting of treatment on study); must be documented in the source document and the eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable serious adverse event.
- An elective treatment of or an elective procedure for a pre-existing medical condition that does not worsen.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an adverse event is considered serious, the adverse event eCRF must be completed.

For each serious adverse event, the Investigator will provide information on severity, start and stop dates, relationship to investigational product, action taken regarding investigational product, and outcome.

Queries pertaining to serious adverse events will be handled through the electronic data capture system or other appropriate means. Urgent queries (e.g., missing causality assessment) may be handled by telephone.

11.1.2.2. Severity/Intensity

For both adverse events and serious adverse events, the Investigator must assess the severity/intensity of the event.

The National Cancer Institute-Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 should be used to grade the severity/intensity of all events. These criteria will be provided in the Site Operations Manual. If a CTCAE criterion does not exist, the Investigator should grade the severity according to the following criteria:

- Grade 1 (mild): does not interfere with the patient's usual function
- Grade 2 (moderate): interferes to some extent with patient's usual function
- Grade 3 (severe): interferes significantly with patient's usual function
- Grade 4 (life-threatening): results in a threat to life or in an incapacitating disability
- Grade 5 (death): results in death

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is not the same as "serious" which is based on patient/event outcome or action criteria associated with events that pose a threat to a patient's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

11.1.2.3. Relationship to Study Drug

Relationship should be assessed and provided for every adverse event/serious adverse event based on currently available information. Relationship is to be reassessed and provided as additional information becomes available. Adverse events will be classified by the Investigator as follows:

Definitely Related: There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The event resolves or improves upon withdrawal of drug (de-challenge). The event would be considered as definitely related to the study drug upon results of a positive re-challenge procedure.

Probably Related: There is evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors that may have contributed to the event (e.g., the patient's clinical condition, other concurrent disease, concomitant medications or events) is unlikely, and the event follows a clinically reasonable response upon withdrawal of drug (de-challenge).

Possibly Related: There is evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the study drug). However, the influence of other factors may have contributed to the event (e.g., the patient's clinical condition, other concurrent disease, concomitant medications or events).

Unlikely Related: A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did

not occur within a reasonable time after administration of the trial medication) and in which other drugs or concurrent or underlying disease provide plausible explanations (e.g., the patient's clinical condition, other concomitant treatments).

Not related: The adverse event is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

11.1.2.4. Duration

For all adverse events whether or not considered serious, the Investigator will provide a record of the start and stop dates of the event. Every effort should be made to resolve all adverse events with continued follow-up with the patient until appropriate resolution can be achieved. If an event is unresolved at the end of the study it will be recorded as ongoing.

11.1.2.5. Action Taken

The Investigator will record the action taken with investigational product as a result of an adverse event or serious adverse event on the eCRF, as applicable (e.g., discontinuation, or interruption of investigational product, as appropriate) and record if concomitant and/or additional treatments were given for the event.

11.1.2.6. Outcome

The Investigator will record the outcome of adverse events on the eCRF, as applicable (e.g., recovered, recovered with sequelae, not recovered, or death (due to the adverse event).

11.1.3. Follow-Up

Adverse events assessed as not related to study drug, including clinically significant laboratory tests, electrocardiograms, or physical examination findings, must be followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the final study visit occurs, whichever comes first.

Adverse events assessed as related to study drug and serious adverse events will be followed for as long as necessary to adequately evaluate the patient's safety, or until the event stabilizes, is otherwise explained, death occurs, or the patient is lost to follow up. If resolved, a resolution date should be provided. The Investigator is responsible for ensuring that follow-up includes any supplemental investigations indicated to elucidate the nature and/or causality of the adverse event. This may include additional clinical laboratory testing or investigations, examinations, or consultation with other health care professionals as is practical.

11.1.4. Pregnancy

The Sponsor must be informed within 24 hours upon learning that a patient, or male patient's partner, has become pregnant any time after the first dose of study drug until 30 days after the last dose of study drug. The Pregnancy Notification eCRF should be used to report the pregnancy to the Sponsor or its designee. Patient pregnancies (or pregnancy of a male patient's partner) must be followed until termination of pregnancy or the birth of the child. The Pregnancy Outcome eCRF should be used to report information regarding the status of the infant.

If a female partner of a male patient taking investigational product becomes pregnant, the male patient taking the investigational product should notify the Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately.

11.1.5. Recording Adverse Events

All adverse events (regardless of seriousness or relationship to study drug) including those from the time informed consent is obtained through to the final study visit are to be recorded in the eCRF. Each individual adverse event is to be listed as a separate entry. The Investigator will provide information about dates of onset and resolution, seriousness, severity, action(s) taken, outcome, and relationship to the study drug. All adverse events should be documented in the patient's source documents.

11.1.6. Reporting Adverse Events

The Investigator must report to Sponsor or its designee all adverse events that occur during the study from the time written informed consent is given until the final study visit or early termination, regardless of their relationship to the study drug. Serious adverse events and pregnancies will be reported from the time written informed consent is given through 30 days beyond the last dose of study drug.

11.1.6.1. Reporting Serious Adverse Events

The Investigator is required to notify the Sponsor, and the Sponsor's designated Drug Safety Unit within 24 hours after becoming aware of the occurrence of a serious adverse event. All serious adverse events will be reported through completion of the adverse event eCRF. The Investigator will be responsible for reporting serious adverse events to the IRB.

Medical Monitor and Emergency Contact Information:

[redacted], MD
Telephone: [redacted]
Facsimile: [redacted]
Email: [redacted] AND [redacted]

Serious Adverse Event Reporting Contact Information:

[redacted] Safety Group Email: [redacted]
Serious Adverse Event Help Line: [redacted]
Serious Adverse Event Fax Line: [redacted]

If an Investigator becomes aware of a serious adverse event within 30 days after the last dose of study drug and it is considered by him/her to be caused by the study drug with a reasonable possibility, the event must be documented and reported through completion of the adverse event eCRF.

11.1.6.2. Reporting Urgent Safety Issues

If the study site staff becomes aware of an actual or potential urgent safety issue, then the Sponsor and Sponsor's designee (Medical Monitor) must be immediately contacted so that appropriate urgent safety measures can be agreed upon. An urgent safety issue is defined as:

- An immediate hazard to the health or safety of patients participating in a clinical study
- A serious risk to human health or potentially a serious risk to human health

An urgent safety issue may include: (1) issues with an investigational drug or comparators; (2) study procedures; (3) inter-current illness (including pandemic infections); (4) concomitant medications; (5) concurrent medical conditions; or (6) any other issues related to the safe conduct of the study or that pose a risk to study patients.

In exceptional circumstances of imminent hazard and in order to safeguard the health or safety of individuals, the Investigators may take urgent safety measures before informing the Sponsor, but the Sponsor must be informed immediately after the hazard has resolved.

12. STATISTICAL METHODS

12.1. Sample Size Rationale

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-square 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 as of Amendment 4, this randomization scheme is expected to provide a similar number of patients in the CTP-543 and the pooled placebo arms. Thus, power calculations for the comparison to placebo are based on a 1:1 treatment ratio for the comparison of 12 mg to placebo. 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-square test. Approximately 150 patients will be randomized in order to provide 120 patients who complete treatment.

12.2. Endpoints

12.2.1. Efficacy

The primary efficacy endpoint will be the proportion of patients achieving at least a 50% relative reduction in SALT score from baseline at Week 24.

Exploratory efficacy endpoints include:

- Relative change in SALT scores from baseline (mean and percent) at Weeks:
  - 4, 8, 12, 16, 20, and 24 in the Blinded Treatment Period
- Relative 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 using the clinician rated 7-point Likert scale CGI-I at Weeks 12 and 24;
- Relative 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 using the patient rated 7-point Likert scale PGI-I at Weeks 12 and 24;
- Patient-reported outcomes: Changes in symptoms from baseline as measured by AASIS and exploratory questions at Week 24

Additional exploratory statistical analyses to further assess for treatment effect will be outlined in the Statistical Analysis Plan finalized prior to database lock for the Primary Efficacy Analysis.

12.2.2. Pharmacokinetic

Pharmacokinetic samples will be collected at the following time points to evaluate plasma concentrations of CTP-543 and metabolites.

- Day 1 and Week 4: 2 samples at each visit; 1 sample pre-dose, and 1 sample post-dose at the end of the visit
- Week 2: 1 sample with the safety lab draw
- Weeks 8, 24: 1 sample post-dose at the end of the visit

12.2.3. Safety

Safety and tolerability of CTP-543 will be assessed by evaluating adverse events, vital signs, concomitant medications, clinical laboratory, and electrocardiogram results, as well as physical examinations.

12.3. Analysis Populations

12.3.1. Treatment Period

The Efficacy Population will include all patients who receive study drug and have at least 1 post-treatment SALT assessment during the Treatment Period.

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.

The Safety Population will include all patients who receive study drug during the Treatment Period.

The Per Protocol Population will include all subjects in the Efficacy Population who were dosed according to protocol and have no major protocol deviations.

12.4. Analyses

For the Treatment Period, data will be summarized by active treatment by cohort dose level versus placebo-treated patients (i.e., by treatment group). The placebo patients from the 3 cohorts will be combined for statistical comparisons to each active treatment group. All data for analysis will be listed by patient.

Continuous measures will be summarized descriptively (mean, standard deviation, median, minimum value, and maximum value) and categorical measures will be presented as number and percentage.

Additional details for statistical methods will be provided in the Statistical Analysis Plan.

12.4.1. Disposition and Baseline Characteristics

Disposition will be summarized by randomized treatment group. The number and percentage of patients, who are randomized, treated, prematurely discontinued, and complete the study will be summarized.

Baseline characteristics will be summarized by treatment group.

The number of patients in each cohort's treatment group will be summarized for each investigative site for the Treatment Period. Medical history will be coded with the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Concomitant medications will be summarized by World Health Organization Drug Dictionary Anatomical-Therapeutic-Chemical classification and preferred term.

12.4.2. Efficacy

All statistical tests will be 2-sided with a significance value of 0.05. Testing will be performed only for the Treatment Period.

An interim analysis of safety and efficacy will be performed when all patients in the 4 mg and the 8 mg cohorts have completed Week 24. The final efficacy analysis will be conducted when all patients in the 12 mg cohort have completed Week 24.

Primary Efficacy Endpoint

The primary efficacy endpoint will be the proportion of patients achieving at least a 50% relative reduction in SALT score from baseline at Week 24. Pairwise treatment group differences from placebo will be assessed with the Cochran-Mantel-Haenszel test using the alopecia areata subtype as the stratification factor.

There will be no adjustment for multiple treatment group comparisons in this dose-ranging Phase 2 study.

The handling of missing data will be summarized in the Statistical Analysis Plan.

Exploratory Efficacy Endpoints

Treatment differences for 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) model. The model will include fixed factors for treatment group, study visit, and treatment by study visit interaction, with baseline SALT score as a covariate. An unstructured variance-covariance matrix will be used.

Treatment differences for the Global Impression of Improvement and VAS scales will be assessed with the Cochran-Mantel-Haenszel test using the alopecia areata subtype as the stratification factor.

Change in symptoms as measured by AASIS and the exploratory questions from baseline to Week 24 will be assessed with the analysis of covariance with a fixed factor for treatment and baseline value as a covariate.

12.4.3. Pharmacokinetics

The collection status of pharmacokinetic samples will be listed for each visit with scheduled pharmacokinetic sampling. Plasma concentrations of study drug may be summarized separately, as appropriate.

12.4.4. Study Drug Exposure

Study drug exposure will be summarized for each cohort's Treatment Period. The number of days on which study drug was dosed will be summarized for each treatment group.

The total number of days on study drug will exclude dose interruptions. The total number of days of exposure to CTP-543 will be summarized with the mean, standard deviation, median, minimum, and maximum number of days on the dose. Drug compliance will also be summarized.

12.4.5. Pharmacodynamics

The collection status of pharmacodynamic samples will be listed for each visit with scheduled pharmacodynamic sampling.

12.4.6. Safety

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.

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.

Laboratory values will be converted to the project-defined unit of measurement, as applicable, before analysis. Abnormal, clinically significant laboratory values will be reported and summarized as adverse events.

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 (TEAEs) will be defined as any adverse event that occurs after administration of the first dose of study drug until Week 24 or the Early Termination Visit. 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.

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

Proportions for adverse events that are gender-specific (e.g., dysmenorrhea) will be based on the number of patients from that gender.

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

- By system organ class and preferred term
- By severity/intensity, system organ class, and preferred term
- By relationship to study drug, system organ class, and preferred term
- Serious adverse events by system organ class and preferred term

- Serious adverse events by relationship to study drug, system organ class, and preferred term
- Adverse events resulting in discontinuation of study drug by system organ class and preferred term
- Adverse events that result in study drug dose interruption by system organ class and preferred term

By-patient listings will be provided for any deaths, serious adverse events, and adverse events leading to discontinuation of treatment. Treatment-emergent adverse events that result in dose interruption will also be identified.

Additionally, treatment-emergent adverse events 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.

Clinical Laboratory

Clinical laboratory variables will be presented in 3 ways. First, change from Baseline to each scheduled assessment will be summarized descriptively. Baseline will be defined as the laboratory 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.

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 CTCAE criteria. Treatment-emergent PCS laboratory values are those in which the baseline value is not PCS and the post-baseline value is PCS. The number and percentage of patients with treatment-emergent PCS laboratory values will be summarized by treatment group for each clinical laboratory variable.

Third, the number and percentage of patients with Abnormal, clinically significant laboratory values (per Investigator judgment) will be summarized by treatment group for each clinical laboratory variable.

Vital Signs

The mean change from baseline to each scheduled assessment will be summarized descriptively by treatment group for each vital sign variable specified in this protocol.

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.

Electrocardiogram

The change from baseline in electrocardiogram intervals (PR, QT, QTcF, QRS, and RR) to each scheduled assessment will be summarized descriptively by treatment group.

13. REGULATORY CONSIDERATIONS

It is the responsibility of the clinical site and staff to notify the Sponsor and Sponsor's designee immediately upon becoming aware of a serious breach of GCP or of the study protocol. It is the responsibility of the Sponsor or its designee to notify appropriate regulatory authorities of any serious breach which is likely to effect, to a significant degree, the safety or mental integrity of the patients of the study or the scientific value of the study.

13.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Sponsor, its authorized representative, and Investigator abide by GCP, as described in ICH Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from the IRB prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

13.2. Sponsor's Responsibilities

The Sponsor or its designee is responsible for the following:

- Selecting qualified Investigators
- Providing Investigators with the information they need to properly conduct an investigation
- Ensuring proper monitoring of the investigation
- Ensuring that the applicable regulatory authorities, and all participating Investigators are properly informed of significant new information regarding adverse events or risks associated with the medication being studied

Before an investigational site can enter a patient into the study, a representative of the Sponsor will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the Investigator.

During the study, a monitor from Concert Pharmaceuticals or its representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed

- Perform source data verification. This includes a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (e.g., clinic charts).
- Record and report any protocol deviations.
- Confirm adverse events and serious adverse events have been properly documented on eCRFs and confirm any serious adverse events have been forwarded to the Sponsor and those serious adverse events that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

As the Sponsor, Concert Pharmaceuticals has delegated some responsibilities to a designee, or Contract Research Organization.

13.3. Investigator's Responsibilities

Investigator responsibilities are set out in the ICH Guideline for GCP and in the local regulations. Each Investigator participating in this study is required to maintain complete and accurate study documentation in compliance with current GCP standards and all applicable local regulations related to the conduct of a clinical study.

The Principal Investigator will ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, the study drug, and their study-related duties and functions. The Principal Investigator will maintain a list of sub-Investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties. Individuals ineligible from conducting or working on clinical studies, including those ineligible as a result of debarment under the Generic Drug Enforcement Act of 1992, will not be allowed to conduct or work on studies sponsored by Concert Pharmaceuticals. The Investigator is required to immediately disclose to the Sponsor in writing, if any person involved in the conduct of the study is debarred pursuant to a hearing by the FDA under this anti-fraud law, or if any proceeding for debarment is pending, or is (to the best of the Investigator's knowledge) threatened.

The Investigator is responsible for keeping a record of all patients who sign an informed consent document and are screened for entry into the study. Patients who fail screening must have the reason(s) recorded in the patient's source documents.

The Investigator should inform the IRB of any event likely to affect the safety of patients or the continued conduct of the study, in particular any change in safety. Additionally, all updates to the Investigator's Brochure will be sent to the IRB. A progress report will be sent to the IRB and the protocol will be reviewed annually (e.g., re-approved) or more frequently, as required by the IRB or local regulations.

The Investigator will maintain a copy of all correspondence with the IRB, including copies of approved documents. The Investigator will also maintain a copy of the IRB membership list with occupation and qualification (or a statement confirming compliance with GCP requirements for committee composition).

The Investigator will notify the IRB of the conclusion of the clinical study within 1 month of completion or termination of the study. The final report sent to the IRB will also be sent to the Sponsor along with the completed electronic case report forms (eCRFs) and all necessary regulatory documents, thereby fulfilling the Investigator's regulatory responsibility.

The Investigator, or a designated member of the Investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to patient records (e.g., medical records, office charts, hospital charts, and study-related charts) for source data verification. The Investigator must ensure timely and accurate completion of eCRFs and queries.

13.4. Protocol Amendments

Any permanent change to the protocol, whether it is an overall change or a change for specific study center(s), must be handled as a protocol amendment. All amendments to the protocol will be written by the Sponsor. The Investigator will not make any changes to this protocol without prior written consent from the Sponsor and subsequent approval by the IRB. Except for administrative amendments, Investigators must await IRB approval of protocol amendments before implementing the change(s). The Sponsor will ensure submission of any protocol amendments to the appropriate regulatory agencies.

Administrative amendments are defined as having no effect on the safety of the research subjects, scope of the investigation, or quality of the study. However, a protocol change intended to eliminate an apparent immediate hazard to patients should be implemented immediately, and the IRB notified within 5 days.

When, in the judgment of the chairman of the local IRB, the Investigators, and/or the Sponsor, the amendment to the protocol substantially alters the study design and/or increases the potential risk to the patient, the currently approved written ICF will require similar modification. In such cases, repeat informed consent will be obtained from patients enrolled in the study before continued participation under the new amendment.

13.5. Audits and Inspections

The Sponsor's Quality Assurance Unit (or representative) may conduct audits at the study site(s). Audits will include, but are not limited to: drug supply, presence of required documents, the informed consent process, laboratory specimen processing, and comparison of eCRFs with source documents. The Investigator agrees to cooperate with audits conducted at a reasonable time and in a reasonable manner.

Regulatory authorities worldwide may also audit the Investigator during or after the study. The Investigator should contact the Sponsor immediately if this occurs, and must fully cooperate with the audits conducted at a reasonable time in a reasonable manner.

The Investigator is required to make all study documentation promptly available for inspection, review or audit at the study site upon request by Sponsor, its representatives, or any appropriate regulatory agencies.

13.6. Quality Control and Quality Assurance

All aspects of the study will be carefully monitored by the Sponsor or its authorized representative for compliance with applicable government regulations with respect to current GCP and standard operating procedures.

A quality control and quality assurance plan addressing aspects of the study that may impact data integrity or the protection of human subjects may be instituted for this study. All audit findings will be summarized and placed on file with appropriate documentation of response/resolution.

14. DATA HANDLING AND RECORDKEEPING

14.1. Confidentiality

All information disclosed or provided by the Sponsor (or designee), or generated or produced during the study including, but not limited to, the protocol, the eCRFs, the Investigator's Brochure, and the results obtained during the course of the study, are confidential. The Investigator or any person under his/her authority agrees to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

Submission of this protocol and any other necessary documentation to the IRB is expressly permitted, IRB members having the same obligation of confidentiality. Authorized regulatory officials and sponsor personnel (or designee) will be allowed full access to inspect and copy the records. The copied and inspected records will remain at the site and will not be transmitted or removed from the site. Study drug, patient bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the Sponsor and responsible ethics committee(s) or regulatory authorities.

Patients' names may, however, be made known to a regulatory agency or other authorized officials in the event of inspections. Documents containing the full name or other personally identifiable information of the patient are to remain at the site. This information will not be transferred to the Sponsor nor be contained in regulatory filings.

14.2. Patient Data Protection

Prior to any testing under this protocol, including screening tests and assessments, candidates must also provide all authorizations required by local law (e.g., protected health information authorization).

Patients will be identified only by unique patient numbers in eCRFs and other datasets generated for this study. The patient will not be identified by name in the eCRF, in any study samples or study reports. All data generated in this study is for research purposes only. The Sponsor, its partner(s) and designee(s), and various government health agencies may inspect the records of this study. Every effort will be made to keep the patient's personal medical data confidential.

The Sponsor will protect individual patient information to the fullest extent possible during this study. At no time will a patient become identified in any publication or presentation. However, the patient may have to become identified in the event of a regulatory authority audit or inspection in order to verify the accuracy of the data. Access to patient information is at the discretion of the Sponsor and cannot occur prior to database lock or other specified events as determined solely by the discretion of the Sponsor.

14.3. Data Collection

All data obtained for analysis in the clinical study described in this protocol will use an electronic data capture system. Data reported in the eCRFs should be consistent with and substantiated by the patient's medical record and original source documents. Any discrepancies must be explained.

Prior to the start of the study, the Principal Investigator will complete a Delegation of Authority form (Site Signature and Delegation Log), showing the signatures and handwritten initials of all

individuals and the delegation of responsibilities, such as identifying those individuals who are authorized to make or change entries on eCRFs.

14.4. Case Report Form Completion

Data within the eCRF will be monitored by a Clinical Research Associate according to the Monitoring Plan. Queries will be generated based on discrepancies found while monitoring. Site personnel will review and respond to these queries appropriately. Additionally, the Sponsor's designee and the Sponsor may periodically perform aggregate data reviews, which could result in queries being generated for site personnel resolution. The completed eCRF for each patient must be signed and dated by the Principal Investigator to signify that the Principal Investigator has reviewed the eCRF and certifies it to be complete and accurate.

14.5. Database Management, Data Clarification, and Quality Assurance

The Sponsor's designee (i.e., a designated Contract Research Organization) will be responsible for data management. Data Management will develop a Data Management Plan (DMP) document, and provide it to the Sponsor for approval. The DMP document will define all activities in the data collection and cleaning process. The detailed DMP will be based on the protocol, work scope, contract, analysis plans, data-flows, eCRFs, data cleaning procedures, other supporting documents, and data management standards and practices.

The programmed data validations will be run to check for database completeness and consistency, and queries will be generated upon data entry or via review by a Clinical Data Manager after entry. The sites will respond to the data queries in a timely manner.

Quality control procedures will be conducted prior to database lock according to the designated Contract Research Organization standard operating procedures.

When the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time will only be made by joint written agreement between the Sponsor, Statistician, Data Manager, and Quality Assurance Auditor according to designated standard operating procedures of the Contract Research Organization.

14.6. Inspection of Records

According to the ICH guidelines for GCP, the Sponsor or designee must verify data entered in the eCRF entries against the source documents. The objective of source document verification is to comply with GCP and international regulatory requirements and to reduce the risks of fraud. Source document verification means ensuring that source documents are an accurate and confirmable reflection of the patient's evaluations during participation in the study and that all relevant information recorded in the source document is accurately entered into the eCRF. All source documents should be correctly labeled and filed and associated with a single, verifiable patient.

All data required for this study should be captured in source notes. No data obtained by the Investigator or other study personnel should be captured directly in the eCRF. All source documents pertaining to this study will be maintained by the Investigator and made available for inspection by authorized persons. If electronic progress notes and other electronic source documents are not compliant with applicable regulatory guidance, they are not considered a valid source for this study. All patient progress notes must be dated and signed at the time of the visit.

The Sponsor reserves the right to terminate the study for refusal of the Investigator to supply original source documentation for this clinical study.

The Investigator will note in a source independent from the eCRF the following information:

- Information to confirm that the patient exists (e.g., initials, date of birth, and sex);
- Confirmation that the patient satisfies the inclusion/exclusion criteria;
- Confirmation that the patient is taking part in the clinical study;
- Confirmation of the informed consent process;
- Visit dates and documentation of protocol assessments and procedures;
- Information concerning all adverse events;
- Details of concomitant and investigational medications.

Source document verification is not a substitute for clinical study monitoring, the purpose of which is to ensure that the protocol has been followed correctly, the eCRF has been fully and accurately completed, source document verification has been carried out, and the study timelines and enrollment goals and requirements have been met.

14.7. Retention of Records

For investigational drug studies, clinical Investigators must retain study records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and FDA is notified.

The Investigator must maintain all study documentation as confidential, and take measures to prevent accidental or premature destruction of these documents.

The Investigator must notify the Sponsor prior to destroying any study essential documents.

If the Investigator can no longer ensure archiving, he/she shall inform the Sponsor. The relevant records shall be transferred to a mutually agreed upon designee.

15. PUBLICATION POLICY

The results of this study may be published in a medical publication, journal, or another public dissemination, or may be presented at a medical conference or used for teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations. Selection of first authorship will be based on several considerations, including, but not limited to study participation, contribution to the protocol development, and analysis and input into the manuscript, related abstracts, and presentations in a study.

16. LIST OF REFERENCES

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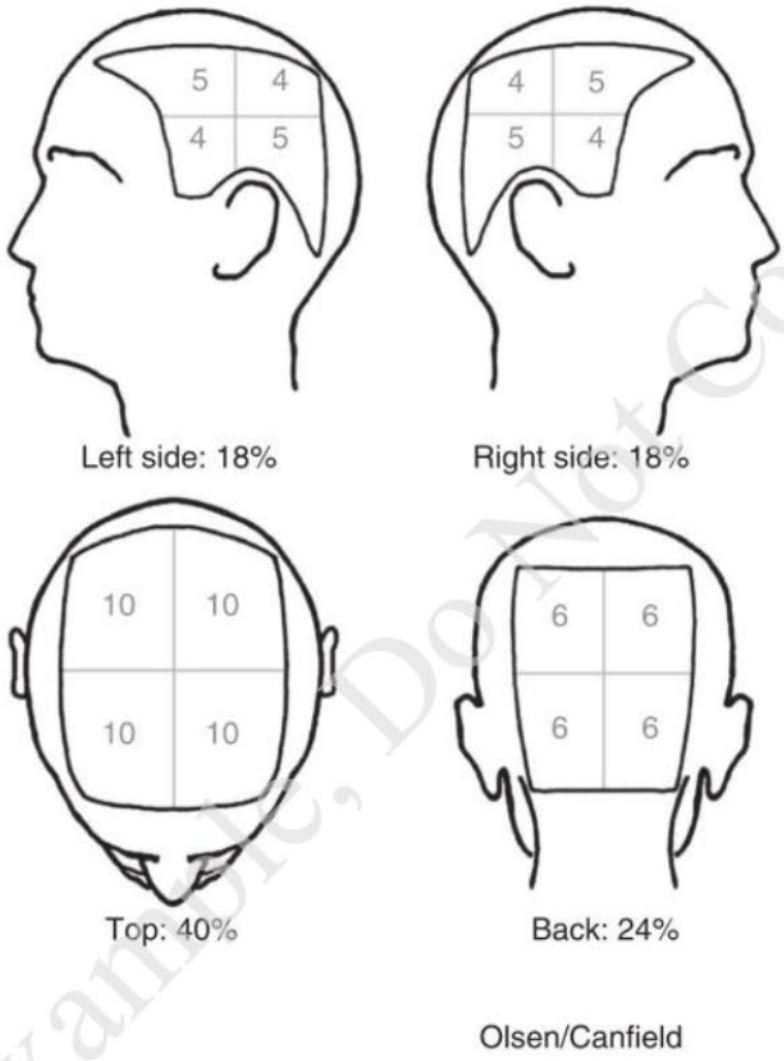
17. APPENDICES

17.1. Severity of Alopecia Tool (SALT)



Olsen/Canfield

Quadrant	Raw Score (% hair loss)
Left	_____ % loss
Right	_____ % loss
Top	_____ % loss
Back	_____ % loss

Quadrant	Quadrant Surface Area	Calculated Score (Raw Score x Surface Area %)
Left	18%	(_____ % loss) x (0.18) =
Right	18%	(_____ % loss) x (0.18) =
Top	40%	(_____ % loss) x (0.40) =
Back	24%	(_____ % loss) x (0.24) =

Total SALT Score (Sum of Calculated Scores for the 4 quadrants) =	_____

17.2. Global Impression Scales

17.2.1. Clinical Global Impression Scale of Improvement

Compared to the patient's alopecia areata prior to treatment at Baseline, the patient's current state of alopecia areata is:

1. Very Much Improved
2. Much Improved
3. Minimally Improved
4. No Change
5. Minimally Worse
6. Much Worse
7. Very Much Worse

17.2.2. Patient Global Impression Scale of Improvement

Compared to my alopecia areata prior to treatment at Baseline, my current state of alopecia areata is:

1. Very Much Improved
2. Much Improved
3. Minimally Improved
4. No Change
5. Minimally Worse
6. Much Worse
7. Very Much Worse

17.3. Patient Reported Outcomes

17.3.1. Alopecia Areata Symptom Impact Scale (AASIS)

Alopecia areata is a condition that may affect you. Please rate how severe the following symptoms of your alopecia areata have been *in the past week*. Please select one response from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not present										As bad as you can imagine
Scalp hair loss	0	1	2	3	4	5	6	7	8	9	10
Body or eye lashes hair loss	0	1	2	3	4	5	6	7	8	9	10
Tingling/numbness of the scalp	0	1	2	3	4	5	6	7	8	9	10
Itchy or painful skin	0	1	2	3	4	5	6	7	8	9	10
Irritated skin	0	1	2	3	4	5	6	7	8	9	10
Feeling anxious or worry	0	1	2	3	4	5	6	7	8	9	10
Feeling sad	0	1	2	3	4	5	6	7	8	9	10

Your alopecia areata may interfere with your daily functioning. Please rate how the following items were interfered with by alopecia areata *in the past week*. Please select one response from 0 (did not interfere) to 10 (interfered completely) for each item.

	Did not interfere										Interfered completely
Work	0	1	2	3	4	5	6	7	8	9	10
Enjoyment of life	0	1	2	3	4	5	6	7	8	9	10
Interaction with others	0	1	2	3	4	5	6	7	8	9	10
Daily activities	0	1	2	3	4	5	6	7	8	9	10
Sexual relationships	0	1	2	3	4	5	6	7	8	9	10
Quality of life	0	1	2	3	4	5	6	7	8	9	10

17.3.2. Exploratory Questions

The following questions are about the hair on your entire scalp (including the front, sides, top, and back of your head). Please answer these questions assuming that you are not wearing a wig.

Circle or mark one answer for each question.

1. Overall, how satisfied are you with your hair?	Very Satisfied ☐	Satisfied ☐	Neutral ☐	Unsatisfied ☐	Very Unsatisfied ☐
2. How satisfied are you with the fullness/thickness of your hair?	Very Satisfied ☐	Satisfied ☐	Neutral ☐	Unsatisfied ☐	Very Unsatisfied ☐
3. How satisfied are you with the amount of hair on your scalp?	Very Satisfied ☐	Satisfied ☐	Neutral ☐	Unsatisfied ☐	Very Unsatisfied ☐
4. How satisfied are you with the way your hair covers your scalp?	Very Satisfied ☐	Satisfied ☐	Neutral ☐	Unsatisfied ☐	Very Unsatisfied ☐

17.4. Visual Analog Scales

17.4.1. Clinician Visual Analog Scale of Severity

Please rate the severity of the patient's alopecia areata at this time by placing a mark on the line below.

17.4.2. Patient Visual Analog Scale of Severity

Please rate the severity of your alopecia areata at this time
by placing a mark on the line below.

Protocol CP543.2001 – Document History

The original Protocol CP543.2001, dated 14 November 2016, was amended 5 times. Study CP543.2001 was initiated under Amendment 2 (05 July 2017). No patients were enrolled under the original protocol or Amendment 1. Significant changes with each protocol amendment are presented below.

Document	Version Date	Summary of Changes and Rationales
Amendment 5	21 January 2019	• Language added for patients participating in Cohort 3 (12 mg BID) to continue receiving treatment in an open-label extension study following the treatment period.
Amendment 4	17 August 2018	• The study design was changed to add a third cohort (12 mg BID). • Added randomization ratio for additional cohort. • Additional DMC meeting added to review accumulated safety data prior to initial of additional cohort for 12 mg BID. • Interim analysis added after all patients in the 4 mg and the 8 mg cohorts completed Week 24. The final efficacy analysis would be conducted after all patients in the 12 mg cohort completed Week 24. • Revised number of patients enrolled with the addition of Cohort 3 (12 mg BID).
Amendment 3	25 September 2017	• Safety parameters revised for dose interruption and safety monitoring of symptoms of infection. • Patient withdrawal criterion revised to clarify experiences of intolerable AE. • Language added for reasons an unscheduled DMC review meeting would be scheduled to ensure appropriate safety monitoring. • Dose interruption language revised for patients who experience Grade 4 neutropenia. • Expectations for monitoring infection, and suspicion of tuberculosis added.

Amendment 2	05 July 2017	• Study design was changed to consist of up to 2 cohorts initiated sequentially in ascending dose order. A cohort within the study was divided into 3 periods: Screening, Treatment, and Post-treatment Safety Follow-up. The Dose Adjustment Period was removed. • Timing of DMC reviews of collective safety data for each cohort clarified for initial of subsequent dosing cohorts. • Randomization ratios for each treatment arm revised. • Number of patients enrolled revised. • Language surrounding dose adjustment period removed. • Statistical methods section revised to reflect adjusted power calculations.
Amendment 1	14 February 2017	• Inclusion/exclusion criteria were revised for patient safety and/or for clarification. • Additional language added for clarification surrounding the parameters for dose interruption, repeat testing for confirmation of laboratory values, and requirements for monitoring and dose resumption. • Each patient's medical history was to be thoroughly probed for vaccination against herpes zoster or other recent live virus vaccinations.
Original protocol	14 November 2016	Not applicable (N/A)