Official Title:	**A Randomized, Parallel-Group Study to Evaluate the Efficacy and Tolerability of Two Dosing Regimens of CTP-543 in Adult Patients With Moderate to Severe Alopecia Areata**
NCT Number:	NCT03811912
Document Dates:	Protocol Amendment 1: 03 January 2019

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

INVESTIGATIONAL PRODUCT:	CTP-543
PROTOCOL NUMBER:	CP543.2002; Amendment 1
AMENDMENT 1 DATE:	03 January 2019
ORIGINAL PROTOCOL:	17 December 2018
EudraCT NUMBER:	Not Applicable
IND NUMBER:	131,423
SPONSOR NAME / ADDRESS:	Concert Pharmaceuticals, Inc. 65 Hayden Avenue, Suite 3000N Lexington, MA 02421

CONFIDENTIAL

This protocol is provided to you as an Investigator, potential Investigator, or consultant for review by you, your staff, and ethics committee/institutional review board. The information contained in this document is regarded as confidential and, except to the extent necessary to obtain informed consent, may not be disclosed to another party unless such disclosure is required by law or regulations. Persons to whom the information is disclosed must be informed that the information is confidential and may not be further disclosed by them.

MEDICAL MONITOR / EMERGENCY CONTACT INFORMATION

Contact Information	
Name	[redacted], MD
Title	[redacted]
Address	[redacted]
Phone	[redacted]
Facsimile	[redacted]
Email	[redacted] AND [redacted]

CONCERT SIGNATURE PAGE

PROTOCOL TITLE: A Randomized Parallel-Group Study to Evaluate the Efficacy and Tolerability of Two Dosing Regimens of CTP-543 in Adult Patients with Moderate to Severe Alopecia Areata

Protocol Number: CP543.2002

[redacted] [redacted]

Sponsor Representative Signature **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: CP543.2002

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

A Randomized Parallel-Group Study to Evaluate the Efficacy and Tolerability of Two Dosing Regimens of CTP-543 in Adult Patients with Moderate to Severe Alopecia Areata

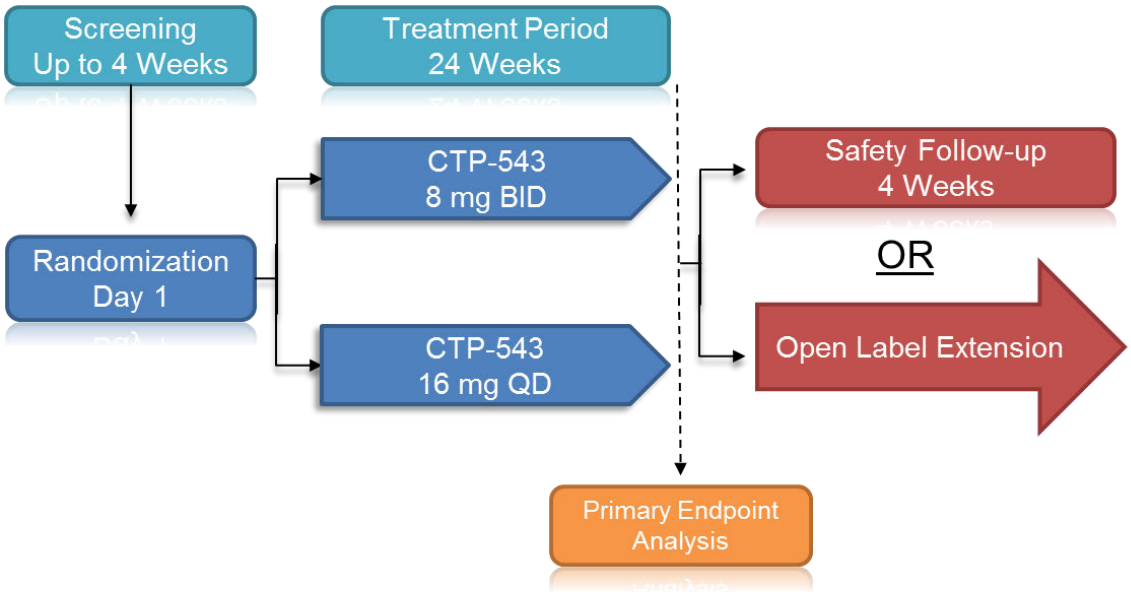
CP543.2002, Protocol Amendment #1
03 January 2019

The main purpose of this amendment #1 (to original protocol dated 17 December 2018), is to modify the Schedule of Assessments. It was noted that an ECG at Screening had not been checked in the table. An 'X' has been subsequently added to the Schedule of Assessments for the Screening visit. The Schedule of Assessments was the only section updated to reflect this change.

1. SYNOPSIS

Name of Sponsor/Company: Concert Pharmaceuticals, Inc.	
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 Randomized Parallel-Group Study to Evaluate the Efficacy and Tolerability of Two Dosing Regimens of CTP-543 in Adult Patients with Moderate to Severe Alopecia Areata	
Study center(s): Multicenter study; approximately 10 sites; US	
Studied period (years): Estimated date first patient enrolled: February 2019 Estimated date last patient completed: November 2019	**Phase of development:** 2
Objectives: The overall objective of the study is to compare the efficacy and tolerability of a 16 mg total daily dose of CTP-543 utilizing two different dosing regimens in adult patients with chronic, moderate to severe alopecia areata. The secondary/exploratory objectives of the study will be for patients to assess their eyebrows and to assess the patient reported outcomes of hair coverage and hair coverage quality.	
Methodology: This is a randomized, multicenter study to evaluate the efficacy and tolerability of two dosing regimens of CTP-543 (8 mg BID vs 16 mg QD), in adult patients with chronic, moderate to severe alopecia areata. Patients will be between 18 and 65 years of age (inclusive), 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 with other treatments that might affect hair regrowth or immune response. Up to approximately 75% of alopecia areata patients with alopecia totalis or universalis, and no more than 10% with only alopecia ophiasis will be enrolled. Subjects will be screened up to 28 days prior to initiation of study drug. The Treatment Period is a 24-week dosing period where patients will be randomized to receive either CTP-543 8 mg BID or CTP-543 16 mg QD and will be analyzed for the primary endpoint of the study. To minimize bias in the evaluation of study endpoints, patients, investigators, and site personnel will be made unaware of the active drug dosing regimen by administering one 16 mg tablet and one placebo tablet 12 hours apart from each other for the 16 mg QD study group.	

Figure 1: CP543.2002 Study Design



Study Design

Patients will provide informed consent prior to completing any screening procedures. Patients meeting screening criteria will continue to the Day 1 Randomization Visit for review of eligibility and baseline assessments, including SALT assessment, physical examination, clinical laboratory assessments, vital signs, and electrocardiogram. Patients meeting all eligibility criteria will be randomized to 1 of 2 CTP-543 treatment 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.

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

Patient safety will be monitored throughout the trial. During the first 8 weeks of the Treatment Period, hematology will be conducted every 2 weeks, followed by an assessment every 4 weeks thereafter through completion of the study at 24 weeks. Lipid levels will be assessed every 12 weeks throughout the Treatment Period. Significant cytopenias or other hematologic abnormalities will be managed by severity through dose interruption, or discontinuation, and signs and symptoms of infection will be closely monitored and treated promptly. Patients who experience intolerable symptoms during treatment may discontinue the study at the discretion of the Investigator. Patients may withdraw consent at any time.

The Treatment Period will last 24 weeks to assess CTP-543 dosed BID vs CTP-543 dosed QD. Assessment of treatment response with SALT for efficacy will occur at 4, 8, 12, 16, 20 and 24 weeks.

Upon completion of the 24-week Treatment Period, patients will be eligible to either complete treatment and exit the study following the safety follow-up visit, or roll-over into a long-term open-label extension study.

Number of patients (planned):

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

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. Totalis or universalis and ophiasis subtypes must have 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 other scalp condition that may interfere with the SALT assessment, 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. Systemic or invasive infection, as evidenced by fever, inflammation, or systemic signs of illness (e.g., malaise, myalgia, specific symptoms like pain, shortness of breath) 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).
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 or $\geq 600 \times 10^9$/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. At screening, any active or previous Hepatitis B or C infection, or known human immunodeficiency virus infection at screening.
18. Vaccination with herpes zoster vaccine or any live virus vaccine within 6 weeks prior to Screening or during the study.
19. Positive TB test, or history of incompletely treated or untreated tuberculosis.

    NOTE: In cases where performance of a QuantiFERON-TB Gold test is not possible, testing with a Tuberculin Skin Test (TST) may be an option after consultation with the Medical Monitor. If the TST is negative, patients can be randomized into the study, assuming they meet all other inclusion and none of the exclusion criteria. If results are equivocal, or there is reason to believe the result is a false positive, a QuantiFERON-TB Gold must be performed before a subject is eligible for randomization.
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 of 8 mg BID, every 12 hours or 16 mg QD in the morning with matching placebo in the evening.

Reference therapy, dosage and mode of administration:

N/A

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). 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 relative change in SALT score for each dose regimen from baseline at Week 24.

Secondary efficacy endpoints in each dose regimen include:

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

Exploratory Endpoints in each dose regimen include:

- Change in patient's eyebrows as measured by the patient's Visual Analog Scale (VAS)
- Change in satisfaction of hair coverage quality as reported by patient

Safety:

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:

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

Efficacy Analyses:

The Efficacy Population will include all patients who receive study drug and have at least 1 post-treatment SALT assessment. For the primary efficacy endpoint and other continuous measures, a 90% confidence interval for the dosing regimen difference at Week 24 will be calculated using the t-distribution.

Data will be summarized by dosing regimen (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.

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

Tolerability Analyses:

The Safety Population will include all patients who receive study drug. 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 dosing regimen. By-patient listings will be provided for any deaths, serious adverse events, adverse events leading to study discontinuation, and adverse events leading to study drug interruption.

Table 1: Schedule of Events: Treatment Period

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

HBV= hepatitis B virus; HCV = hepatitis C virus

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

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

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

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

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

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

[7] Includes hematology and serum chemistry.

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

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

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

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

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

[13] Collection is ongoing.

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
BID	Twice daily dosing
CFR	Code of Federal Regulations
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
QD	Once daily dosing
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	Visual Analog Scale

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. 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. Rationale for the Study

4.2.1. Scientific Rationale

CTP-543 is a deuterated form of ruxolitinib (Jakafi), a selective JAK inhibitor that modulates immune response through reduced intracellular JAK1 and JAK2 signaling. There is growing evidence that hair loss in AA may be mediated by cytotoxic T cell attack of the hair follicle after loss of immune privilege, and that this process may be regulated by upstream JAK signaling (Xing, 2014).

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 (Levy, 2015).

In nonclinical pharmacology testing, it was confirmed that CTP-543 inhibited cytokine-stimulated phosphorylation of signal transducer and activator of transcription (STAT) proteins in human cells, suggesting that suppression of JAK/STAT signaling is the primary mechanism of

action for CTP-543. In *in vitro* kinase inhibition assays, the target potency and selectivity profile of CTP-543 for the JAK kinases JAK1, JAK2, JAK3 and Tyk2 was as shown in Table 2.

Table 2: Potency of CTP-543 in *In Vitro* Kinase Inhibition Assays

Enzyme	Inhibition of JAK Kinase Activity IC_{50} (nM)
JAK1	4.7
JAK2	20
JAK3	1335
Tyk2	37

Based on the data for CTP-543 summarized above, and published clinical data for other JAK inhibitors, including ruxolitinib, baricitinib and tofacitinib (Xing, 2014; Craiglow, 2014; Mackay-Wiggan, 2016; Jabbari et al, 2015; Harris 2016; Crispin, 2016; Liu, 2018), JAK inhibition may represent a viable therapeutic approach to treating AA, thus supporting Concert's development of CTP-543 as a potential oral treatment for AA.

Concert Pharmaceuticals is currently conducting a Phase 2 study CP543.2001, "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 CP543.2001 is a double-blind, randomized, placebo-controlled trial of approximately 125 adults with moderate-to-severe alopecia areata. Patients were sequentially randomized to receive one of three doses of CTP-543 (4, 8, 12 mg twice daily) or placebo for 24 weeks.

Recently, interim top line analysis was performed for the 4 and 8 mg cohorts. The primary efficacy endpoint in the 8 mg twice-daily cohort was met with 47% of patients achieving a $\geq$ 50% reduction in their overall SALT score from baseline compared to placebo ($p<0.001$). In light of these data, this current study will compare the known effect established for 8 mg BID with a once daily equivalent dose, 16 mg QD.

Dosing Regimen Rationale

Analyses suggest that across acute and chronic disease states, reducing dosage frequency from multiple dosing to QD dosing may improve adherence to therapies among patients, and may result in subsequent decreases in health care costs (Srivastava, 2013).

Based on the established effect for 8 mg BID, a randomized, parallel-group study will be conducted to compare tolerability and efficacy of 8 mg BID with a once daily equivalent dose of 16 mg QD.

Patients, investigators, and site personnel will be unaware of the active drug dosing regimen to minimize bias in the evaluation of study endpoints.

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. Clinical Studies of CTP-543

To date, 3 clinical studies have evaluated 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.

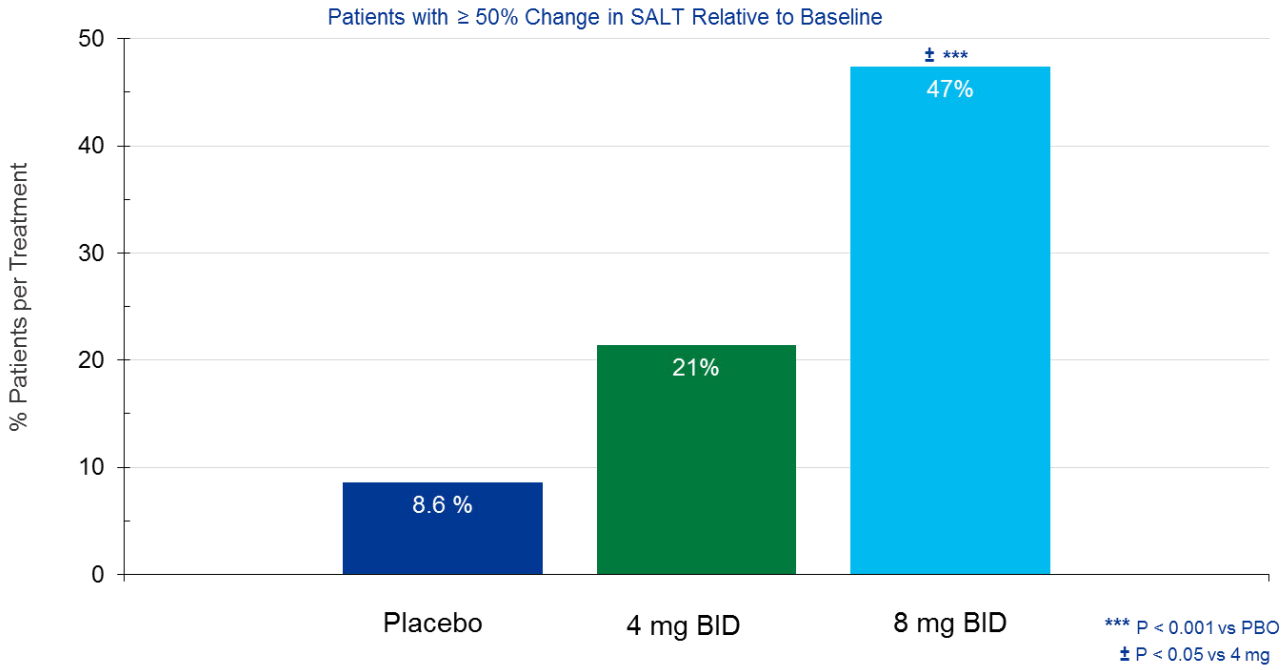
The second clinical study CP543.1002, also performed in healthy volunteers was a single dose cross-over study to assess safety and tolerability and to compare the metabolite and pharmacokinetic profiles of CTP-543 versus ruxolitinib. A total of 12 subjects were enrolled in the study; 2 groups of 6 subjects 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 Phase 2 study CP543.2001, 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, is ongoing.

CP543.2001 is a double-blind, randomized, placebo-controlled trial of approximately 125 adults with moderate-to-severe alopecia areata. Patients were sequentially randomized to receive one of three doses of CTP-543 (4, 8, 12 mg twice daily) or placebo for 24 weeks.

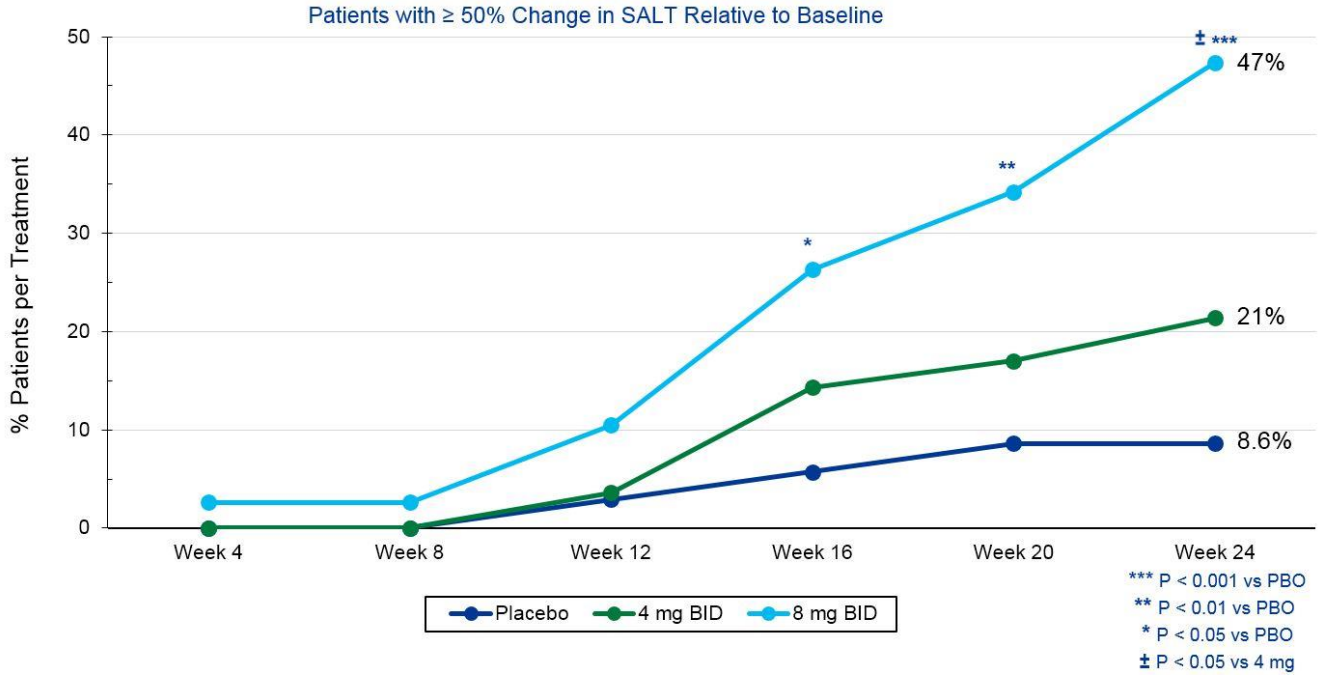
Interim top line analysis for the 4 and 8 mg cohorts showed that the primary efficacy endpoint in the 8 mg twice-daily cohort was met with 47% of patients achieving a $\geq$ 50% reduction in their overall SALT score from baseline compared to placebo ($p<0.001$) (Figure 2).

Figure 2: Primary Analysis: Responders at Week 24



For the 4 mg cohort, 21% of patients achieved a ≥ 50% reduction in their overall SALT score from baseline, however these differences were not significantly different from placebo. In the primary analysis, the response observed in the 8 mg twice-daily dose was significantly different than the 4 mg twice daily dose ($p < 0.05$) (Figure 3). The average baseline SALT score across all patients enrolled in the trial was approximately 88.

Figure 3: Primary Analysis: Responders by Visit



CTP-543 was generally well tolerated and there have been no serious adverse events reported. The most common adverse events reported across treatment groups (4 mg, 8 mg, and placebo)

were headache, upper respiratory tract infection, cough, acne and nausea. For the upper respiratory tract infections, there was a higher incidence in the placebo group. In terms of hematologic changes, there were only 3 incidents of Grade 3 or 4 changes and these 3 cases were distributed equally across the dose groups including placebo.

The 12 mg dosing cohort is currently ongoing.

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

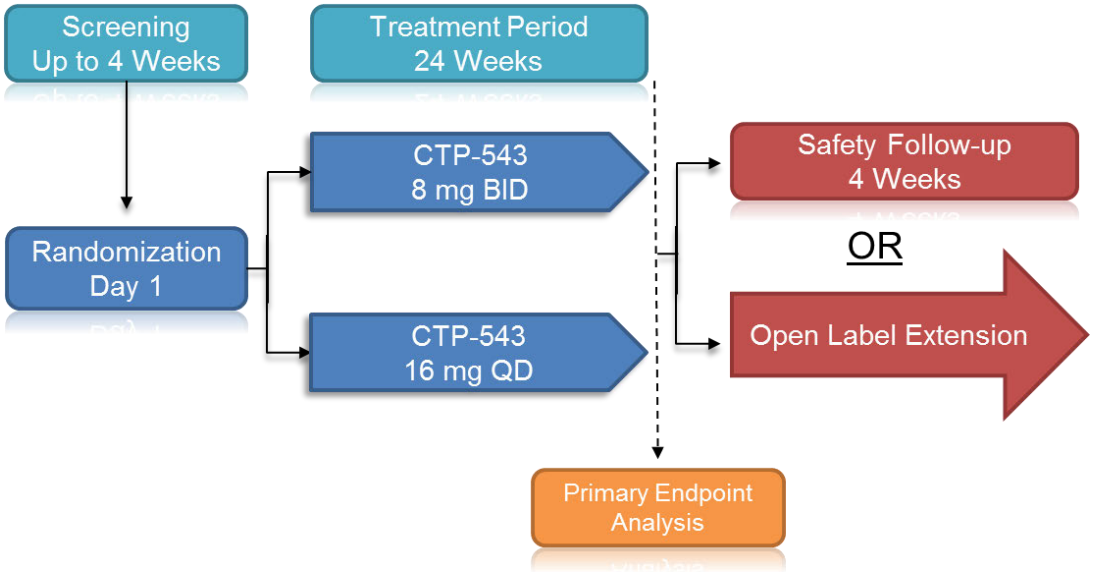
The secondary/exploratory objectives of the study will be to assess the patient reported outcomes of hair coverage and hair coverage quality.

6.3 Study Design

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

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

Figure 4: Study Design



Patients will provide informed consent prior to completing any screening procedures.

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

Patient safety will be monitored throughout the trial. The subject will be tested to ensure they do not have the Hepatitis B or C virus, thyroid function abnormalities or latent or active Tuberculosis, during the screening period. During the first 8 weeks of the Treatment Period, hematology and serum chemistry will be conducted every 2 weeks, followed by an assessment every 4 weeks thereafter through completion of the study at 24 weeks. Lipid levels will be assessed every 12 weeks throughout the Treatment Period. Significant cytopenias or other hematologic abnormalities will be managed by severity through dose interruption, or discontinuation, and signs and symptoms of infection will be closely monitored and treated promptly. Patients who experience intolerable symptoms during treatment may discontinue the study at the discretion of the Investigator. Patients may withdraw consent at any time.

The Treatment Period will last 24 weeks to assess BID and QD doses, in parallel. Assessment of treatment response with SALT for efficacy will occur at 4, 8, 12, 16, 20 and 24 weeks.

Upon completion of the 24-week Treatment Period patients will be eligible to either complete treatment and exit the study following the safety follow-up visit, or roll-over into a long-term open-label extension study.

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

6.4 Method of Treatment Assignment

Patients meeting screening criteria will continue to the Day 1 Randomization Visit for review of eligibility and baseline assessments, including SALT assessment, physical examination, clinical laboratory assessments, vital signs, and electrocardiogram. Patients meeting all eligibility criteria will be randomized to 1 of 2 CTP-543 treatment arms (8 mg BID or 16 mg QD). Randomization will also 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.

7. 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.

7.1. 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. Totalis or universalis and ophiasis subtypes must have 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 (not all intrauterine devices meet this criterion).
6. Willing to comply with the study visits and requirements of the study protocol.

7.2. Patient Exclusion Criteria

1. History or presence of hair transplants.
2. Treatment with other medications within 1 month of Screening or during the study that may affect hair regrowth or immunosuppression, such as: corticosteroids administered orally, by injection, or applied to areas of skin affected by alopecia; topical application 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 within 3 months of Screening (ruxolitinib, tofacitinib, etc), etanercept; or biologics (adalimumab, atlizumab, canakinumab, certolizumab, fontolizumab, golimumab, infliximab, mepolizumab, rituximab, secukinumab, tocilizumab, ustekinumab) within 6 months of Screening.
4. Active scalp inflammation, psoriasis, or seborrheic dermatitis requiring topical treatment to the scalp, significant trauma to the scalp, or untreated actinic keratosis on the scalp at Screening and/or Baseline.

5. Known history of moderate to severe androgenic alopecia or 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 visits), 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 with recurrence within the 5 years prior to the first study drug administration, 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 undiagnosed but suspicious for malignancy.
10. History of solid organ or hematological transplantation.
11. Systemic or invasive infection, as evidenced by fever, inflammation, or systemic signs of illness (e.g., malaise, myalgia, specific symptoms like pain, shortness of breath) 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).
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 ≤120 x 10^9/L or ≥600 x 10^9/L
    b. Absolute neutrophil count ≤1.5 x 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 ≥2 × ULN of any 3 or more of the following: serum alanine transaminase, serum aspartate transaminase, serum alkaline phosphatase, total bilirubin.
16. Abnormal renal function (estimated glomerular filtration rate <60 mL/min/1.73 m^2 using the MDRD equation).
17. At screening, any 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 prior to Screening or during the study.
19. Positive TB test, or history of incompletely treated or untreated tuberculosis.

    NOTE: In cases where performance of a QuantiFERON-TB Gold test is not possible, testing with a Tuberculin Skin Test (TST) may be an option after consultation with the Medical Monitor. If the TST is negative, patients can be randomized into the study, assuming they meet all other inclusion and none of the exclusion criteria. If results are

equivocal, or there is reason to believe the result is a false positive, a QuantiFERON-TB Gold must be performed before a subject is eligible for randomization.

20. Prolonged QT or heart-rate corrected QT (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).
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).
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 that, as determined by the Investigator, may unfavorably alter the risk-benefit of study participation, adversely affect study compliance, or confound interpretation of study results.

7.3. 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
- 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.

7.3.1. 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 (See Table 3). 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 consecutive days for management of adverse events 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 10 Adverse Events. The data will be recorded on the appropriate eCRF.

7.4. Criteria for Study Termination

There are no prospective stopping criteria for this study. The Sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons.

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.

8. DESCRIPTION OF STUDY TREATMENTS

8.1. Description of Treatments

In the Treatment Period, patients will be stratified by alopecia areata subtype and randomized to 1 of 2 CTP-543 treatment arms in a 1:1 ratio. Treatments arms will include:

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

8.2. Safety Criteria and Management for Stopping Doses

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 or be discontinued from the study at the discretion of the Investigator. The Medical Monitor should be consulted whenever possible prior to decisions for dose interruption or patient discontinuation from the study.

Patients who require a dose interruption lasting more than 21 consecutive 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 7.3.1 Patient Withdrawal Procedures, and associated adverse events followed as described in See Section 10 Adverse Events.

Hematology and serum chemistry parameters will be assessed every 2 weeks for the first 8 weeks of the Treatment, and every 4 weeks thereafter for the remainder of the study. Prior to dose interruption, hematology parameters should be confirmed with repeat testing at an interval deemed appropriate by the Investigator (e.g., at the next protocol-defined visit or an Unscheduled Visit), except in severe cases 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**
Less than 1 x 10^9/L	Interrupt dose until recovered to greater than 1.5 x 10^9/L and resume dosing at previous dose
Female Hemoglobin Level	**Dose Adjustment**
Less than 10 g/dL	Interrupt dose until recovered to greater than 11.5 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 13 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 75 x 10^9/L and resume dosing at previous dose
Greater than 750 x 10^9/L	Interrupt dose until recovered to less than 600 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 interruption has elapsed. In the case of severe neutropenia (neutrophil counts less than 0.5 x 10^9/L) patients should discontinue the study drug 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 21 consecutive day dose interruption period should continue to be monitored as appropriate through acceptable clinical resolution.

If the patient recovers above the threshold for interruption before the 21 consecutive day interruption period ends, they may remain in the study. Subsequent dose interruptions within a patient should be discussed with the Medical Monitor to determine continued participation in the study.

8.3. 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.

8.4. 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.

8.4.1. Physical Description of Study Drug

Study drug will be CTP-543, a deuterated analog of ruxolitinib or an identical placebo tablet. Details regarding formulation and dosage are presented in Table 4.

Table 4: Investigational Product

	Investigational Product (CTP-543 or Placebo)
Product Name:	CTP-543
Dosage Form:	Tablet
Dosage Strength of CTP-543	8 mg,16 mg or placebo
Route of Administration	Oral
Physical Description	White, capsule-shaped tablets

8.4.2. 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 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.

8.4.3. 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. 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 consistently 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.

8.4.4. 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.

8.4.5. 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.

8.5. 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.

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 immunosuppression (such as: corticosteroids administered orally, by injection, or applied to areas of skin affected by alopecia; topical application 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);
- 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).

9. STUDY ASSESSMENTS AND PROCEDURES

The schedule of assessments and procedures is presented in

Table 1 should be referenced for details regarding the collection of each assessment at each visit.

9.1. 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.

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

9.2. 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 16.1.

9.3. Photographs

Sites will take photographs of their patient's scalps to provide visual support of Baseline assessment of SALT as well as potential changes in SALT scores throughout the study. No analyses of photographs will occur. The 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.

9.4. 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.

As specified in the Schedule of Events, patients will rate his/her eyebrows on the patient VAS. The left and right anchor points for the patient's eyebrow VAS are "None" and "Full", respectively. The patient VAS will measure the patient's eyebrows at the time of completion. An example of the patient VAS is provided in Appendix 16.3.

9.5. Patient Satisfaction Questions

Questions regarding the patient's assessment of satisfaction with hair coverage will be performed as indicated in the schedule of assessments (see Section 16.2).

9.6. 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.

9.7. 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, 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 will be performed at all other intermediate visits as specified in Table 1.

9.8. 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.

9.9. 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 prior to the first daily dose on all Study Visit Days.

The results of clinical laboratory tests conducted at the Screening Visit 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)

Table 5: Clinical Laboratory Assessments (Continued)

Serology	Lipids	Other
Hepatitis B virus Hepatitis C virus	Total cholesterol Low-density lipoprotein High-density lipoprotein triglycerides	Tuberculosis Test - QuantiFERON-TB Gold (QFT) -Tuberculin skin test (TST), also called purified protein derivative or PPD (with MM consultation) Thyroid stimulating hormone

9.10. 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, 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.

10. ADVERSE EVENTS

10.1. 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 (i.e., 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 or if an ongoing Adverse Event worsens after dosing is initiated.

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).

10.2. 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.

10.2.1. 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.

10.2.2. 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.

10.2.3. 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.

10.2.4. 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.

10.2.5. 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.

10.2.6. 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).

10.3. 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.

10.4. 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.

10.5. 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.

10.6. 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.

10.6.1. 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]
[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.

10.6.2. 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.

11. STATISTICAL METHODS

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

11.1. Sample Size Rationale

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

11.2. Endpoints

11.2.1. Efficacy

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

Secondary efficacy endpoints in each dose regimen include:

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

Exploratory endpoints in each dose regimen include:

- Change in patient's eyebrows as measured by the patient's Visual Analog Scale (VAS)
- Change in satisfaction of hair coverage quality as reported by patient

11.2.2. Safety

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

11.3. Analysis Populations

The Efficacy Population will include all patients who receive study drug and have at least 1 post-treatment SALT assessment. The Safety Population will include all patients who receive study drug. Patients will be summarized according to study drug regimen received (i.e., as treated) should it differ from the randomized arm.

11.4. Analyses

For the Treatment Period, data will be summarized by dosing regimen (BID versus QD). 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.

11.4.1. Disposition and Baseline Characteristics

Disposition will be summarized by randomized dosing regimen. The number and percentage of patients, who are randomized, treated, prematurely discontinued, and completers will be summarized.

Baseline characteristics will be summarized by dosing regimen for patients participating in 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.

Concomitant medications will be summarized by World Health Organization Drug Dictionary for Anatomical-Therapeutic-Chemical classification and preferred term.

11.4.2. Efficacy

For the primary efficacy endpoint and other continuous measures, a 90% confidence interval for the dosing regimen difference at Week 24 will be calculated using the t-distribution. For categorical measures (e.g. proportion of responders), a 90% confidence interval for the dosing regimen difference at Week 24 will be calculated based on normal approximation for the binomial distribution, using the Wald continuity correction [(1/n1 + 1/n2/2].

11.4.3. Study Drug Exposure

For each patient, the number of days of exposure to CTP-543 will be summed across the Treatment Period. 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.

11.4.4. Safety

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

The number and percentage of patients who experience TEAEs will be summarized by dosing regimen 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.

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.

Third, treatment-emergent adverse events that result in dose interruption will also be identified.

The mean change from Baseline to each scheduled assessment will be summarized descriptively by dosing regimen for each clinical laboratory variable specified in this protocol.

The number and percentage of patients with Abnormal, clinically significant laboratory values (per Investigator judgment) and the number and percentage of patients with treatment-emergent PCS laboratory values will be summarized by dosing regimen for each clinical laboratory variable.

Vital Signs

The mean change from baseline to each scheduled assessment will be summarized descriptively by dosing regimen 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 dosing regimen.

Exploratory Endpoints

VAS scale for eyebrows will be tabulated and analyzed by dosing regimen, as appropriate.

Patient reported outcomes of satisfaction of hair coverage and satisfaction of hair coverage quality will be tabulated and analyzed by dosing regimen, as appropriate.

Additional detail will be outlined in the Statistical Analysis Plan.

12. 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.

12.1. 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.

12.2. 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.

12.3. 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.

12.4. 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.

12.5. 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.

12.6. 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.

13. DATA HANDLING AND RECORDKEEPING

13.1. 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.

13.2. 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.

13.3. 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.

13.4. 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.

13.5. 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.

13.6. 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.

13.7. 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.

14. PUBLICATION POLICY

The results of this study may be published in a medical publication, journal, 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.

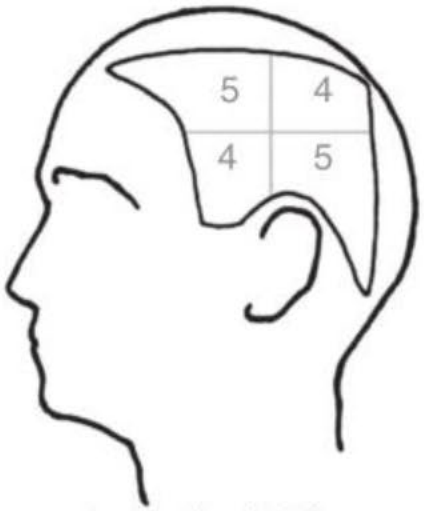
15. LIST OF REFERENCES

First Author (Year)	Citation
Al-Mutairi (2011)	Al-Mutairi N, Eldin ON. Clinical profile and impact on quality of life: seven years experience with patients of alopecia areata. Indian J Dermatol Venereol Leprol. 2011 Jul-Aug;77(4):489-93.
Bilgic (2013)	Bilgiç Ö, Bilgiç A, Bahalı K, Bahali AG, Gürkan A, Yılmaz S. Psychiatric symptomatology and health-related quality of life in children and adolescents with alopecia areata. J Eur Acad Dermatol Venereol. 2014 Nov;28(11):1463-8.
Craiglow (2014)	Craiglow BG, King BA. Killing two birds with one stone: oral tofacitinib reverses alopecia universalis in a patient with plaque psoriasis. J Invest Dermatol. 2014:134(12): 2988-2990.
Crispin (2016)	Crispin MK, Ko JM, Craiglow BG, et al. Safety and efficacy of the JAK inhibitor tofacitinib citrate in patients with alopecia areata. JCI Insight. 2016 Sep:1(15):e89766.
CTP-543 Investigator's Brochure	Investigator's Brochure, CTP-543 (D8-ruxolitinib), Concert Pharmaceuticals, Inc. 2017
Ghoreschi (2009)	Ghoreschi K., Laurence A., O'Shea JJ. Janus kinases in immune cell signaling. Immunol Rev. 2009;228(1):273-87.
Harris (2016)	Harris JE, Rashighi M, Nguyen N, Jabbari A, Ulerio G, Clynes R, Christiano AM, Mackay-Wiggan J. J Am Acad Dermatol. 2016:74(2):370-371.
Jabbari (2015)	Jabbari A, Dai Z, Xing L, et al. Reversal of Alopecia Areata Following Treatment with the JAK1/2 Inhibitor Baricitinib. EBioMedicine. 2015(2): 351–355.
Jakafi (2016)	Jakafi prescribing information. Incyte Corporation. Wilmington, DE. 2016.
Mackay-Wiggan (2016)	Mackay-Wiggan J, Jabbari A, Nguyen N, et al. Oral ruxolitinib induces hair regrowth in patients with moderate-to-severe alopecia areata. JCI Insight. 2016 Sep:1(15):e89790.
Olsen (2004)	Olsen EA, Hordinsky MK, Price VH, et al. Alopecia areata investigational assessment guidelines--Part II. National Alopecia Areata Foundation. J Am Acad Dermatol. 2004 Sep;51(3):440-7.
Safavi (1992)	Safavi K. Prevalence of alopecia areata in the First National Health and Nutrition Examination Survey. Arch Dermatol. 1992;128(5):702.
Sellami (2014)	Sellami R, Masmoudi J, Ouali U, et al. The relationship between alopecia areata and alexithymia, anxiety and depression: a case-control study. Indian J Dermatol. 2014 Jul;59(4):421.
Shi (2011)	Shi JG, Chen X, McGee RF, et al. The pharmacokinetics, pharmacodynamics, and safety of orally dosed INCB018424 phosphate in healthy volunteers. J Clin Pharmacol. 2011;51:1644-54.
Srivastava (2013)	Kunal Srivastava, Anamika Arora, Aditi Kataria, et al. Impact of reducing dosing frequency on adherence to oral therapies: a literature review and meta-analysis. Patient Prefer Adherence. 2013; 7: 419–434.

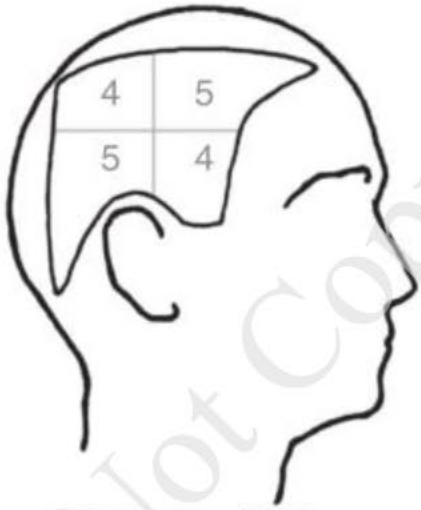
Villasante Fricke (2015)	Villasante Fricke AC, Miteva, M. Epidemiology and burden of alopecia areata: a systematic review. Clin Cosmet Investig Dermatol. 2015 Jul 24;8:397-403.
Xing (2014)	Xing L, Dai Z, Jabbari A, et al. Alopecia areata is driven by cytotoxic T lymphocytes and is reversed by JAK inhibition. Nat Med. 2014 Sep;20(9):1043-9.

16. APPENDICES

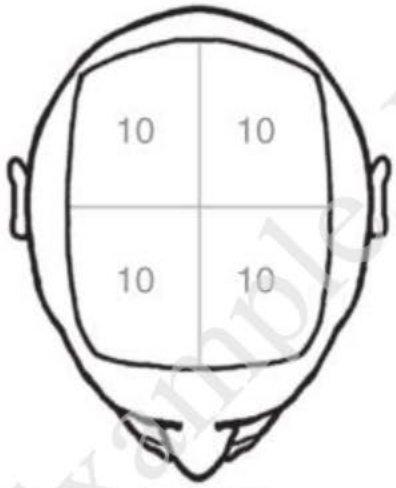
16.1. Severity of Alopecia Tool (SALT)



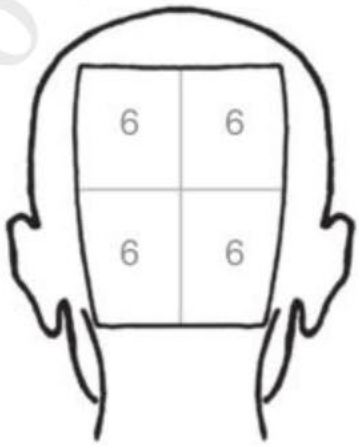
Left side: 18%



Right side: 18%



Top: 40%



Back: 24%

Olsen/Canfield

Left Quadrant Raw Score (LRS)		Top Quadrant Raw Score (TRS)	
Right Quadrant Raw Score (RRS)		Back Quadrant Raw Score (BRS)	
Total SALT Score [(LRS x 0.18) + (RRS x 0.18) + (TRS x 0.40) + (BRS x 0.24)]			

Example, Do Not Copy

16.2. Patient Satisfaction Questions

16.2.1. Satisfaction of Hair Coverage Question

How satisfied are you with the hair coverage on your scalp today?

0 ☐ Very dissatisfied
1 ☐ Dissatisfied
2 ☐ Somewhat satisfied
3 ☐ Mostly satisfied
4 ☐ Very satisfied

Example, Do Not Copy

16.2.2. Satisfaction of Hair Coverage Quality Questions

For the next set of questions, please choose the best answer that represents how you feel today.

1. How satisfied are you with the **thickness of the hair** coverage on your scalp?	1☐ Very dissatisfied	2☐ Dissatisfied	3☐ Somewhat satisfied	4☐ Mostly satisfied	5☐ Very satisfied
2. How satisfied are you with the **evenness of the hair coverage** on your scalp?	1☐ Very dissatisfied	2☐ Dissatisfied	3☐ Somewhat satisfied	4☐ Mostly satisfied	5☐ Very satisfied
3. How satisfied are you with the thickness **of the individual hairs** on your scalp?	1☐ Very dissatisfied	2☐ Dissatisfied	3☐ Somewhat satisfied	4☐ Mostly satisfied	5☐ Very satisfied
4. How satisfied are you with the texture/feel *(coarseness, softness etc.)* **of the individual hairs** on your scalp?	1☐ Very dissatisfied	2☐ Dissatisfied	3☐ Somewhat satisfied	4☐ Mostly satisfied	5☐ Very satisfied
5. How satisfied are you with the current color **of the hair** on your scalp?	1☐ Very dissatisfied	2☐ Dissatisfied	3☐ Somewhat satisfied	4☐ Mostly satisfied	5☐ Very satisfied
6. How satisfied are you with your eyebrows?	1☐ Very dissatisfied	2☐ Dissatisfied	3☐ Somewhat satisfied	4☐ Mostly satisfied	5☐ Very satisfied
7. How satisfied are you with your eyelashes?	1☐ Very dissatisfied	2☐ Dissatisfied	3☐ Somewhat satisfied	4☐ Mostly satisfied	5☐ Very satisfied

Example, Do Not Copy

16.3. Patient Visual Analog Scale (VAS) for Eyebrows

At this time, please describe your eyebrows by placing a mark on the line.

Example, Do Not Copy