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| **Official Title:** | **A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of CTP-543 in Adult Patients With Moderate to Severe Alopecia Areata** |
| **NCT Number:** | NCT04797650 |
| **Document Date:** | Protocol (Original Version) : 23 February 2021 |

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

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|---|---|
| **INVESTIGATIONAL PRODUCT:** | CTP-543 |
| **PROTOCOL NUMBER:** | CP543.3002 |
| **ORIGINAL PROTOCOL (NORTH AMERICA):** | 23 February 2021 |
| **IND NUMBER:** | 131,423 |
| **SPONSOR NAME / ADDRESS:** | Concert Pharmaceuticals, Inc.<br>65 Hayden Avenue, Suite 3000N<br>Lexington, MA 02421 |

## [redacted] / EMERGENCY CONTACT INFORMATION

| North American [redacted] Contact Information | |
|---|---|
| Name | [redacted], MD |
| Title | [redacted] |
| Address | [redacted]<br>[redacted]<br>[redacted] |
| Phone | [redacted] |
| Facsimile | [redacted] |
| Email | [redacted] AND<br>[redacted] |

## CONCERT SIGNATURE PAGE

**PROTOCOL TITLE:** A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of CTP-543 in Adult Patients with Moderate to Severe Alopecia Areata

Protocol Number: CP543.3002

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| [redacted] Electronically signed by [redacted] Reason [redacted] Date Feb 23, 2021 09 58 EST | 23-Feb-2021 |
| **Sponsor Representative Signature** | **dd mmm yyyy** |
| **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: CP543.3002

| | |
|---|---|
| **Signature of Site Principal Investigator** | **dd mmm yyyy** |
| **Printed Name of Site Principal Investigator**<br>**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/Ethics Committee procedures, instructions from Concert representatives, the Declaration of Helsinki, International Council on Harmonization Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies. | |

# 1. SYNOPSIS

**Name of Sponsor/Company:**
Concert Pharmaceuticals, Inc.

**Name of Investigational Product:**
CTP-543

**Name of Active Ingredient:**
Deuterated ruxolitinib

**Title of Study:**
A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of CTP-543 in Adult Patients with Moderate to Severe Alopecia Areata

**Study center(s):** Multicenter study; approximately 50 sites (North America and European Union)

| **Studied period (years):** | **Phase of development:** 3 |
|---|---|
| Estimated date first patient first visit: April 2021<br>Estimated date last subject last visit: June 2022 | |

**Objectives:**

The overall objectives of the study are to assess the efficacy and safety following administration of CTP-543 in adult patients with moderate to severe alopecia areata.

The primary objectives of the study are to assess:

- The efficacy of CTP-543 on regrowth of hair following 24 weeks of treatment
- The safety of CTP-543 following 24 weeks of treatment.

The secondary objectives of the study are to assess:

- Clinician- and patient-reported impression of the severity and improvement of alopecia areata
- Patient-reported satisfaction with their scalp hair
- Patient-reported levels of anxiety and depression
- Changes in eyebrows and eyelashes.

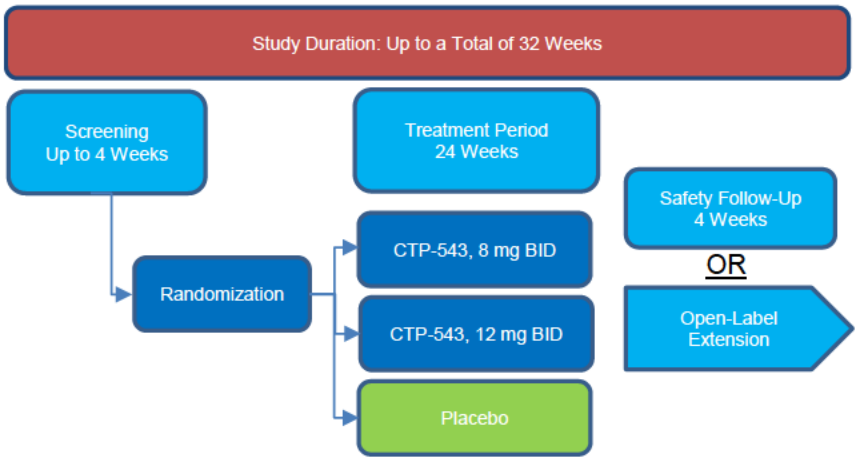
**Methodology:**

This is a double-blind, randomized, placebo-controlled multicenter study to evaluate the efficacy and safety of CTP-543 in adult patients with moderate to severe alopecia areata. Patients will be between 18 and 65 years of age and experiencing an episode of hair loss associated with alopecia areata lasting at least 6 months and not exceeding 10 years. Patients not currently being treated for alopecia areata or with other treatments that might affect hair regrowth or immune response must have at least 50% hair loss as measured by SALT at Screening and Baseline.

An independent Data Monitoring Committee (DMC) will perform regular safety assessments based on a review of cumulative safety data. The DMC may advise study and/or treatment arm cessation due to intolerability at any time.

The Screening Period may last up to 28 days prior to initiation of study drug. The Treatment Period is a 24-week, double-blind, placebo-controlled period. Following the 24-week Treatment Period, patients will have the opportunity to continue receiving treatment in an Open-Label Extension study. If a patient does not wish to continue into the Open-Label Extension study, they will complete treatment at Week 24 and return in 4 weeks for the Post-Treatment Safety Follow-up to assess safety following treatment completion.

**Study Design**




Patients will provide appropriately-obtained informed consent prior to initiating any screening procedures. Patients meeting initial screening criteria will be eligible to continue to the Day 1 visit for review of eligibility and baseline assessments, including SALT assessment, physical examination, clinical laboratory assessments, and vital signs. Patients meeting all inclusion criteria and none of the exclusion criteria will be randomized to twice-daily treatment with either 12 mg CTP-543, 8 mg CTP-543 or placebo. Patients will be randomized in a 1:2:1 ratio (12 mg BID:8 mg BID:placebo). Randomization will be stratified by scalp hair loss into one of the following two categories: 1) Partial scalp hair loss (SALT $\geq$ 50 and $<$ 95); 2) complete or near-complete scalp hair loss (SALT $\geq$ 95).

Patients will take the first dose of study drug in the clinic on Day 1 and will be instructed to take study drug daily approximately every 12 hours for the duration of the Treatment Period. Patients should dose study drug in the clinic on all Study Visit Days after clinical laboratory blood draws are completed. Other baseline assessments will include patient and clinician global impression of disease severity (CGI-S and PGI-S), Patient Reported Outcome for Satisfaction (SPRO) and Hair Quality (QPRO), the Hospital Anxiety and Depression Scale (HADS), and assessments for eyelash and eyebrow involvement.

The double-blind, placebo-controlled Treatment Period will last 24 weeks. Assessment of treatment response using SALT for efficacy will occur at 4, 8, 12, 16, 20 and 24 weeks.

Patient safety will be monitored throughout the trial by the Investigator and supported by regular review by the Medical Monitor and DMC. Chemistry and hematology laboratory values will be assessed under fasted conditions bi-weekly for the first month of the treatment period, followed by every 4 weeks through the remainder of the study. Lipid levels will be assessed every 4 weeks throughout the Treatment Period. In light of the COVID-19 pandemic, challenges in the conduct of study visits may arise from quarantines, site closures, and/or travel limitations. To ensure the safety of trial participants and to minimize risk to trial integrity, alternative methods for drug dispensation and assessments, including telemedicine visits and clinical laboratory blood draws at a local laboratory or via a Home Health Care agency, may be offered for those trial participants who may no longer have access to the investigational site. 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 treatment at the judgement of the Investigator, but will be followed for safety and efficacy assessments until Week 24, unless they withdraw consent. Patients may withdraw consent at any time.

Following the 24-week Treatment Period, patients will have the opportunity to continue receiving treatment in an Open-Label Extension study. If a patient does not wish to continue into the Open-label

Extension study, they will complete treatment at Week 24 and return in 4 weeks for the Post-Treatment Safety Follow-up to assess safety following treatment completion.

**Number of patients (planned):**

Approximately 440 patients are planned to be randomized in the study. Patients will be randomized in a 1:2:1 ratio (12 mg BID:8 mg BID:placebo).

**Diagnosis and main criteria for inclusion:**

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

***Inclusion Criteria:***

1. Written informed consent, and authorization for release and use of protected health information.
2. Between 18 and 65 years of age, inclusive, at the time of informed consent.
3. Definitive diagnosis of alopecia areata with a current episode of scalp hair loss 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, female participants and female partners of male participants, willing and able to use a medically highly effective form of birth control from at least 4 weeks prior to Baseline until at least 30 days following last dose of study drug. Examples of medically highly effective forms of birth control are:
    a. Confirmed infertility due to surgical procedure
    b. Post-menopausal (cessation of menses for at least 12 months prior to screening)
    c. Infertility of sexual partner or partner of the same sex
    d. Implants of levonorgestrel in females
    e. Contraceptive (combined oral, patch, vaginal ring, injectable, implant) in females
    f. Double-barrier method (any combination of physical and chemical methods)
    g. Intrauterine device with a failure rate less than 1% per year
6. Male participants must:
    a. Agree to use, with their partners, one of the highly effective contraceptive methods listed in Inclusion Criterion 5, from Baseline until at least 30 days following last dose of study drug.
    b. Refrain from donating sperm during the study and for at least 30 days after the end of the study.
7. 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 Baseline or during the study that may affect hair regrowth or immune response, including but not limited to: corticosteroids administered orally, intravenously or intramuscularly, or applied to areas of skin affected by alopecia (intranasal and inhaled corticosteroids are allowed, eye and ear drops containing corticosteroids are also allowed); oral retinoids, oral cyclines (minocin, tetracycline); platelet-rich plasma injections; topical application to affected areas of retinoids, anthralin, squaric acid, diphenylcyclopropenone, or minoxidil.
3. Treatment with systemic immunosuppressive medications including but not limited to methotrexate, cyclosporine, azathioprine, chloroquine derivatives, etanercept, JAK inhibitors within 3 months of Screening or during the study.

NOTE: Patients previously treated with a Janus Kinase inhibitor more than 3 months prior to Screening may be allowed to enter the study at the discretion of the PI, if their previous treatment with a JAK inhibitor was well tolerated, and subsequent JAK treatment would not be thought to put the subject at risk. Consultation with the Medical Monitor may be warranted should questions arise with regard to prior tolerability.

4. Treatment with biologics (e.g., adalimumab, atlizumab, canakinumab, certolizumab, fontolizumab, golimumab, infliximab, mepolizumab, rituximab, secukinumab, tocilizumab, ustekinumab) within 6 months of Screening or during the study.
5. 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.
6. Known history of moderate to severe androgenic alopecia or female pattern hair loss prior to alopecia areata.
7. 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.
8. Use of adhesive wigs, other than banded perimeter wigs, during the study.
9. 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.
10. History of solid organ or hematological transplantation.
11. Fever, inflammation, or systemic signs of illness suggestive of systemic or invasive infection or a positive SARS-CoV-2 test result within 2 weeks prior to Baseline.
12. Abnormal levels of thyroid stimulating hormone at Screening, defined as <0.9 x the lower limit of normal (LLN) and >1.5 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 $\leq 100 \times 10^9$/L or $\geq 600 \times 10^9$/L
    b. Absolute neutrophil count $\leq 1.5 \times 10^9$/L
    c. Hemoglobin levels ≤10.5 g/dL for females, or hemoglobin levels ≤12.0 g/dL for males
14. Screening blood level of hemoglobin A1c ≥7.5% (58 mmol/mol, 9.3 mmol/L).
15. Abnormal liver function at Screening, defined as ≥2 × ULN of serum alanine transaminase, serum aspartate transaminase, and serum alkaline phosphatase, or ≥1.5 x ULN total bilirubin (unless isolated Gilbert's syndrome).
16. Abnormal renal function (estimated glomerular filtration rate <60 mL/min/1.73 $m^2$ using the CKD-EPI 2009 equation) at Screening.
17. Patient has positive results for hepatitis B surface antigens (HBsAg), antibodies to hepatitis B core antigens (anti-HBc), or hepatitis C virus (HCV) at Screening, or known history of human immunodeficiency virus infection. Subjects who test positive for HCV but who are in remission (sustained virologic response as evidenced by undetectable HCV RNA level using a sensitive assay≥ 12 weeks after completion of HCV therapy) are allowed inclusion in the study.
18. . Vaccination with a live attenuated vaccine during the study or up to 6 weeks prior to randomization.

19. History of previous active disease due to *M. tuberculosis* (TB) without documentation of successful treatment; OR, patient has a positive result from a Tuberculin Skin Test (TST) or a QuantiFERON-TB Gold (QFT) test performed at Screening.

    NOTE: If the patient has a positive QFT result at Screening and: (1) has no history of successful treatment for either active disease or latent infection due to M. tuberculosis, or (2) currently resides in an area with low prevalence of tuberculosis, or (3) has no lifetime history of occupational or household exposure to person(s) with tuberculosis, then the initial Screening QFT result may be a false-positive. In this instance, a second Screening test for latent TB infection should be obtained – either: (1) a repeat QFT test or (2) a Tuberculin Skin Test (TST). The repeat QFT test must be negative or the TST should show <15mm induration (considered negative TST) before being considered eligible for the study.
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 drug.
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 > 499 mL of blood or plasma within 56 days of Screening (during a clinical trial or at a blood bank donation) and for 30 days after last dose of study drug.
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 or 12 mg every 12 hours during the Treatment Period.

**Reference therapy, dosage and mode of administration:**

Matching placebo will be dosed orally as tablets every 12 hours during the Treatment Period

**Duration of treatment:**

Patients will receive up to 24 weeks of study drug.

**Duration of study participation:**

Upon completion of the 24-week Treatment Period, patients will be eligible to either enroll in the Open-Label Extension study or complete treatment and exit the study following the 4-week Safety Follow-up visit. Patients will participate in the study for up to 32 weeks if they decide not to enroll in the Open-Label Extension study (4-week Screening, 24-week Treatment, 4-week Safety Follow-up). Otherwise study duration will be up to approximately 28 weeks.

**Criteria for evaluation:**

**Primary Efficacy Endpoint**

- The primary efficacy endpoint will be the percentage of patients achieving an absolute SALT score ≤20 at Week 24.

**Key Secondary Endpoints**

- Percentage of responders (defined as "satisfied" or "very satisfied") on the Hair Satisfaction Patient Reported Outcome (SPRO) scale at Week 24
- Percentage of patients achieving an absolute SALT score of ≤20 at Week 20, 16, 12 and 8

For the primary efficacy analysis and in a hierarchical fashion within each dose level, key secondary efficacy analysis, a ≤ 0.025 (two-sided) alpha-level will be allocated to each dose for comparison with placebo to adjust for multiplicity of testing associated with two doses. Additional testing for secondary endpoints, in the order specified (see Section 12.4.3) (within each dose versus placebo) will continue to be tested at 0.025, in an alpha-level protected fashion, until not significant at 0.025. Nominal p-values will be reported for all tests, irrespective. Testing will be performed only for the Treatment Period.

**Secondary Endpoints**

- Relative change in SALT scores from Baseline at Weeks 4, 8, 12, 16, 20, and 24
- Percentage of responders (defined as "much improved" or "very much improved") using the CGI-I at Weeks 12, 16, 20, and 24
- Percentage of responders (defined as "much improved" or "very much improved") using the PGI-I at Weeks 12, 16, 20, and 24
- Change from Baseline in the CGI-S at Weeks 12, 16, 20, and 24
- Change from Baseline in the PGI-S at Weeks 12, 16, 20, and 24
- Percentage of patients achieving at least a 75% relative reduction in SALT score from Baseline at Weeks 12 and 24
- Percentage of patients achieving at least a 90% relative reduction in SALT score from Baseline at Weeks 12 and 24
- Change from Baseline on the Brigham Eyebrow Tool for Alopecia (BETA) score at Weeks 12 and 24
- Change from Baseline on the Brigham Eyelash Tool for Alopecia (BELA) score at Weeks 12 and 24
- Percentage of responders (defined as "satisfied" or "very satisfied") on the Hair Satisfaction Patient Reported Outcome (SPRO) scale at Weeks 12, 16, and 20
- Change from Baseline in the Hair Satisfaction Patient Reported Outcome (SPRO) scale at Weeks 12, 16, 20, and 24
- Percentage of patients achieving a ≥ 2-point change from Baseline in the Hair Satisfaction Patient Reported Outcome (SPRO) scale at Weeks 12, 16, 20, and 24
- Change from Baseline on the individual items of the Hair Quality Patient Reported Outcome (QPRO) scale at Weeks 12, 16, 20, and 24
- Change from Baseline in the depression scale of the Hospital Anxiety and Depression Scale (HADS) at Week 24
- Change from Baseline in the anxiety scale of the Hospital Anxiety and Depression Scale (HADS) at Week 24
- Percentage of patients achieving an absolute SALT score of ≤20 at Weeks 8 and 4
- Percentage of patients achieving an absolute SALT score of ≤10 at Week 24

There is no additional control for Type-1 error for the secondary endpoints.

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

**Safety**

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

**Statistical methods:**

***Sample Size:***

Power is calculated for the Primary Efficacy Endpoint for the continuity-corrected chi-square test using a 2-sided significance level of 0.025. Based on Phase 2 results, the percentage of patients achieving an absolute SALT score ≤20 at Week 24 is assumed to be 40%, 26%, and 9% for the 12 mg BID CTP-543, 8 mg BID CTP-543, and placebo groups, respectively. Patients will be randomized in a 1:2:1 ratio with a total N of approximately 440 patients (i.e., 110 for 12 mg BID, 220 for 8 mg BID, and 110 for placebo). These sample sizes will provide >99% power for the comparison of CTP-543 12 mg BID versus placebo and approximately 92% power for the comparison of CTP-543 8 mg BID versus placebo.

***Efficacy Analyses:***

The Efficacy Population will include all patients who are randomized in the study and dispensed study drug during the Treatment Period. The primary efficacy endpoint will be the proportion of patients achieving an absolute SALT score of ≤20 at Week 24. Pairwise treatment group differences from placebo will be assessed with the Cochran-Mantel-Haenszel test using baseline scalp hair loss (partial vs complete/near-complete) as the stratification factor, for each active treatment group versus placebo. Data will be summarized by active treatment versus placebo-treated patients (i.e., by treatment group). All data for analysis will be listed by patient. Continuous measures will be summarized descriptively (mean, standard deviation, median, minimum value, and maximum value) and categorical measures will be presented as number and percentage.

The final efficacy analysis will be conducted when all patients in the study have had the opportunity to complete Week 24. Additional details for statistical methods will be provided in the Statistical Analysis Plan.

***Population Pharmacokinetic Analyses:***

CTP-543 population PK analysis will be conducted using sparse PK sampling in a subset of patients. Population PK analysis will include the evaluation of various covariates that may include the effects of age, gender, race, and weight (or BMI) on the PK of CTP-543. Exposure-response relationships for both efficacy and safety parameters will also be assessed.

***Safety Analyses:***

The Safety Population will include all patients who receive study drug during the Treatment Period. 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. Adverse events, vital sign measurements, physical examination findings, clinical laboratory information, and concomitant medications will be tabulated and summarized by treatment and dose level. By-patient listings will be provided for any deaths, serious adverse events, and adverse events leading to discontinuation of treatment.

# 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 1: Abbreviations and Specialist Terms**

| Abbreviation or Specialist Term | Explanation |
|---|---|
| BID | Twice daily dosing |
| CFR | Code of Federal Regulations |
| CGI-I | Clinician Global Impression of Improvement |
| CGI-S | Clinician Global Impression of Severity |
| CTCAE | Common terminology criteria for adverse events |
| CYP3A4 | Cytochrome P450 3A4 |
| DMP | Data Management Plan |
| EC | Ethics Committee |
| eCRF | Electronic case report form |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| HADS | Hospital Anxiety and Depression Scale |
| HIV | Human Immunodeficiency Virus |
| ICF | Informed consent form |
| ICH | International Council on Harmonisation |
| IRB | Institutional Review Board |
| JAK | Janus kinase |
| LLN | Lower Limit of Normal |
| CKD-EPI | Chronic Kidney Disease Epidemiology Collaboration |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PCS | Potentially clinically significant |
| PGI-I | Patient Global Impression of Improvement |
| PGI-S | Patient Global Impression of Severity |
| QPRO | Quality of Hair Patient Reported Outcome |
| QTc | QT interval corrected for heart rate |
| QTcF | QT interval corrected for heart rate (Fridericia's method) |
| SALT | Severity of Alopecia Tool |
| SPRO | Satisfaction of Hair Patient Reported Outcome |
| STAT | Signal transducers and activators of transcription |
| TEAE | Treatment-emergent adverse events |
| ULN | Upper Limit of Normal |

# 4. INTRODUCTION

## 4.1. Overview of Alopecia Areata

Alopecia areata (AA) is an autoimmune disorder characterized by patches of non-scarring alopecia affecting scalp or scalp and body hair. Alopecia areata is clinically heterogeneous, affects males and females, and has a prevalence rate of approximately 0.2% of the United States population (Safavi, 1992; Benigno, 2020). 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). 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), Health Canada, or any Competent Authority in the European Union indicating a significant unmet medical need.

## 4.2. Scientific Rationale for the Study

Recent advances in the understanding of the pathogenesis of AA have shown Janus kinase (JAK) inhibitors to be a promising novel therapy.

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 a murine model of AA, CD81 T cells were shown to be central in AA, causing up-regulation of interleukin-15 in hair follicles and ultimately production of interferon-gamma, which targets the hair follicle for attack (Xing, 2014). As downstream regulators of interferon-gamma and interleukin-15, JAK inhibitors have been shown to eliminate the interferon signature and reverse disease.

CTP-543 is a selective JAK inhibitor. 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 determined. CTP-543 was found to have potent and selective inhibitory activity for intracellular JAK1 and JAK2 ($IC_{50}$ (nM) = 4.7 and 20, respectively) signaling.

There is evidence that CTP-543 has benefit in patients with moderate to severe alopecia areata. Three Phase 2 clinical studies of CTP-543 have been conducted in patients with moderate to severe alopecia areata. The first Phase 2 study was a double-blind, randomized, placebo-controlled, dose-ranging clinical trial. The overall objectives of the study were to assess the safety and efficacy of a 24-week regimen of administration of 4, 8, or 12 mg BID CTP-543 compared with matching placebo in adult patients with moderate to severe alopecia areata. The primary efficacy endpoint was the proportion of responders, defined as patients achieving at least a 50% relative reduction in SALT score at Week 24 relative to Baseline. The primary efficacy endpoint was met in both the 8 mg BID group and 12 mg BID groups. The difference between the 4 mg BID group and the placebo group was not statistically significant. The 8 mg BID and 12 mg BID doses also produced significant results vs placebo when other analyses of SALT data (i.e., percentage of patients achieving SALT $\leq$ 20) were conducted as well as analyses of patient and clinician reported global impression. The 8 mg BID and 12 mg BID doses were further assessed in two additional Phase 2 dose regimen clinical trials (see Section 4.4.2) in which once-daily versus twice-daily dosing with CTP-543 were assessed.

The definitive dose-ranging study (CP543.2001) and the completed dose regimen studies (CP543.2002 and CP543.2003) demonstrated that both the 8 mg BID and 12 mg BID doses of CTP-543 are effective and generally well tolerated. Consequently, both of these doses will be studied in this Phase 3 registration study in adult patients with alopecia areata.

Summaries of all clinical studies conducted to-date can be found in Section 4.4 below. Further details are provided in the current CTP-543 Investigator's Brochure.

## 4.3. Nonclinical Information for CTP-543

A series of nonclinical studies were performed with CTP-543, which evaluated the *in vitro* and *in vivo* pharmacokinetic (PK) and metabolism properties, safety pharmacology, toxicology and toxicokinetics, and genotoxicity. All safety pharmacology and toxicology studies considered necessary for human safety assessment were conducted in compliance with Good Laboratory Practice regulations.

Further details of the nonclinical studies for CTP-543 are described in the Investigator's Brochure.

## 4.4. Clinical Information for CTP-543

### 4.4.1. Clinical Studies of CTP-543 in Healthy Subjects

To date, five Phase 1 studies have been completed in healthy subjects, evaluating the safety, tolerability, and PK profile of single and multiple ascending doses of CTP-543: a single dose crossover study of CTP-543 versus ruxolitinib; a food effect study of CTP-543; a mass-balance study, and a drug-drug interaction (DDI) study with oral contraceptive (OC). A brief description of these studies is described below. Further details of the Phase 1 studies for CTP-543 are described in the Investigator's Brochure.

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 subjects. 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. CTP-543 was generally well tolerated in these studies and showed a dose proportional PK profile.

Study CP543.1002 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 or 16 mg of CTP-543 in Period 1 who then crossed over to the alternate treatment for Period 2. CTP-543 was generally well tolerated in this study and showed an increase in PK parameters compared to ruxolitinib.

Study CP543.1003 was a cross-over study to characterize and compare the relative bioavailability and PK profile of CTP-543 and metabolites under both fed and fasted conditions. A total of 14 subjects were enrolled and received single oral doses of 16 mg CTP-543. The administration of 16 mg CTP-543 under fed conditions resulted in a statistically significant decrease (approximately 40%) in peak exposure but not in total exposure compared to administration under fasted conditions. Single oral doses of 16 mg CTP-543 appeared to be well tolerated in both fasted and fed conditions.

Study CP543.1004 assessed the absorption, metabolism, excretion, and mass balance of oral [14C]-CTP-543 in healthy adult male subjects. The study showed that there are no circulating metabolites above 10% of drug related material. Additionally, all metabolites in excreta are below 25% of drug related material. No adverse events were reported in this study.

Study CP543.1005 was a 2-period, fixed-sequence study to determine the effect of multiple doses of CTP-543 on single dose pharmacokinetics (PK) of the components of a combination OC, ethinyl estradiol (EE) and levonorgestrel (LNG). Multiple oral doses of 12 mg CTP-543 administered BID on Days 1 – 8 had no impact on EE overall and peak exposures following coadministration with a single dose of combination OC (0.03 mg EE / 0.15 mg LNG). Multiple oral doses of 12 mg CTP-543 administered BID on Days 1 - 8 increased LNG overall and peak exposures by approximately 17% and 16%, respectively, following coadministration with a single dose of combination OC (0.03 mg EE / 0.15 mg LNG) compared to Combination OC alone. This small increase in LNG exposure is not expected to impact the efficacy or safety of the OC. Overall, there were no new findings and AEs reported were consistent with previously reported safety data from other CTP-543 studies.

### 4.4.2. Clinical Studies of CTP-543 in Patients with Alopecia Areata

Three Phase 2 studies in patients with moderate to severe AA have been completed and one Phase 2 trial is currently ongoing. An Open-Label Extension study (CP543.5001) and a Phase 3 study (CP543.3001) are currently ongoing.

Study CP543.3001 is a double-blind, randomized, placebo-controlled trial in 700 patients with moderate to severe alopecia areata being conducted in the US, Canada, and select EU countries. For more details of these studies, please see the CTP-543 Investigator's Brochure.

Study CP543.2001 was a double-blind, randomized, placebo-controlled Phase 2 dose ranging study to evaluate the safety and efficacy of CTP-543 in adult patients with moderate to severe alopecia areata. A total of 149 adults with moderate to severe alopecia areata were enrolled

across three cohorts. Patients were sequentially randomized to receive one of three doses of CTP-543 (4, 8, 12 mg twice daily) or placebo for 24 weeks.

The overall objectives of the study were to assess the safety and efficacy of a 24-week regimen of administration of 4, 8, or 12 mg BID CTP-543 compared with matching placebo in adult patients with moderate to severe alopecia areata. The primary efficacy endpoint was the proportion of responders, defined as patients achieving at least a 50% relative reduction in SALT score, from Baseline at Week 24. The primary efficacy endpoint was met in both the 8 mg BID group and the 12 mg BID group. The difference between the 4 mg BID group and the placebo group was not statistically significant.

The primary efficacy endpoint result was supported by results of exploratory endpoints utilizing SALT as well as clinician-based assessments and patient reported outcomes. The 8 mg BID and 12 mg BID groups differentiated from placebo on various SALT analyses and had significant improvements in alopecia areata as measured by the CGI-I and PGI-I compared with the placebo group.

The improvements in alopecia areata symptoms observed in the CTP-543 treatment groups were progressive over time through 24 weeks and appeared to be dose responsive. Significant differences from placebo were noted as early as 12 weeks into treatment.

CTP-543 was generally well tolerated in all Cohorts.

Study CP543.2002 was a randomized, open-label study to evaluate the efficacy and tolerability of two dosing regimens (8 mg BID versus 16 mg QD) of CTP-543 in adult patients with moderate to severe alopecia areata. Fifty-seven patients were randomized to receive CTP-543 either 8 mg BID or 16 mg QD over a 24-week treatment period. The trial measured the relative change in SALT score between Week 24 and Baseline. Efficacy results in the 8 mg BID arm were consistent with the previously-reported 8 mg BID results from the CP543.2001 trial and showed superiority of the 8 mg BID dose group over the 16 mg QD dose group. Treatment was generally well tolerated in both arms of the study.

CP543.2003 was a randomized, open-label study to evaluate the efficacy and tolerability of two dosing regimens (12 mg BID versus 24 mg QD) of CTP-543 in adult patients with moderate to severe alopecia areata. Sixty-six patients were randomized to receive CTP-543 either 12 mg BID or 24 mg QD over a 24-week treatment period. The trial measured the relative change in SALT score between Week 24 and Baseline. The primary outcome for the CP543.2003 study was the relative change in SALT score for each dose regimen from Baseline at Week 24. Following 24 weeks of dosing, subjects in the 12 mg BID dose group had a 60% relative change to Baseline in total SALT score at Week 24 compared to 52% in the 24 mg QD dose group. CTP-543 was generally well tolerated in both 24 mg/day dosing regimens.

Both dose regimen studies support the continued use of the BID dosing regimen in the Phase 3 program.

Study CP543.5001 is an Open-Label Extension study in patients with alopecia areata who were previously enrolled in a qualifying clinical trial with CTP-543 and completed through the 24-week Treatment Period. Patients will receive daily treatment with CTP-543 at a dose of 8 mg BID or 12 mg BID for up to 164 weeks in this study. Previously qualifying CTP-543 clinical trials include: Cohort 3 from Study CP543.2001, Study CP543.2002, and Study CP543.2003.

Taken together, the safety results of the Phase 2 clinical trials performed to-date appeared to show an overall acceptable risk-benefit profile for CTP-543.

# 5. ETHICS

The procedures set out in this study protocol, pertaining to the conduct, evaluation and documentation of this study, are designed to ensure that the Sponsor and the Investigator abide by Good Clinical Practice (GCP), including but not limited to Title 21 Code of Federal Regulations (CFR) Parts 50, 56, and 312, and the International Council 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)/Ethics Committee (EC)

The Institutional Review Board (IRB)/Ethics Committee (EC) will meet all regulatory authority requirements governing IRBs/ECs according to local regulations (e.g., 21 CFR Part 56, ICH E6). The study protocol and any amendments, the Sponsor's approved informed consent form(s) (ICF), patient information sheets, patient recruitment materials, and other appropriate documents must be submitted to the IRB/EC by delegated study personnel 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) or Investigator dependent upon who is responsible for the initial submission.

Any advertisements used to recruit patients for the study will be reviewed by the Sponsor and the IRB/EC 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/EC, must follow the Protection of Human Subjects regulations listed in the Code of Federal Regulations, Title 21, Part 50 or Directive 2001/20/EC, and local country regulations. 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/EC and by the Sponsor. The ICF must not be altered without the prior agreement of the relevant IRB/EC and the Sponsor.

# 6. STUDY OBJECTIVES

The overall objectives of the study are to assess the efficacy and safety of CTP-543 in adult patients with moderate to severe alopecia areata.

## 6.1. Primary Objectives

The primary objectives of the study are to assess:

- The efficacy of CTP-543 on regrowth of hair following 24 weeks of treatment
- The safety of CTP-543 following 24 weeks of treatment.

## 6.2. Secondary Objectives

The secondary objectives of the study are to assess:

- Clinician- and patient-reported impression of the severity and improvement of alopecia areata
- Patient-reported satisfaction with their scalp hair
- Patient-reported levels of anxiety and depression
- Changes in eyebrows and eyelashes.

# 7. OVERALL STUDY DESIGN

## 7.1. Study Design

This is a double-blind, randomized, placebo-controlled, multicenter study to evaluate the efficacy and safety of CTP-543 in adult patients with moderate to severe alopecia areata. Patients will require a definitive diagnosis of alopecia areata by the Investigator based on clinical evaluation involving physical examination and medical history. The patient's alopecia areata will be classified by the Investigator into one of two categories defined for this study:

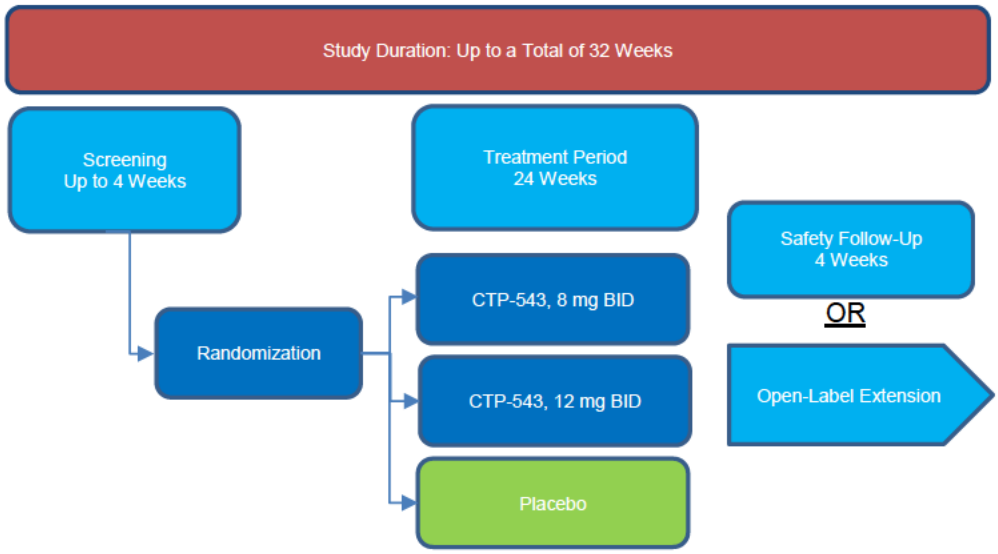
1) Partial scalp hair loss (SALT score ≥ 50 and < 95);
2) Complete or near-complete scalp hair loss (SALT ≥ 95).

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

An independent Data Monitoring Committee (DMC) will perform regular safety assessments. The DMC will convene to review accumulated safety data at regular intervals specified in the DMC Charter. The DMC will determine if there are adequate safety data to support continuation of a particular dose group or individual patient and may advise study and/or treatment arm cessation due to intolerability at any time.

The Screening Period may last up to 28 days prior to initiation of study drug. The Treatment Period is a 24-week, double-blind, placebo-controlled period to define efficacy and safety for CTP-543. Following the 24-week Treatment Period, patients will have the opportunity to continue receiving treatment in an Open-Label Extension study. If a patient does not wish to continue into the Open-Label Extension study, they will complete treatment at Week 24 and return in 4 weeks for the Post-Treatment Safety Follow-up to assess safety following treatment completion.

**Figure 1: Study Design**




Patients will provide appropriately-obtained informed consent prior to initiating any screening procedures. Patients meeting initial screening criteria will be eligible to continue to the Day 1 visit for review of eligibility and baseline assessments, including SALT assessment, physical examination, clinical laboratory assessments, and vital signs. Patients will be randomized in a 1:2:1 ratio (12 mg BID:8 mg BID:placebo). Randomization will be stratified by scalp hair loss into one of the following two categories: 1) Partial scalp hair loss (SALT $\geq$ 50 and $<$ 95); 2) Complete or near-complete scalp hair loss (SALT $\geq$ 95).

The double-blind, placebo-controlled Treatment Period for each group will last 24 weeks. Assessment of treatment response using SALT will occur at 4, 8, 12, 16, 20 and 24 weeks. All SALT assessments will be performed with a live physical examination of the patient by qualified, trained site personnel. Photographs of the scalp will be used to provide a visual record at the time of SALT assessments. Photographs of the eyebrows and eyelashes will be taken at Baseline, Week 12, and Week 24 as outlined in Table 2. Photographs of hands will be taken at the same timepoints as eyebrows and eyelashes to document nail involvement in those patients for whom it applies. The primary efficacy analysis will be conducted when all patients have completed Week 24.

Enrolled patients will take the first dose of study drug in the clinic on Day 1 and will be instructed to take study drug daily approximately every 12 hours without regard to food, for the duration of the Treatment Period. Patients should take study drug in the clinic on all Study Visit Days after clinical laboratory blood draws are completed. All efficacy, patient and clinician reported outcomes, and laboratory and safety assessments will be conducted according to the Schedule of Assessments (Table 2).

Patient safety will be monitored throughout the study by the Investigator and appropriate staff, and supported by regular review by the Medical Monitor, and DMC. Chemistry, hematology, and lipid laboratory values will be monitored closely for the duration of the study. Chemistry and hematology laboratory values will be assessed under fasted conditions bi-weekly for the first month of the treatment period, followed by every 4 weeks through the remainder of the study.

Lipid levels will be assessed every 4 weeks throughout the Treatment Period. In light of the COVID-19 pandemic, challenges in the conduct of study visits may arise from quarantines, site closures, and/or travel limitations. To ensure the safety of trial participants and to minimize risk to trial integrity, alternative methods for drug dispensation and assessments, including telemedicine visits and clinical laboratory blood draws at a local laboratory or via a Home Health Care agency, may be offered for those trial participants who may no longer have access to the investigational site. Additional information will be documented in study manuals. 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 treatment at the judgement of the Investigator, but will continue in the study and complete all assessments unless they withdraw consent. Patients may withdraw consent at any time.

## 7.2. Number of Patients and Sites

Approximately 440 patients are planned to be randomized in the study. Approximately 50 sites total will be identified in North America and select EU countries.

## 7.3. Method of Treatment Assignment and Blinding

Patients will be randomized in a 1:2:1 ratio (12 mg BID:8 mg BID:placebo). Randomization will be stratified by scalp hair loss into one of the following two categories: 1) Partial scalp hair loss (SALT ≥ 50 and < 95); 2) Complete or near-complete scalp hair loss (SALT ≥ 95). The randomization schedule will be generated prior to study start.

All study patients, Investigators, and site study staff will be blinded to study drug assignment for the duration of the study. Tablets and packaging of CTP-543 and placebo will be identical in appearance.

## 7.4. Rationale for Study Design, Doses, and Primary Endpoint

Double-blind, randomized, placebo-controlled studies are considered optimal for obtaining unbiased estimates of the efficacy and safety of investigational products. The Severity of Alopecia Tool (SALT) (Olsen, 2004) was introduced as part of investigative guidelines published by the National Alopecia Areata Foundation is widely used to assess the extent of the scalp surface hair loss in AA. The SALT has been used as the hair loss measurement scale in all the studies of CTP-543 in patients with alopecia areata to date. The 24-week duration of the Treatment Period has been shown to be sufficient in establishing hair regrowth with CTP-543 and to significantly differentiate active doses from placebo as well as differentiate between doses of CTP-543.

The selection of the 8 mg and 12 mg BID doses of CTP-543 for this study is supported by the efficacy and safety of CTP-543 observed in the completed and analyzed Phase 2 CP543.2001, CP543.2002, and CP543.2003 studies. Analysis of the primary efficacy endpoint in CP543.2001 showed that the proportions of responders (patients achieving at least a 50% relative reduction in SALT score from Baseline at Week 24) were significantly greater in the 8 mg BID group and 12 mg BID group compared with the placebo group ($P$ <0.001 for both) and compared with the 4 mg BID group ($P$ = 0.030 and $P$ = 0.003, respectively). For the analysis performed on the efficacy population, 9.3% of patients in the placebo group and 21.4% of patients in the 4 mg BID

group were responders, compared with 47.4% in the 8 mg BID group and 58.3% in the 12 mg BID group. Results also showed a significantly greater proportion of responders in the 8 mg BID and 12 mg BID groups which had at least 50%, 75%, and 90% relative reduction in SALT score by Week 24 compared with both the placebo group and the 4 mg BID group.

Additionally, both the 8 mg BID group and the 12 mg BID group had significantly greater proportions of patients who achieved an absolute SALT score ≤20 at Week 24 compared with the placebo group. Achieving a SALT score ≤ 20 has been reported by AA patients and clinicians to represent clinically-meaningful treatment success for AA (Wyrwich, 2020). In the Wyrwich study, qualitative interviews were conducted in the US with hair expert dermatologists and AA patients who had experienced ≥50% scalp hair loss. The clinicians judged that 80% scalp hair represented treatment success. Adult and adolescent AA patients participating in the study perceived that, short of 100% scalp hair, the presence of ~70-90% scalp hair (median 80%) represented treatment success. Nearly all queried clinicians and patients in this study agreed that for patients with ≥ 50% scalp hair loss, successful treatment would be hair regrowth resulting in ≤ 20% scalp hair loss.

Therefore, based on the efficacy and safety data observed in the CP543.2001, CP543.2002, and CP543.2003 studies, 8 mg BID and 12 mg BID of CTP-543 will be assessed further for efficacy and safety in the Phase 3 program in patients with moderate to severe alopecia areata. This Phase 3 study will employ SALT as the hair loss assessment tool and the primary efficacy endpoint will be the percentage of patients who achieve a SALT score ≤ 20, as this represents a clinically-meaningful treatment success for patients with AA. This same primary endpoint is currently being used in the ongoing Phase 3 study, CP543.3001.

**Table 2: Schedule of Assessments**

| Event[1] | Screening | Baseline/ Randomization | Treatment Period[4] | | | | Safety Follow-Up |
|---|---|---|---|---|---|---|---|
| | Day -28 to Day -1[2] (Visit 1) | Day 1[3] (Visit 2) | Week 2 (Visit 3) | Week 4, 8, 12 (Visit 4, 5, 6) | Week 16, 20 (Visit 7, 8) | Week 24 (Visit 9)/ ET Visit | Week 28 (Visit 10)[5] |
| Informed consent | X | | | | | | |
| Eligibility assessment | X | X | | | | | |
| Demographics | X | | | | | | |
| Medical history | X | X | | | | | |
| Randomization | | X | | | | | |
| Complete physical examination | X | X | | | | X | X |
| Brief physical examination | | | | X | X | | |
| Height | X | | | | | | |
| Weight | X | X | | X | X | X | X |
| Pregnancy test[6] | X | X | | X | X | X | X |
| Tuberculosis test | X | | | | | | |
| Clinical laboratory testing[7,8] | X[9] | X | X[10] | X | X | X | X |
| Pharmacokinetic Sampling for Population Pharmacokinetics | | X | | X[12] | | X | |
| HBV and HCV test | X | | | | | | |
| 12-lead electrocardiogram | X | | | X[12] | | X | |
| Vital signs | X | X | | X | X | X | X |
| Severity of Alopecia Tool assessment[11] | X | X | | X | X | X | |
| Photographs of the scalp | X | X | | X | X | X | |
| Photographs of eyebrows, eyelashes, and hands | | X | | X[12] | | X | |
| Eyebrow Assessment (BETA) | | X | | X[12] | | X | |
| Eyelash Assessment (BELA) | | X | | X[12] | | X | |
| Patient Reported Outcome Scales: SPRO and QPRO | | X | | X[12] | X | X | |
| Patient and Clinical Global Impression of Improvement (PGI-I, CGI-I[11]) | | | | X[12] | X | X | |
| Patient and Clinical Global Impression of Severity (PGI-S, CGI-S[11]) | | X | | X[12] | X | X | |
| Hospital Anxiety and Depression Scale (HADS) | | X | | | | X | |
| Dispense study drug[13] | | X | | X | X | | |
| Study drug accountability | | | | X | X | X | |
| Adverse events[14] | X | X | X | X | X | X | X |
| Concomitant medications[14] | X | X | X | X | X | X | X |

HBV = hepatitis B virus; HCV = hepatitis C virus

[1] Due to the COVID-19 pandemic, patient study visits may be performed remotely when the provider and patient are not able to be physically present in the clinic. Study personnel should strive to perform assessments per the schedule of events above with the understanding that all assessments may not be able to be performed (ECGs, vitals, SALT assessments).

[2] Randomization/Day 1 may occur any time after eligibility has been confirmed.

[3] All subsequent visits and week increments should be based on the date of Visit 2 (Day 1).

[4] All visit windows are ±2 days.

[5] The Safety Follow-Up Visit is intended for those patients who do not roll over into the Open-Label Extension.

[6] For females of childbearing potential, a serum pregnancy test will be performed at Screening. Throughout the Treatment Period, and at the safety follow-up (if applicable), urine pregnancy tests will be performed.

[7] Includes fasted hematology, serum chemistry, and lipids performed by the central lab.

[8] Collected pre-dose.

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

[10] Will include hematology and serum chemistry **only**.

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

[12] Performed at **Week 12 only**.

[13] Due to COVID-19, Site to Subject (STS) or Direct to Subject (DTS) shipping services may be warranted in cases where a patient is not able to attend in clinic visits or a site is closed.

[14] Collection is ongoing.

# 8. SELECTION AND WITHDRAWAL OF PATIENTS

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

## 8.1. Patient Inclusion Criteria

1. Written informed consent, and authorization for release and use of protected health information.
2. Between 18 and 65 years of age, inclusive, at the time of informed consent.
3. Definitive diagnosis of alopecia areata with a current episode of scalp hair loss 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, female participants and female partners of male participants, willing and able to use a medically highly effective form of birth control from at least 4 weeks prior to Baseline until at least 30 days following last dose of study drug. Examples of medically highly effective forms of birth control are:
    a. Confirmed infertility due to surgical procedure
    b. Post-menopausal (cessation of menses for at least 12 months prior to screening)
    c. Infertility of sexual partner or partner of the same sex
    d. Implants of levonorgestrel in females
    e. Contraceptive (combined oral, patch, vaginal ring, injectable, implant) in females
    f. Double-barrier method (any combination of physical and chemical methods)
    g. Intrauterine device with a failure rate less than 1% per year
6. Male participants must:
    a. Agree to use, with their partners, one of the highly effective contraceptive methods listed in Inclusion Criterion 5, from Baseline until at least 30 days following last dose of study drug.
    b. Refrain from donating sperm during the study and for at least 30 days after the end of the study.
7. Willing to comply with the study visits and requirements of the study protocol.

## 8.2. Patient Exclusion Criteria

1. History or presence of hair transplants.
2. Treatment with other medications or agents within 1 month of Baseline or during the study that may affect hair regrowth or immune response, including but not limited to: corticosteroids administered orally, intravenously or intramuscularly, or applied to areas of skin affected by alopecia (intranasal and inhaled corticosteroids are allowed, eye and ear drops containing corticosteroids are also allowed); oral retinoids, oral cyclines

(minocin, tetracycline); platelet-rich plasma injections; topical application to affected areas of retinoids, anthralin, squaric acid, diphenylcyclopropenone, or minoxidil.

3. Treatment with systemic immunosuppressive medications including but not limited to methotrexate, cyclosporine, azathioprine, chloroquine derivatives, etanercept, JAK inhibitors within 3 months of Screening or during the study.

   NOTE: Patients previously treated with a Janus Kinase inhibitor more than 3 months prior to Screening may be allowed to enter the study at the discretion of the PI, if their previous treatment with a JAK inhibitor was well tolerated, and subsequent JAK treatment would not be thought to put the subject at risk. Consultation with the Medical Monitor may be warranted should questions arise with regard to prior tolerability.

4. Treatment with biologics (e.g., adalimumab, atlizumab, canakinumab, certolizumab, fontolizumab, golimumab, infliximab, mepolizumab, rituximab, secukinumab, tocilizumab, ustekinumab) within 6 months of Screening or during the study.
5. 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.
6. Known history of moderate to severe androgenic alopecia or female pattern hair loss prior to alopecia areata.
7. 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.
8. Use of adhesive wigs, other than banded perimeter wigs, during the study.
9. 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.
10. History of solid organ or hematological transplantation.
11. Fever, inflammation, or systemic signs of illness suggestive of systemic or invasive infection or a positive SARS-CoV-2 test result within 2 weeks prior to Baseline.
12. Abnormal levels of thyroid stimulating hormone at Screening, defined as <0.9 x the lower limit of normal (LLN) and >1.5 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 $\leq 100 \times 10^9$/L or $\geq 600 \times 10^9$/L
    b) Absolute neutrophil count $\leq 1.5 \times 10^9$/L
    c) Hemoglobin levels ≤10.5 g/dL for females, or hemoglobin levels ≤12.0 g/dL for males
14. Screening blood level of hemoglobin A1c ≥7.5% (58 mmol/mol, 9.3 mmol/L).

15. Abnormal liver function at Screening, defined as ≥2 × ULN of serum alanine transaminase, serum aspartate transaminase, and serum alkaline phosphatase, or ≥1.5 x ULN total bilirubin (unless isolated Gilbert's syndrome).
16. Abnormal renal function (estimated glomerular filtration rate <60 mL/min/1.73 m2 using the CKD-EPI 2009 equation) at Screening.
17. Patient has positive results for hepatitis B surface antigens (HBsAg), antibodies to hepatitis B core antigens (anti-HBc), or hepatitis C virus (HCV) at Screening, or known history of human immunodeficiency virus infection. Subjects who test positive for HCV but who are in remission (sustained virologic response as evidenced by undetectable HCV RNA level using a sensitive assay≥ 12 weeks after completion of HCV therapy) are allowed inclusion in the study.
18. Vaccination with a live attenuated vaccine during the study or up to 6 weeks prior to randomization.
19. History of previous active disease due to *M. tuberculosis* (TB) without documentation of successful treatment; OR, patient has a positive result from a Tuberculin Skin Test (TST) or a QuantiFERON-TB Gold (QFT) test performed at Screening.

    NOTE: If the patient has a positive QFT result at Screening and: (1) has no history of successful treatment for either active disease or latent infection due to M. tuberculosis, or (2) currently resides in an area with low prevalence of tuberculosis, or (3) has no lifetime history of occupational or household exposure to person(s) with tuberculosis, then the initial Screening QFT result may be a false-positive. In this instance, a second Screening test for latent TB infection should be obtained – either: (1) a repeat QFT test or (2) a Tuberculin Skin Test (TST). The repeat QFT test must be negative or the TST should show <15mm induration (considered negative TST) before being considered eligible for the study.
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 drug.
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 > 499 mL of blood or plasma within 56 days of Screening (during a clinical trial or at a blood bank donation) and for 30 days after last dose of study drug.
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.

## 8.3. Patient Withdrawal Criteria

For all patients, it is the intent that patients who discontinue study medication (at any time) for any reason will continue to be followed for all protocol-planned study visits through the completion of the 24-week treatment period, and will have all endpoints (including efficacy) collected accordingly.

The Investigator, Sponsor, or its designee may decide a patient should discontinue treatment at any time and for any reason. In addition, patients will discontinue randomized treatment if they:

- Experience an intolerable adverse event: such events include, but are not limited to, adverse events ≥ Grade 4*, bone marrow-related events, a ≥ Grade 3* cardiac event (*CTCAE v5.0 criteria);
- Require a medication that is prohibited by the protocol. However, under certain circumstances, and in consultation with the Medical Monitor, short-term use of a prohibited medication may not necessitate withdrawal of treatment when its use is unlikely to unfavorably alter the risk-benefit of subject participation;
- In the opinion of the Investigator, have any medically appropriate reason;
- Become pregnant;
- Have a serious adverse event associated with a SARS-CoV-2 infection;
- The Investigator believes that further treatment is undesirable or the risk-benefit profile has become unfavorable.

Furthermore, dose interruptions lasting more than 21 days may require treatment discontinuation on a case by case basis following consultation with the Medical Monitor.

In addition, 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 withdraws consent and requests to stop participating in the study. Patients who withdraw or are withdrawn from the study will not be replaced.

### 8.3.1. Patient Withdrawal Procedures

If a patient withdraws consent from further participation in 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.

## 8.4. Emergency Unblinding of Treatment Assignment

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

## 8.5. Criteria for Study Termination

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

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

High frequency of dose interruptions

High frequency of, or a trend in, SAEs

High frequency of Grade 3/4 adverse events

Trend in organ system-specific moderate and/or severe adverse events

High frequency of patient discontinuation of treatment due to adverse events

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

Any termination required by the Sponsor must be implemented by the Investigator, if instructed to do so, in a time frame that is compatible with the patient's well-being. The Sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons.

# 9. DESCRIPTION OF STUDY TREATMENTS

## 9.1. Description of Treatments

Patients will be stratified by extent of scalp hair loss and randomized to CTP-543 or placebo in a 1:2:1 ratio (12mg BID:8 mg BID: placebo).

Treatments arms will include:

- 12 mg CTP-543 every 12 hours
- 8 mg CTP-543 every 12 hours
- Placebo every 12 hours

For each treatment arm, patients will take the first dose of study drug in the clinic on Day 1 of the Treatment Period and will be instructed to take study drug approximately every 12 hours (± 3 hours) without regard to food for the duration of the study.

## 9.2. Dose-Adjustment Criteria

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

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

### 9.2.1. Dose Interruption Safety Criteria and Management

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

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

Hematology parameters will be assessed bi-weekly for the first 4 weeks of the Treatment Period, 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 Unscheduled Visit within 72 hours, except in severe cases (i.e.: neutrophil counts below 0.5 x $10^9$/L) where immediate interruption of dosing is necessary for the safety of the patient. **Blood draws confirming dose interruption criteria should occur prior to the first daily dose on the day of draw.**

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

**Table 3: Selected Hematologic Thresholds for Dose Interruption**

| **Neutrophil Count** | **Dose Adjustment** |
|---|---|
| Between 0.5 to 1 x $10^9$/L (Grade 3) | Interrupt dose until recovered to greater than 1.5 x $10^9$/L and resume dosing at previous dose |
| Less than 0.5 x $10^9$/L (Grade 4) | Severe case: Interrupt dose **immediately** and repeat CBC with differential within 72 hours. Recommend hematology consult and contact medical monitor. Permanent discontinuation of treatment should occur upon repeat confirmation of value |
| **Female Hemoglobin Level** | **Dose Adjustment** |
| Less than 10 g/dL | Interrupt dose until recovered to greater than 10.5 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 12 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 100 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 as prescribed by the Investigator |

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) a 21-day dose interruption period has elapsed, at which time a discussion between the PI and the Medical Monitor should occur to evaluate whether or not the subject should discontinue treatment permanently. In the case of severe neutropenia (neutrophil counts less than 0.5 x $10^9$/L) patient should interrupt dose **immediately** and repeat CBC with differential within 72 hours. The Medical Monitor should be contacted and a hematology consult should be made if appropriate. Permanent discontinuation of treatment should occur upon repeat confirmation of value. Patients who discontinue treatment due to lack of acceptable recovery of parameters should continue to be followed for all safety and efficacy assessments through the completion of the 24-week treatment period, and will have all endpoints (including efficacy) collected accordingly.

Subjects with both a positive SARS-CoV-2 test (antigen or antibody) AND signs or symptoms consistent with SARS-CoV-2 infection should immediately interrupt dosing with study drug. Dose interruption should continue until symptoms subside (it is not necessary to have a negative SARS-CoV-2 test result). If symptoms do not subside within a 21-day dose interruption period, a discussion between the PI and the Medical Monitor should occur to evaluate whether or not the

subject should discontinue treatment permanently. Signs and symptoms include, but are not limited to: fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, diarrhea, trouble breathing, persistent pain or pressure in the chest, new confusion, inability to wake or stay awake, bluish lips or face.

Subjects who have signs or symptoms consistent with SARS-CoV-2 infection should be tested for SARS-CoV-2 and do not have to dose interrupt unless the test result is positive. Subjects who have a positive SARS-CoV-2 test (antigen or antibody) but do not have any signs or symptoms consistent with SARS-CoV-2 infection are not required to dose interrupt.

**Table 4: SARS-CoV-2 Dose Interruption Criteria**

| SARS-CoV-2 Test Result | SARS-CoV-2 Symptoms | Dose Interruption |
|---|---|---|
| Positive | Yes | Yes |
| Positive | No | No |
| Negative | Yes | No |

### 9.2.2. Pharmacokinetic Criteria for Stopping Doses

There are no pharmacokinetic criteria for stopping study drug doses.

## 9.3. Treatment Compliance

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

## 9.4. Study Drug Materials and Management

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

### 9.4.1. Physical Description of Study Drug

Study drug will include CTP-543 and matching placebo. Details regarding formulation and dosage are presented in Table 5.

**Table 5: Investigational Product**

| | **Investigational Product (CTP-543 or Placebo)** |
|---|---|
| **Product Name:** | CTP-543 or Matching placebo |
| **Dosage Form:** | Tablet |

| | |
|---|---|
| **Dosage Strength of CTP-543** | 8 mg, 12 mg |
| **Route of Administration** | Oral |
| **Physical Description** | White, capsule-shaped tablets |

### 9.4.2. Study Drug Packaging, Labeling, and Storage

Study drug will be packaged and labeled by an appropriately qualified vendor. Each patient will receive one 60 count bottle of study medication at each 4-week study visit. Details of the packaging, labeling and dispensing instructions can be found in the Pharmacy Manual.

The label(s) for the investigational product and placebo will include the required caution statements and/or regulatory statements, as applicable per local regulations.

Adequate supplies of study drug will be provided to each site by the sponsor or designee. Study drug should be stored in the original container 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 bottle at room temperature as stated on the package label. No special handling procedures are required. Due to the COVID-19 pandemic, Site to Subject (STS) or Direct to Subject (DTS) shipping services may be warranted in cases where a patient is not able to attend in clinic visits or a site is closed. Additional information can be found in the Pharmacy Manual.

### 9.4.3. Study Drug Preparation and Administration

No study drug preparation is required. Patients will take the first dose of study drug in the clinic on Day 1 and will be instructed to take study drug approximately every 12 hours for the duration of the Treatment Period. Patients should dose study drug in the clinic on all Study Visit Days after clinical laboratory blood draws are completed.

Study drug should be taken at approximately the same times each day, with water, and without regard to food. Patients should be instructed to take one tablet in the morning and one tablet in the evening, approximately 12 hours apart. If a dose is missed, the patient should skip the missed dose and resume dosing at the next scheduled dose. The patient should not take two doses at the same time. Deviations from prescribed dosing should be discussed at each visit for assessment of compliance and retraining when necessary.

### 9.4.4. Study Drug Return and Disposal

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

### 9.4.5. Study Drug Accountability

To satisfy regulatory requirements regarding drug accountability, all study drug will be reconciled in full. The Investigator or designee must maintain accurate records of the receipt of

study drug, including date received, lot number, amount received, condition of the package, and the disposition of study drug.

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

## 9.5. Concomitant Medications and Procedures

All medications, including over-the-counter therapies (e.g., vitamins, herbal, and nutritional supplements) and vaccinations (including the SARS-CoV-2 vaccination), 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. Additionally, any prior janus kinase (JAK) inhibitor use or live virus vaccinations (including Herpes Zoster) will be recorded.

To date, there is no clear evidence of any safety concern for receipt of a SARS-CoV-2 vaccine during the treatment period. Existing data on JAK inhibitors and vaccines, including the SARS-CoV-2 vaccine, are insufficient to conclude whether JAK inhibitors, including CTP-543, have an effect on vaccine effectiveness, though data to date do not suggest that a major effect is likely. Subjects considering enrollment in this CP543.3002 trial may wish to receive their vaccine(s) before entering the trial. As subject and public health are paramount, SARS-CoV-2 vaccination should not be delayed or withheld for subjects already enrolled in the CTP-543 trial.

Knowledge about the vaccines and virus is continually growing. The Sponsor [redacted] will notify sites as new information is obtained that might further inform vaccine-related questions during the study. Please also carefully read the product information (package insert) for the vaccine being used, noting any specific precautions or warnings for concomitant administration with JAK inhibitors or immunosuppressants.

Any concomitant medication deemed necessary for the wellbeing of the patient may be given at the discretion of the Investigator. Use of medications that are prohibited per protocol will require patient withdrawal from the study. However, under certain circumstances, and in consultation with the Medical Monitor, short-term use of a prohibited medication may not necessitate withdrawal when its use is unlikely to unfavorably alter the risk-benefit of subject participation or confound the study endpoints.

The following treatments are not permitted during the study:

- Medications that may affect hair regrowth or immune response (such as: corticosteroids administered orally, by injection, or applied to areas of skin affected by alopecia; platelet-rich injections; topical application to affected areas of anthralin, squaric acid, diphenylcyclopropenone, or minoxidil;
- Chronic or long-term 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);

  - NOTE: a short course of steroid treatment for acute treatment of a condition during the trial may be allowed following discussion with the Medical Monitor

- Use of strong CYP3A4 inhibitors (such as, but not limited to clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, saquinavir, telaprevir, telithromycin, voriconazole, or fluconazole) dosed for systemic exposure;
- Use of strong CYP3A4 inducers (such as, but not limited to barbiturates, carbamazepine, efavirenz, glucocorticoids, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's Wort, or troglitazone) dosed for systemic exposure.
- Live vaccines including, but are not limited to) the measles, mumps, and rubella (MMR) vaccine; intranasal flu vaccine; and Zostavax (but not Shingrix) for herpes zoster.

# 10. STUDY ASSESSMENTS AND PROCEDURES

The schedule of assessments and procedures is presented in Table 2 and should be referenced for details regarding the collection of each assessment at each visit. Due to the COVID-19 pandemic, patient safety and some other assessments outlined below may be performed remotely if travel restrictions, quarantine, and/or site closures are presented and the Principal Investigator and the patient are not able to be physically present in the clinic.

## 10.1. Demographic Characteristics and Medical History

Demographic characteristics [i.e., sex, ethnic origin, date of birth (as appropriate per local regulations), 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 scalp hair loss into one of two categories defined for this study:

1) Partial scalp hair loss (SALT ≥ 50 and < 95);
2) Complete or near-complete scalp hair loss (SALT ≥ 95).

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 and any prior Janus kinase (JAK) inhibitor use, nail and facial hair involvement, co-morbidities, serious infection history and exposure risk, including HIV, as well as history or vaccination against herpes zoster will be collected at the Screening Visit, and at the Randomization Visit on Day 1 for each dose group.

Medical history should be thoroughly probed for potential exposure to serious infections such as HIV, history or vaccination against herpes zoster or other recent live virus vaccinations, prior SARS-CoV-2 infection, as well as cancer risk due to the potential immunosuppressive properties and known adverse events associated with JAK inhibitors.

## 10.2. Severity of Alopecia Tool (SALT)

The SALT score was introduced as part of investigative guidelines published by the National Alopecia Areata Foundation (Olsen, 2004). The SALT is a measure of hair loss that quantifies the amount of scalp surface without hair in a pre-specified quadrant of the scalp (right side, top, left side, back), that is further summed after applying a quadrant-specific multiplier indicative of scalp surface area contribution, to provide an overall score of total hair loss. The SALT assessment will occur via live examination of the patient during clinic visits. If a patient is unable to attend an in-person clinic visit due to COVID-19, a SALT assessment will not be performed. Missed assessments will be recorded in the eCRF as due to COVID-19.

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 will 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 Section 17.2.

## 10.3. Photographs

Photographs of the scalp will be used to provide a visual record at the time of Baseline assessment of SALT as well as potential changes in SALT scores throughout the study. Scalp photographs will correspond to the 4 defined quadrants of the SALT assessment and will be taken when SALT assessments are performed. Photographs of the scalp will be used to support rater training and continued monitoring throughout the course of the trial. However, no formal analyses will be performed on the photographs.

Photographs of the eyebrows and eyelashes will be taken at Baseline, Week 12, and Week 24 as outlined in Table 2. A formal analysis via photographs will be performed for those patients with eyebrow and/or eyelash involvement.

A photograph of the hands will be taken at the same timepoints as eyebrows and eyelashes to document potential changes for those with nail involvement throughout the study compared to Baseline. No formal analyses of nail involvement will occur.

If a patient is unable to attend an in-person clinic visit due to COVID-19, photographs will not be performed. Missed assessments will be recorded in the eCRF as due to COVID-19.

## 10.4. Global Impression Scales

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

In this study, the Global Impression Scale of Severity and the Global Impression Scale of Improvement will be performed by both the clinician and the patient at selected times during the study as indicated in Table 2.

### 10.4.1. Clinical Global Impression of Severity (CGI-S)

The Clinical Global Impression Scale of Severity will be assessed by the Investigator and will consider the severity of the patient's alopecia areata at the time of assessment. The Investigator may select one of seven numeric choices representing "Among the most extreme hair loss" to "Normal, no hair loss". To reduce variability, one rater should perform the CGI-S assessment for the patient. An example of the CGI-S is provided in Section 17.3.1. If a patient is unable to attend an in-person clinic visit due to COVID-19, the CGI-S will not be performed. Missed assessments will be recorded in the eCRF as due to COVID-19.

### 10.4.2. Clinical Global Impression of Improvement (CGI-I)

The Clinical Global Impression Scale of Improvement will be assessed by the Investigator. Compared to the patient's alopecia areata prior to treatment at Baseline, the patient's current state of alopecia areata will be assessed according to the Investigator's perceived change. The Investigator may select one of seven numeric choices representing "Very Much Worse" to "Very Much Improved". To reduce variability, one rater should perform the CGI-I assessment for the patient for the duration of the study. An example of the CGI-I is provided in Section 17.3.2. If a patient is unable to attend an in-person clinic visit due to COVID-19, the CGI-I will not be performed. Missed assessments will be recorded in the eCRF as due to COVID-19.

### 10.4.3. Patient Global Impression of Severity (PGI-S)

The Patient Global Impression Scale of Severity will be assessed by the patient and will consider the severity of his/her alopecia areata at the time of assessment. The Patient may select one of seven numeric choices representing "Among the most extreme hair loss" to "Normal, no hair loss". An example of the PGI-S is provided in Section 17.3.3. If a patient is unable to attend an in-person clinic visit due to COVID-19, the PGI-S should be performed via a virtual visit with video capability.

### 10.4.4. Patient Global Impression of Improvement (PGI-I)

The Patient Global Impression Scale of Improvement will be assessed by the patient. Compared to the patient's alopecia areata prior to treatment at Baseline, the patient's current state of alopecia areata will be assessed according to his/her perceived change. The patient may select one of seven numeric choices representing "Very Much Worse" to "Very Much Improved". An example of the PGI-I is provided in Section 17.3.4. If a patient is unable to attend an in-person clinic visit due to COVID-19, the PGI-I should be performed via a virtual visit with video capability.

## 10.5. Hair Satisfaction and Hair Quality Patient Reported Outcomes

The Hair Satisfaction Patient Reported Outcome (SPRO) is a single item questionnaire answered by the patient designed to measure how satisfied alopecia areata patients are with their hair at the time of the assessment. The Hair Quality Patient Reported Outcome (QPRO) questionnaire provides additional details on key attributes of their hair and to help provide context to the SPRO response. The SPRO and QPRO are provided in Section 17.4. If a patient is unable to attend an in-person clinic visit due to COVID-19, the SPRO and QPRO should be performed via a virtual visit with video capability.

## 10.6. HADS

The Hospital Anxiety and Depression Scale (HADS) is a 14-item measure designed to assess anxiety and depression symptoms in medical patients. Items are rated on a 4-point severity scale. The HADS produces two scales, one for anxiety (HADS–A) and one for depression (HADS–D). An example of the HADS is provided in Section 17.5. If a patient is unable to attend an in-person clinic visit due to COVID-19, the HADS should be performed via a virtual visit with video capability.

## 10.7. BETA

The Brigham Eyebrow Tool for Alopecia (BETA) is a clinician-rated scale that assesses the total eyebrow hair present. The scale is used for each eyebrow in which the Individual Eyebrow Score is derived by assessment of density (D) x surface area (SA). An expert panel will perform central readings based on photographs of the eyebrows and will provide a score for each patient with eyebrow involvement. The BETA will be performed at Baseline, Week 12, and Week 24. Additional detail on how to take the photographs for the central read of the BETA will be outlined in a separate study manual. If a patient is unable to attend an in-person clinic visit due to COVID-19, the BETA may not be performed due to the inability to take photographs of the eyebrows. Missed assessments will be recorded in the eCRF as due to COVID-19.

## 10.8. BELA

The Brigham Eyelash Tool for Alopecia (BELA) is a clinician-rated scale that assesses the total eyelash hair present. The scale is used for each eye in which the Total Eyelash Score is derived by assessment of density (D) and distribution on the right and left eye. An expert panel will perform central readings based on photographs of the eyelashes and will provide a score for each patient with eyelash involvement. The BELA will be performed at Baseline, Week 12, and Week 24. Additional detail on how to take the photographs for the central read of the BELA will be outlined in a separate study manual. If a patient is unable to attend an in-person clinic visit due to COVID-19, the BELA may not be performed due to the inability to take photographs of the eyelashes. Missed assessments will be recorded in the eCRF as due to COVID-19.

## 10.9. Pharmacokinetic Assessments

Whole blood (4 mL each) will be collected in $K_2$EDTA vacutainer collection tubes to evaluate plasma concentrations of CTP-543.

The exact time of blood collection as well as the exact time of the preceding dose will be recorded. To document the preceding dose time, patients should be instructed to record the last dosing time prior to the Week 12 and 24 visits directly on their dosing bottles. All attempts to adhere to the pharmacokinetic schedule should be made. However, the inability to follow the schedule or to obtain/process a sample will not be considered a protocol deviation.

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

## 10.10. 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 temperature.

Weight will be measured per institution standard of care. Patients should wear light clothing, empty pockets of heavy objects, 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 according to the Schedule of Assessments. Weight and height will be used to calculate the patient's body mass index at Screening. Refer to the Schedule of Assessments for assessment timepoints (Table 2).

In the event a patient is unable to attend an in-clinic visit due to COVID-19, vital signs may be performed by a Home Health Care agency.

## 10.11. Physical Examination

Per the Schedule of Assessments (Table 2) a complete physical examination will consist of an examination of all major organ systems to include, but not be limited to, chest auscultation, abdominal auscultation and palpation, head, eyes, ears, nose and throat. An assessment for active signs and symptoms of infection including tuberculosis, and skin examinations for non-melanoma skin cancers, will be performed. Evaluation for progressive multifocal leukoencephalopathy (PML) symptoms such as facial droop, general weakness, clumsiness, trouble speaking, personality changes, memory problems, and vision changes will be assessed. Additionally, an assessment for the presence or absence of nasal hair will be performed during complete physical exams.

Per the Schedule of Assessments (Table 2), brief physical examinations will include assessment for active signs and symptoms of infection, including tuberculosis, skin examinations for non-melanoma skin cancers, and an evaluation for progressive multifocal leukoencephalopathy (PML) symptoms such as facial droop, general weakness, clumsiness, trouble speaking, personality changes, memory problems, and vision changes.

If telemedicine visits are warranted due to COVID-19, the focus of a virtual physical exam should be on evaluation of safety, including assessing for active signs and symptoms of infection, exposure to TB, and inquiry on changes to skin lesions and/or moles indicative of skin cancers and signs and symptoms of PML.

## 10.12. Electrocardiogram

Twelve-lead electrocardiograms will be performed at the screening visit, Week 12, and end of study 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. A central reading center will be used to read all ECGs and determine QT/QTc intervals. The Investigator should indicate review of the electrocardiogram report by signing and dating the report. If a patient is unable to attend an in-person clinic visit due to COVID-19, an ECG may not be performed. Missed assessments will be recorded in the eCRF as due to COVID-19.

## 10.13. Clinical Laboratory Assessments

Clinical laboratory assessments are presented in Section 17.1. Clinical laboratory samples should be collected at the beginning of each clinic visit and just prior to a dose on all Study Visit Days and will be processed by a central laboratory. In the event a patient is unable to attend an in-clinic visit due to COVID-19, clinical laboratory blood draws may be performed by a Home Health Care agency or a local laboratory. Patients should try to have laboratory blood draws performed in the morning and dose study drug after clinical laboratory blood draws are completed.

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

All clinical laboratory results that fall outside the reference range will be interpreted by the Investigator as Abnormal, not clinically significant, or Abnormal, clinically significant. Laboratory results deemed Abnormal, clinically significant will be recorded as an adverse event in the eCRF (see additional criteria outlined in Section 11.1). Clinically significant laboratory abnormalities indicative of hematologic or other effects requiring intervention should be discussed with the Medical Monitor(s). 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.

## 10.14. Unscheduled Visit

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

# 11. ADVERSE EVENTS

## 11.1. Definition of Adverse Event

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

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

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

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

- Is considered clinically significant; OR
- results in discontinuation from the study; OR
- 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).

Vaccine-related AEs (e.g. fever, fatigue, headache) resulting directly from the vaccination may occur. The temporal relationship of the event(s) to the vaccination should be clearly described and the PI should consider whether these AEs are "unlikely" to be, or are "not related" to study medication.

## 11.2. Evaluation of Adverse Events

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

### 11.2.1. Serious Adverse Event

A serious adverse event is an adverse event, as per Title 21 CFR 312.32 and ICH E2A.II.B that fulfills the following criteria:

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

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

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

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

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

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

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

### 11.2.2. 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) (v5.0) should be used to grade the severity/intensity of all events. These criteria will be provided in the Site Operations Manual. If a CTCAE criterion does not exist, the Investigator should grade the severity according to the following criteria:

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

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

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

### 11.2.3. 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:

**Related for Regulatory Reporting Assessment:**

- **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).

**Unrelated for Regulatory Reporting Assessment:**

- **Unlikely Related**: A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or concurrent or underlying disease provide plausible explanations (e.g., the patient's clinical condition, other concomitant treatments).
- **Not related**: The adverse event is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

### 11.2.4. Duration

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

### 11.2.5. Action Taken

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

### 11.2.6. Outcome

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

## 11.3. Follow-Up

Adverse events, severe adverse events and serious adverse events, including clinically significant laboratory tests, electrocardiograms, or physical examination findings, will be followed, regardless of causality, for as long as necessary to adequately evaluate the patient's safety, or until the event stabilizes, is otherwise explained, death occurs, or the patient is lost to follow up. If resolved, a resolution date should be provided. The Investigator is responsible for ensuring

that follow-up includes any supplemental investigations indicated to elucidate the nature and/or causality of the adverse event. This may include additional clinical laboratory testing or investigations, examinations, or consultation with other health care professionals as is practical.

## 11.4. 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 in EDC 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 pregnancy occurs in a female patient, then study drug should be discontinued immediately. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication should be reported as an adverse event or serious adverse event if reporting criteria are met. Spontaneous abortion, and any congenital anomaly or birth defect in the patient's (or male patient's partner's) newborn should be reported as an SAE.

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

## 11.5. Recording Adverse Events

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

## 11.6. 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 completion of the safety follow-up visit, as applicable.

### 11.6.1. 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/EC.

**United States and Canada [redacted] 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]

### 11.6.2. 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(s)] must be immediately contacted so that appropriate urgent safety measures can be agreed upon. An urgent safety issue is defined as:

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

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

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

# 12. STATISTICAL METHODS

## 12.1. Sample Size Rationale

Power is calculated for the Primary Efficacy Endpoint for the continuity-corrected chi-square test using a 2-sided significance level of 0.025. Based on Phase 2 results, the percentage of patients achieving an absolute SALT score ≤20 at Week 24 is assumed to be 40%, 26%, and 9% for the CTP-543 12 mg, CTP-543 8 mg BID, and placebo groups, respectively. Patients will be randomized in a 1:2:1 ratio with a total N of approximately 440 patients (i.e., 110 for 12 mg BID, 220 for 8 mg BID, and 110 for placebo BID). These sample sizes will provide >99% power for the comparison of CTP-543 12 mg BID versus placebo and approximately 92% power for the comparison of CTP-543 8 mg BID versus placebo.

## 12.2. Endpoints

### 12.2.1. Efficacy

**Primary Efficacy Endpoint**

- The primary efficacy endpoint will be the percentage of patients achieving an absolute SALT score of ≤20 at Week 24.

**Key Secondary Endpoints**

1. Percentage of responders (defined as "satisfied" or "very satisfied") on the Hair Satisfaction Patient Reported Outcome (SPRO) scale at Week 24
2. Percentage of patients achieving an absolute SALT score of ≤20 at Week 20, 16, 12 and 8

See Section 12.4.3 for details on multiple comparisons control for Primary and Key Secondary Endpoints.

**Secondary Endpoints**

- Relative change in SALT scores from Baseline at Weeks 4, 8, 12, 16, 20, and 24
- Percentage of responders (defined as "much improved" or "very much improved") using the CGI-I at Weeks 12, 16, 20, and 24
- Percentage of responders (defined as "much improved" or "very much improved") using the PGI-I at Weeks 12, 16, 20, and 24
- Change from Baseline in the CGI-S at Weeks 12, 16, 20, and 24
- Change from Baseline in the PGI-S at Weeks 12, 16, 20, and 24
- Percentage of patients achieving at least a 75% relative reduction in SALT score from Baseline at Weeks 12 and 24
- Percentage of patients achieving at least a 90% relative reduction in SALT score from Baseline at Weeks 12 and 24

- Change from Baseline on the Brigham Eyebrow Tool for Alopecia (BETA) score at Weeks 12 and 24
- Change from Baseline on the Brigham Eyelash Tool for Alopecia (BELA) score at Weeks 12 and 24
- Percentage of responders (defined as "satisfied" or "very satisfied") on the SPRO scale at Weeks 12, 16, and 20
- Change from Baseline in the SPRO scale at Weeks 12, 16, 20 and 24
- Percentage of patients achieving a ≥ 2-point change from Baseline in the SPRO scale at Weeks 12, 16, 20, and 24
- Change from Baseline on the individual items of the Hair Quality Patient Reported Outcome (QPRO) scale at Weeks 12, 16, 20 and 24
- Change from Baseline in the depression scale of the Hospital Anxiety and Depression Scale (HADS) at Week 24
- Change from Baseline in the anxiety scale of the Hospital Anxiety and Depression Scale (HADS) at Week 24
- Percentage of patients achieving an absolute SALT score of ≤20 at Weeks 8 and 4
- Percentage of patients achieving an absolute SALT score of ≤10 at Week 24

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

#### 12.2.2. Safety

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

#### 12.2.3. Pharmacokinetic

CTP-543 population PK analysis will be conducted using sparse PK samples in a subset of patients. Pharmacokinetic samples will be collected per the schedule of assessments (Table 2).

### 12.3. Analysis Populations

#### 12.3.1. Treatment Period

The Efficacy Population will include all patients who are randomized in the study and dispensed study drug during the Treatment Period.

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

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

The Per Protocol Population will include all patients in the Efficacy Population who were dosed according to protocol and have no major protocol deviations. Inclusion in the Per Protocol Population will be determined prior to breaking the study blind.

In the event patients incorrectly receive treatment associated with a different treatment group, they will be analyzed "as randomized" for efficacy and "as treated" for safety.

## 12.4. Analyses

For the Treatment Period, data will be summarized by active treatment versus placebo-treated patients (i.e., by treatment group). All data for analysis will be listed by patient.

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

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

### 12.4.1. Disposition and Baseline Characteristics

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

Baseline characteristics will be summarized by treatment group.

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

### 12.4.2. Efficacy

The primary analysis targets an effect of treatment (response rates at 24 weeks) among subjects given the opportunity for treatment who are dispensed study drug. The treatment policy strategy is used for the intercurrent event of discontinuation of study treatment (either temporarily or permanently) and so the response rates at 24 weeks are of interest, irrespective of continued therapy, in line with the intent-to-treat principle.

For the primary efficacy analysis and the key secondary efficacy analysis, a 0.025 (two-sided) alpha-level will be allocated to each dose for comparison with placebo to adjust for multiplicity of testing associated with two doses. Additional secondary endpoints will be tested in the following order (see Section 12.4.3) and be considered statistically significant and alpha-level protected if they (and all prior endpoints in the hierarchy for that dose versus placebo) achieve statistical significance at the 0.025 level of significance. Irrespective, nominal p-values will be provided. Testing will be performed only for the Treatment Period. Missing values will be handled as specified in Section 12.4.4.

**Primary Efficacy Endpoint**

The primary efficacy endpoint will be the proportion of patients achieving an absolute SALT score $\leq 20$ at Week 24. Pairwise treatment group differences from placebo will be assessed with the Cochran-Mantel-Haenszel test using baseline scalp hair loss (partial vs complete/near-complete) as the stratification factor, for each active treatment group versus placebo.

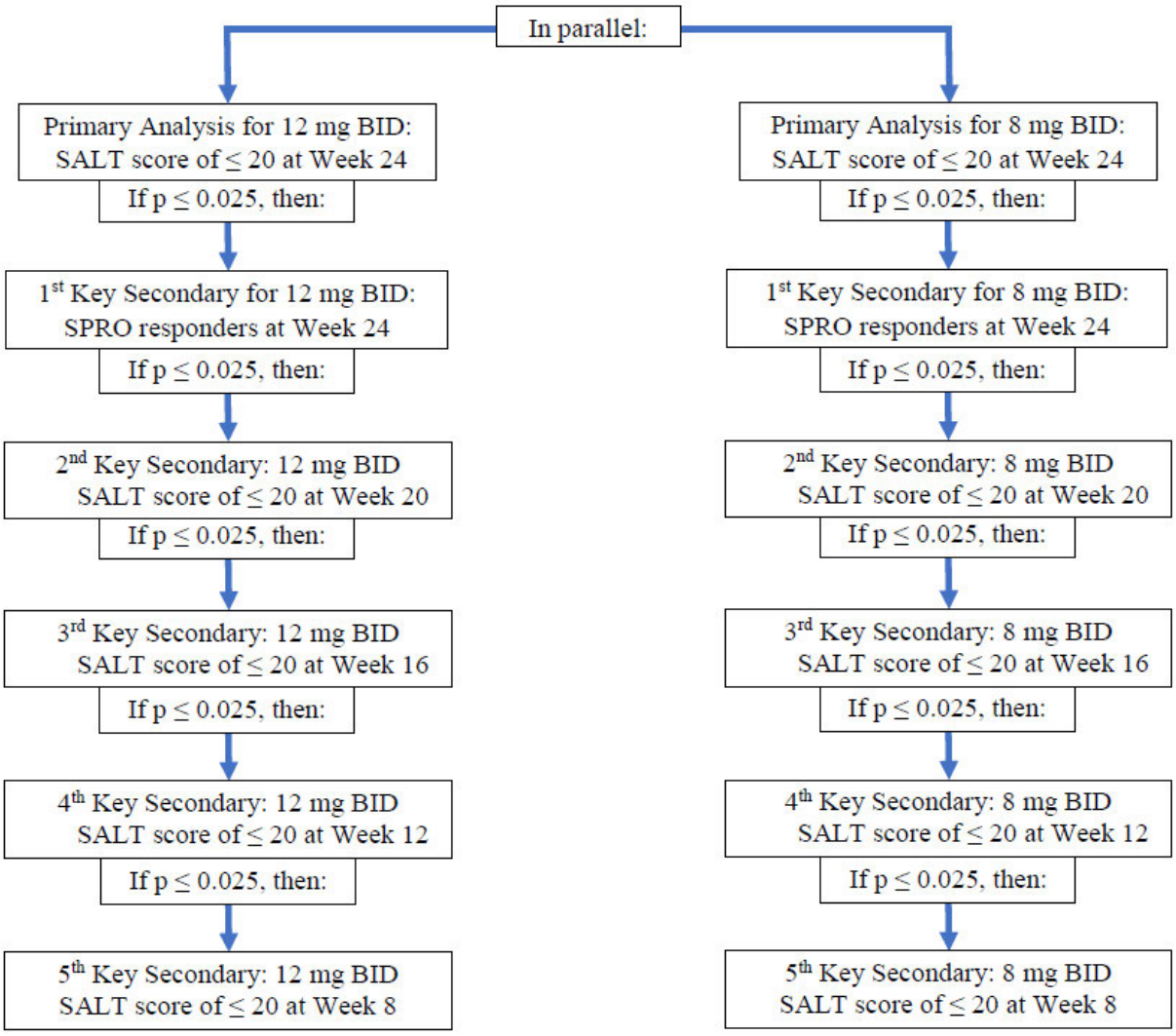
**Other Efficacy Endpoints**

For proportions of patients achieving specified improvement criteria (eg, CGI-I and PGI-I responders), pairwise treatment group differences from placebo at each scheduled evaluation will be assessed with the Cochran-Mantel-Haenszel test using baseline scalp hair loss as the stratification factor.

Absolute and/or relative changes in SALT score, SPRO score, CGI-S and PGI-S values, BELA and BETA score, QPRO scores, and HADS anxiety and depression scores, will be assessed with a mixed effects repeated measures (MMRM) model. The model will include fixed factors for treatment group, study visit, and treatment by study visit interaction, with baseline SALT score as a covariate. Treatment group comparisons at each visit will be based on least squares mean estimates. An unstructured covariance structure will be used to model the within-subject errors. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

### 12.4.3. Multiplicity

Hierarchical testing will be used to control for multiple comparisons. For the primary efficacy analysis and the key secondary efficacy analyses, a ≤0.025 (two-sided) alpha-level will be allocated to each dose for comparison with placebo to adjust for multiplicity of testing associated with two doses. The below figure displays the order of testing of the key secondary endpoints. Once p>0.025 is observed for a treatment group comparison, inference for additional endpoints is no longer alpha-level protected for that dose group, however nominal p-values will still be reported.




### 12.4.4. Missing Data for SALT-based endpoints

Prior to database lock, the classification of the missing data pattern for missing SALT scores will be finalized based on blinded data review and documented as either considered to be missing at random (MAR) or potentially missing not at random (MNAR), consistent with general categories of reasons for missingness. Subjects with missing data due to COVID-19 will have data reviewed to determine the specific limitation imposed by COVID-19 leading to the inability to have captured the protocol-specified assessments. For example, missing at random will be considered plausible for COVID-19 related reasons such as site closures and travel limitations. In general, however, if a MAR assumption is not considered plausible, MNAR will be assumed. Patterns of missing values across visits will be listed and summarized with numbers and percentages by treatment and visit.

### 12.4.5. Multiple Imputation

A multiple imputation (MI) approach will be used to estimate missing SALT scores. Analyses of the multiply imputed datasets will be performed for both the primary endpoint (percentage of subjects with absolute SALT scores ≤ 20) as well as key secondary endpoints employing SALT scores, between each dose and placebo, using the MMRM approach.

The imputation will be implemented separately for each treatment, under the assumption that different treatments may have distinct posterior distributions. Missing values will be imputed with a sequential regression approach under the assumption of multivariate normality. Missing SALT scores will be imputed in a sequential manner using regression models with a number of predictor variables. Covariates to be included are the baseline SALT score, in addition to the observed or imputed values of the previous time points.

One hundred independent imputations will be done with SAS® PROC MI using the Fully Conditional Specification (FCS) regression method for all imputed continuous variables and the discriminant function method for all imputed classification variables, if needed. For each continuous variable, all other variables are used as covariates, and for each imputed classification variable, all other continuous variables are used as covariates. The FCS method combines both the monotone and arbitrary missing data patterns into one procedure.

#### 12.4.5.1. Analysis of Imputed Datasets

For the analysis of the primary endpoint (i.e., the binary endpoint denoting a SALT score ≤ 20) the individual SALT scores will be categorized (≤ 20 versus > 20) and analyzed using a Mantel-Haenszel test (comparing each dose to placebo, separately). For each imputed dataset, treatment differences will be assessed using the Mantel-Haenszel estimate of a common risk difference, with the variance estimator due to Sato (used to construct confidence limits for the Mantel-Haenszel estimate of the common risk difference in the SAS FREQ Procedure). The resulting 100 estimates of the treatment differences and standard errors will then be combined using SAS PROC MIANALYZE.

#### 12.4.5.2. Tipping Point Analyses

For the primary endpoint categorized as absolute SALT score ≤ 20, tipping point sensitivity analyses will be conducted for each dose compared to placebo at week 24 if the result of the MI analysis is statistically significant at the alpha ≤ 0.025 level, in favor of treatment, for the given dose.

The patterns of interest for the tipping point analysis will consider two cases and will estimate tipping points for values where only missing values not at random (MNAR) are adjusted and also where all missing values are adjusted (i.e., two separate tipping point analyses).

The tipping point analyses will use the imputed datasets generated for the primary analysis with the delta adjustments for both treated and placebo. For the tipping point analysis, $\delta_T$ values (adjustments for treated subjects) will represent a percentage difference between the imputed value and baseline and can vary from 0% to 100% of the difference for subjects with an imputed SALT score less than baseline, or zero otherwise. For the placebo arm, $\delta_P$ values will represent a percentage difference between the imputed value and 0 hair loss. Accordingly, the maximum

delta value of 100% provides for an adjusted imputed value equal to either baseline (for treated subjects, representing non-response) or zero hair loss for placebo, representing response. Tipping points will therefore be provided for combinations of $\delta_T$ and $\delta_P$ to provide a range of assumptions about hypothetical improvements on placebo missing data values and reduction in efficacy for treated imputed values such that there is no longer evidence of efficacy.

Missing values will not be imputed for efficacy endpoints which are not derived from SALT scores.

### 12.4.6. Population Pharmacokinetics

Population PK analysis will include the evaluation of various covariates including age, gender, race, weight (or BMI), on the PK of CTP-543. Exposure-response relationships for both efficacy and safety parameters will also be assessed.

### 12.4.7. Study Drug Exposure

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

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

### 12.4.8. Safety

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

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

Laboratory values will be converted to the project-defined unit of measurement, as applicable, before analysis. Abnormal, clinically significant laboratory values will be reported and summarized as adverse events (refer to Section 11.1).

**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 through to the final study visit. The number and percentage of patients who report TEAEs will be summarized by system organ class and preferred term.

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

Patients who report the same preferred term on multiple occasions will be counted once for the preferred term: under the highest severity when summarized by severity and under the closest relationship to study drug when summarized by relationship. If a patient reports multiple preferred terms for a system organ class, the patient will be counted only once for that system organ class.

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

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

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

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

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

**Clinical Laboratory**

Clinical laboratory variables will be presented in 3 ways. First, change from Baseline to the smallest post-baseline value, largest post-baseline value, and final value will be summarized. 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, shift tables will summarize the number and percentage of patients with categorical changes from baseline defined by the laboratory normal reference range for each laboratory parameter (Below reference range, Within reference range, and Above reference range). The baseline category will be cross-tabulated with post-baseline category (3 × 3 table). The

post-baseline category will be assigned and summarized in 2 ways for each laboratory parameter: smallest post-baseline value and largest post-baseline value.

Third, treatment-emergent potentially clinically significant (PCS) laboratory values will be identified. Potentially clinically significant values are defined as those that meet Grade 3 or Grade 4 toxicity criteria from the CTCAE criteria. Treatment-emergent PCS laboratory values are those in which the baseline value is not PCS and the post-baseline value is PCS. The number and percentage of patients with treatment-emergent PCS laboratory values will be summarized by treatment group for each clinical laboratory variable.

**Vital Signs**

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

Baseline will be defined as the last vital sign value obtained before the first dose of study drug on Day 1; if Day 1 values are unavailable, then values obtained at the Screening Visit will be used.

The number and percentage of patients with at least 1 PCS vital sign value will be summarized descriptively.

### 12.4.9. Interim Analyses

An independent Data Monitoring Committee (DMC) will perform regular safety assessments based on a review of cumulative safety data. The DMC may advise study and/or treatment arm cessation due to intolerability at any time. There are no plans to perform interim efficacy analyses or to discontinue the study early due to demonstration of efficacy differences. Therefore, no adjustment of Type I error is required for interim analyses.

# 13. REGULATORY CONSIDERATIONS

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

## 13.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Sponsor, its authorized representative, and Investigator abide by GCP, as described in ICH Guideline E6 (R2) and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from the IRB/EC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

## 13.2. Sponsor's Responsibilities

The Sponsor or its designee is responsible for the following:

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

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

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

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.
- Due to the COVID-19 pandemic and the possibility for site closures and/or travel restrictions, source data verification may be performed remotely.
- 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/EC by designated study personnel.

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

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

## 13.3. Investigator's Responsibilities

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

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

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

The Investigator or designee should inform the IRB/EC 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/EC and Regulatory Agencies, as required per country regulations. Where applicable, a progress report will be sent to the IRB/EC and the protocol will be reviewed annually (e.g., re-approved) or more frequently, as required by the IRB/EC or local regulations.

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

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

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

## 13.4. Protocol Amendments

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

Trial conduct may be impacted in light of the COVID-19 pandemic. Challenges may arise (e.g., quarantines, site closures, travel limitations, interruptions to the supply chain for the investigational product, etc.) leading to difficulties in meeting protocol-specified procedures, including administering or using the investigational product or adhering to protocol-mandated visits and laboratory/diagnostic testing. Taking into consideration Regulatory Agency guidance, amendments to protocol defined criteria may be implemented without IRB approval or before filing an amendment to the IND/CTA in order to minimize or eliminate immediate hazards or to protect the life and well-being of research participants (e.g., to limit exposure to COVID-19).

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/EC notified within 5 days or per local regulations.

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

## 13.5. Audits and Inspections

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

source documents. The Investigator agrees to cooperate with audits conducted at a reasonable time and in a reasonable manner.

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

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

## 13.6. Quality Control and Quality Assurance

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

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

In light of the COVID-19 pandemic, patient safety will be ensured by maintaining compliance with Good Clinical Practice (GCP) and minimizing risks to patient safety and data integrity. These efforts include additional risk mitigation strategies and appropriate documentation of protocol deviations occurring prior to implementation of protocol amendments.

# 14. DATA HANDLING AND RECORDKEEPING

## 14.1. Confidentiality

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

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

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

## 14.2. Patient Data Protection

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

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

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

## 14.3. Data Collection

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

Prior to the start of the study, the Principal Investigator will complete a Delegation of Authority form (Site Signature and Delegation Log), showing the signatures and handwritten initials of all individuals and the delegation of responsibilities, such as identifying those individuals who are authorized to make or change entries on eCRFs.

## 14.4. Case Report Form Completion

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

## 14.5. Database Management, Data Clarification, and Quality Assurance

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

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

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

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

## 14.6. Inspection of Records

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

All data required for this study should be captured in source notes. No data obtained by the Investigator or other study personnel should be captured directly in the eCRF. All source documents pertaining to this study will be maintained by the Investigator and made available for

inspection by authorized persons. If electronic progress notes and other electronic source documents are not compliant with applicable regulatory guidance, they are not considered a valid source for this study. All patient progress notes must be dated and signed at the time of the visit. The Sponsor reserves the right to terminate the study for refusal of the Investigator to supply original source documentation for this clinical study.

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

- Information to confirm that the patient exists [e.g., initials, date of birth (applicable per local regulations), 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. In light of the COVID-19 pandemic, source document verification may occur remotely. Additional detail on remote source document verification will be provided in the study plans.

## 14.7. Retention of Records

Clinical Investigators must retain study records from investigational drug studies 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 the appropriate regulatory authority is notified.

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

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

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

# 15. PUBLICATION POLICY

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

# 16. LIST OF REFERENCES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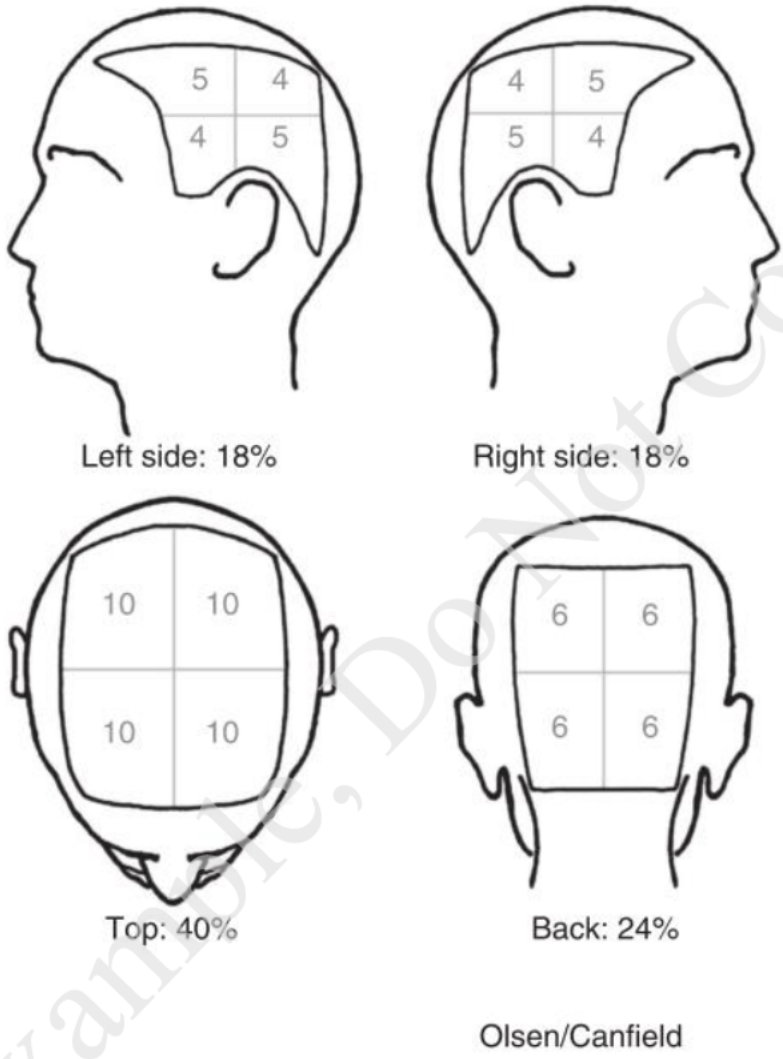
# 17. APPENDICES

## 17.1. Clinical Laboratory Assessments

| **Hematology** | **Chemistry** | **Pregnancy Testing** |
|---|---|---|
| Complete blood count<br>Absolute neutrophil count<br>Absolute eosinophil count<br>Platelet count<br>White blood cell count with differential<br>Absolute reticulocyte count<br>Hemoglobin A1c | Alanine aminotransaminase<br>Albumin<br>Alkaline phosphatase<br>Amylase<br>Aspartate aminotransaminase<br>Total bilirubin<br>Direct bilirubin<br>Indirect bilirubin<br>Blood urea nitrogen<br>C-Reactive Protein (CRP)<br>Calcium<br>Carbon dioxide<br>Chloride<br>Creatinine<br>Creatine kinase<br>Glucose<br>Lipase<br>Total protein<br>Phosphorus<br>Potassium<br>Sodium<br>Uric Acid | Human chorionic gonadotropin (females of childbearing potential only) serum (screening) and urine (Treatment Period and Safety Follow-up Visit, if applicable) |
| **Serology** | **Lipids** | **Other** |
| Hepatitis B Surface Antigen (HBsAg)<br>Hepatitis C Virus Antibodies (HCV Ab) | Total cholesterol<br>Low-density lipoprotein<br>High-density lipoprotein<br>Triglycerides | Tuberculosis<br>Thyroid stimulating hormone |

## 17.2. Severity of Alopecia Tool (SALT)




Olsen/Canfield



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

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

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

## 17.3. Global Impression Scales

### 17.3.1. Clinical Global Impression of Severity (CGI-S)

How would you rate the severity of the patient's alopecia areata at this time:

1. Normal, no hair loss
2. Borderline hair loss
3. Mild hair loss
4. Moderate hair loss
5. Marked hair loss
6. Severe hair loss
7. Among the most extreme hair loss

### 17.3.2. Clinical Global Impression of Improvement (CGI-I)

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

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

### 17.3.3. Patient Global Impression of Severity (PGI-S)

How would you rate the severity of your alopecia areata at this time:

1. Normal, no hair loss
2. Borderline hair loss
3. Mild hair loss
4. Moderate hair loss
5. Marked hair loss
6. Severe hair loss
7. Among the most extreme hair loss

### 17.3.4. Patient Global Impression of Improvement (PGI-I)

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

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

## 17.4. Patient Reported Outcome

### 17.4.1. Satisfaction of Hair Patient Reported Outcome (SPRO)

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

5 ☐ Very dissatisfied
4 ☐ Dissatisfied
3 ☐ Neither satisfied nor dissatisfied
2 ☐ Satisfied
1 ☐ Very satisfied

### 17.4.2. Quality of Hair Patient Reported Outcome (QPRO)

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** on your scalp? | 5☐ Very dissatisfied | 4☐ Dissatisfied | 3☐ Neither satisfied nor dissatisfied | 2☐ Satisfied | 1☐ Very satisfied |
| 2. How satisfied are you with the **evenness of the hair** on your scalp? | 5☐ Very dissatisfied | 4☐ Dissatisfied | 3☐ Neither satisfied nor dissatisfied | 2☐ Satisfied | 1☐ Very satisfied |
| 3. How satisfied are you with your eyebrows? | 5☐ Very dissatisfied | 4☐ Dissatisfied | 3☐ Neither satisfied nor dissatisfied | 2☐ Satisfied | 1☐ Very satisfied |
| 4. How satisfied are you with your eyelashes? | 5☐ Very dissatisfied | 4☐ Dissatisfied | 3☐ Neither satisfied nor dissatisfied | 2☐ Satisfied | 1☐ Very satisfied |

# 17.5. Hospital Anxiety and Depression Scale (HADS)

**Hospital Anxiety and Depression Scale (HADS)**

**Tick the box beside the reply that is closest to how you have been feeling in the past week.**
**Don't take too long over you replies: your immediate is best.**

| D | A | | D | A | |
|---|---|---|---|---|---|
| | | **I feel tense or 'wound up':** | | | **I feel as if I am slowed down:** |
| | 3 | Most of the time | 3 | | Nearly all the time |
| | 2 | A lot of the time | 2 | | Very often |
| | 1 | From time to time, occasionally | 1 | | Sometimes |
| | 0 | Not at all | 0 | | Not at all |
| | | | | | |
| | | **I still enjoy the things I used to enjoy:** | | | **I get a sort of frightened feeling like 'butterflies' in the stomach:** |
| 0 | | Definitely as much | | 0 | Not at all |
| 1 | | Not quite so much | | 1 | Occasionally |
| 2 | | Only a little | | 2 | Quite Often |
| 3 | | Hardly at all | | 3 | Very Often |
| | | | | | |
| | | **I get a sort of frightened feeling as if something awful is about to happen:** | | | **I have lost interest in my appearance:** |
| | 3 | Very definitely and quite badly | 3 | | Definitely |
| | 2 | Yes, but not too badly | 2 | | I don't take as much care as I should |
| | 1 | A little, but it doesn't worry me | 1 | | I may not take quite as much care |
| | 0 | Not at all | 0 | | I take just as much care as ever |
| | | | | | |
| | | **I can laugh and see the funny side of things:** | | | **I feel restless as I have to be on the move:** |
| 0 | | As much as I always could | | 3 | Very much indeed |
| 1 | | Not quite so much now | | 2 | Quite a lot |
| 2 | | Definitely not so much now | | 1 | Not very much |
| 3 | | Not at all | | 0 | Not at all |
| | | **Worrying thoughts go through my mind:** | | | **I look forward with enjoyment to things:** |
| | 3 | A great deal of the time | 0 | | As much as I ever did |
| | 2 | A lot of the time | 1 | | Rather less than I used to |
| | 1 | From time to time, but not too often | 2 | | Definitely less than I used to |
| | 0 | Only occasionally | 3 | | Hardly at all |
| | | | | | |
| | | **I feel cheerful:** | | | **I get sudden feelings of panic:** |
| 3 | | Not at all | | 3 | Very often indeed |
| 2 | | Not often | | 2 | Quite often |
| 1 | | Sometimes | | 1 | Not very often |
| 0 | | Most of the time | | 0 | Not at all |
| | | | | | |
| | | **I can sit at ease and feel relaxed:** | | | **I can enjoy a good book or radio or TV program:** |
| | 0 | Definitely | 0 | | Often |
| | 1 | Usually | 1 | | Sometimes |
| | 2 | Not Often | 2 | | Not often |
| | 3 | Not at all | 3 | | Very seldom |

Please check you have answered all the questions

Scoring:
Total score: Depression (D) _____ Anxiety (A) _____
0-7 = Normal
8-10 = Borderline abnormal (borderline case)
11-21 = Abnormal (case)