Official title: A Multicenter, Open-Label, Extension Study to Assess the Long-Term Safety and Efficacy of CTP-543 in Adult Patients With Moderate to Severe Alopecia Areata

Document: Study Protocol

NCT number: NCT05041803

Document date: 13 Nov 2023

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

INVESTIGATIONAL PRODUCT:	CTP-543
STUDY NUMBER:	CP543.5002
[redacted]	[redacted]
EudraCT NUMBER:	2021-002365-18
CLINICALTRIALS.GOV IDENTIFIER (NCT Number):	NCT05041803
SPONSOR NAME / ADDRESS:	Sun Pharmaceutical Industries, Inc. 2 Independence Way Princeton, NJ 08540
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MEDICAL MONITOR / EMERGENCY CONTACT INFORMATION

SUN PHARMACEUTICAL INDUSTRIES, INC. SIGNATURE PAGE

PROTOCOL TITLE: A Multicenter, Open-Label, Extension Study to Assess the Long-Term Safety and Efficacy of CTP-543 in Adult Patients with Moderate to Severe Alopecia Areata

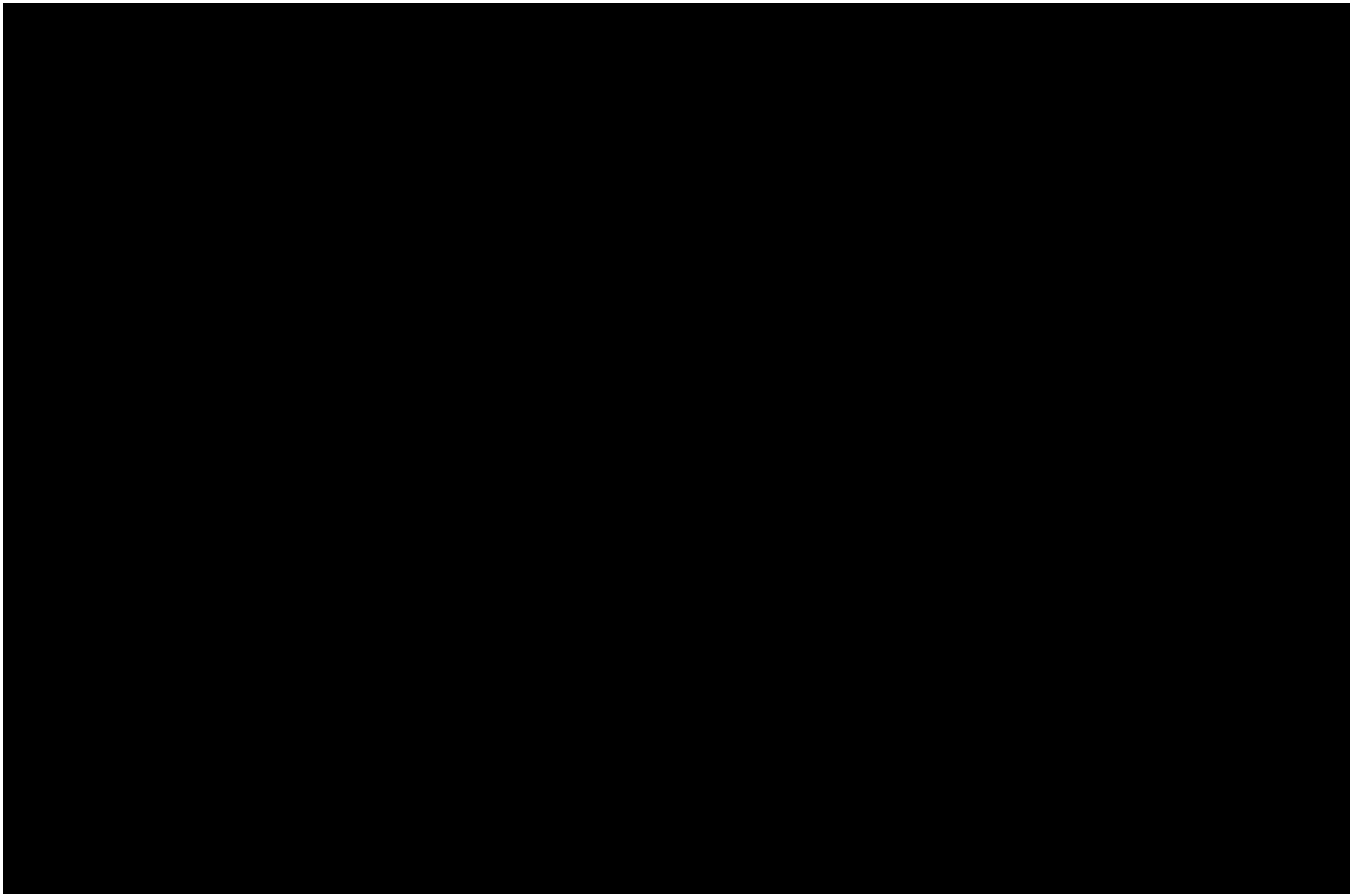
Study Number: CP543.5002; Amendment 5.2

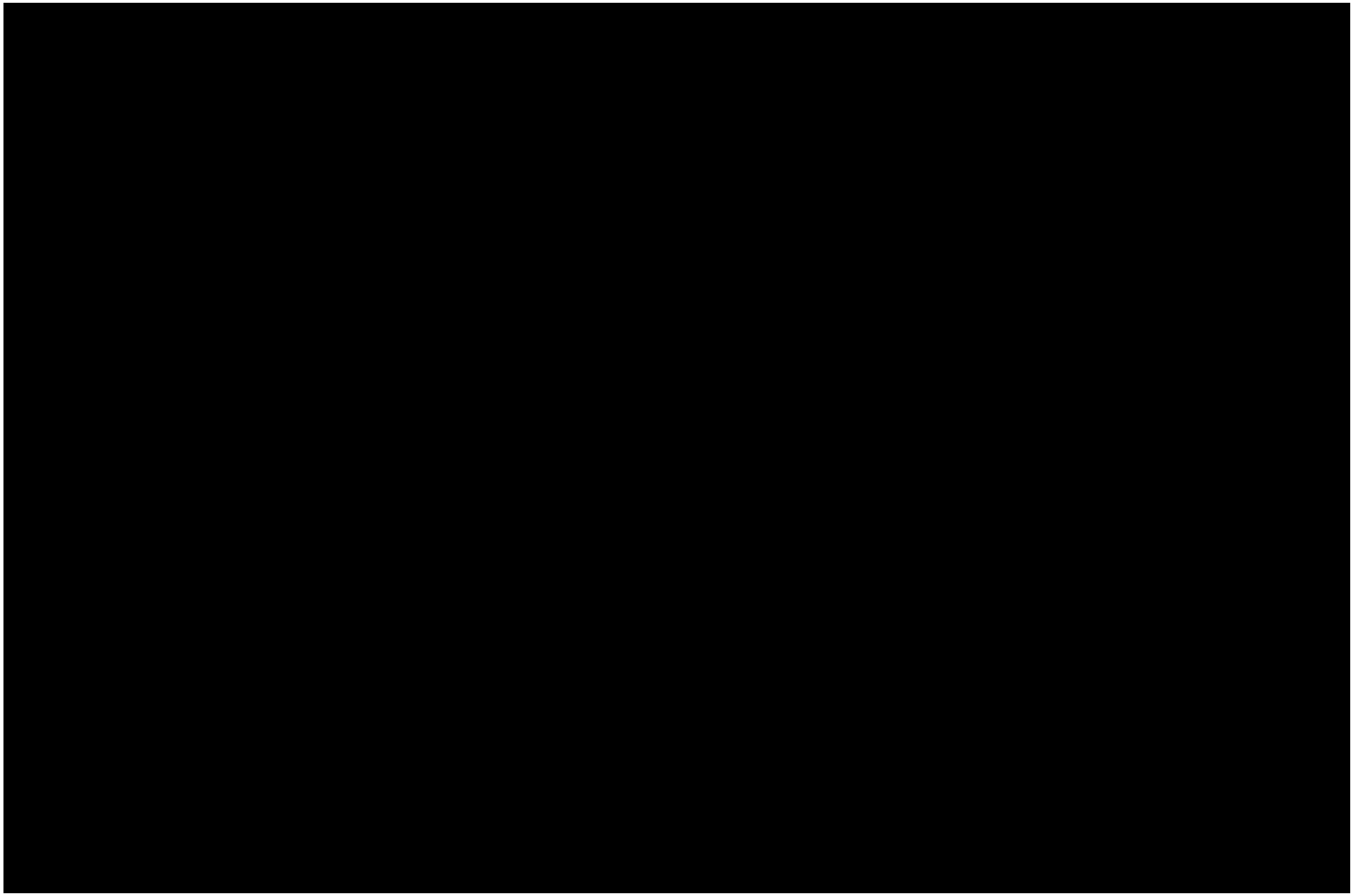
SITE PRINCIPAL INVESTIGATOR'S AGREEMENT

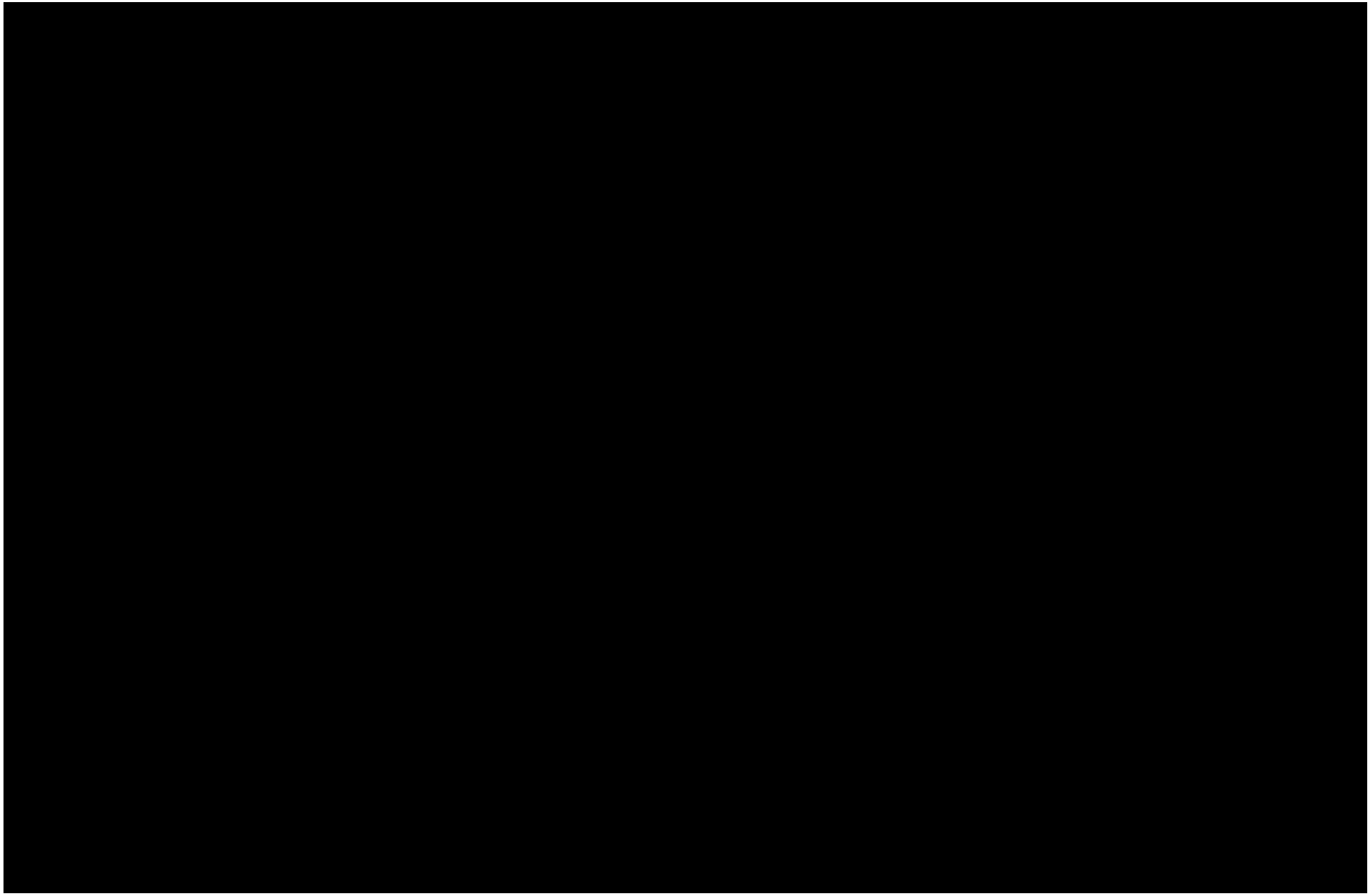
Protocol Number: CP543.5002, Amendment 5.2

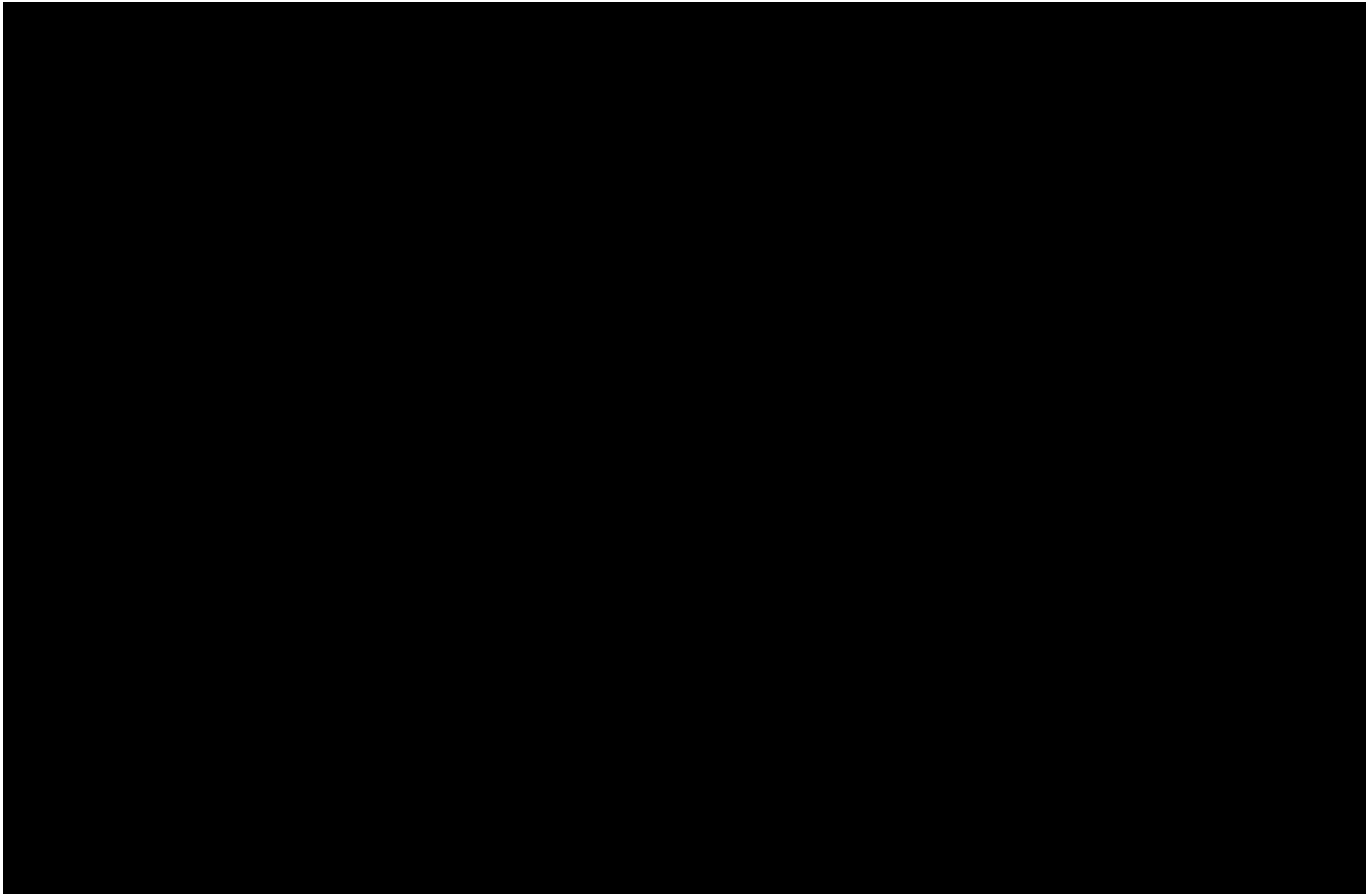
Signature of Site Principal Investigator	**dd mmm yyyy**
Printed Name of Site Principal Investigator **Institution Name:**	

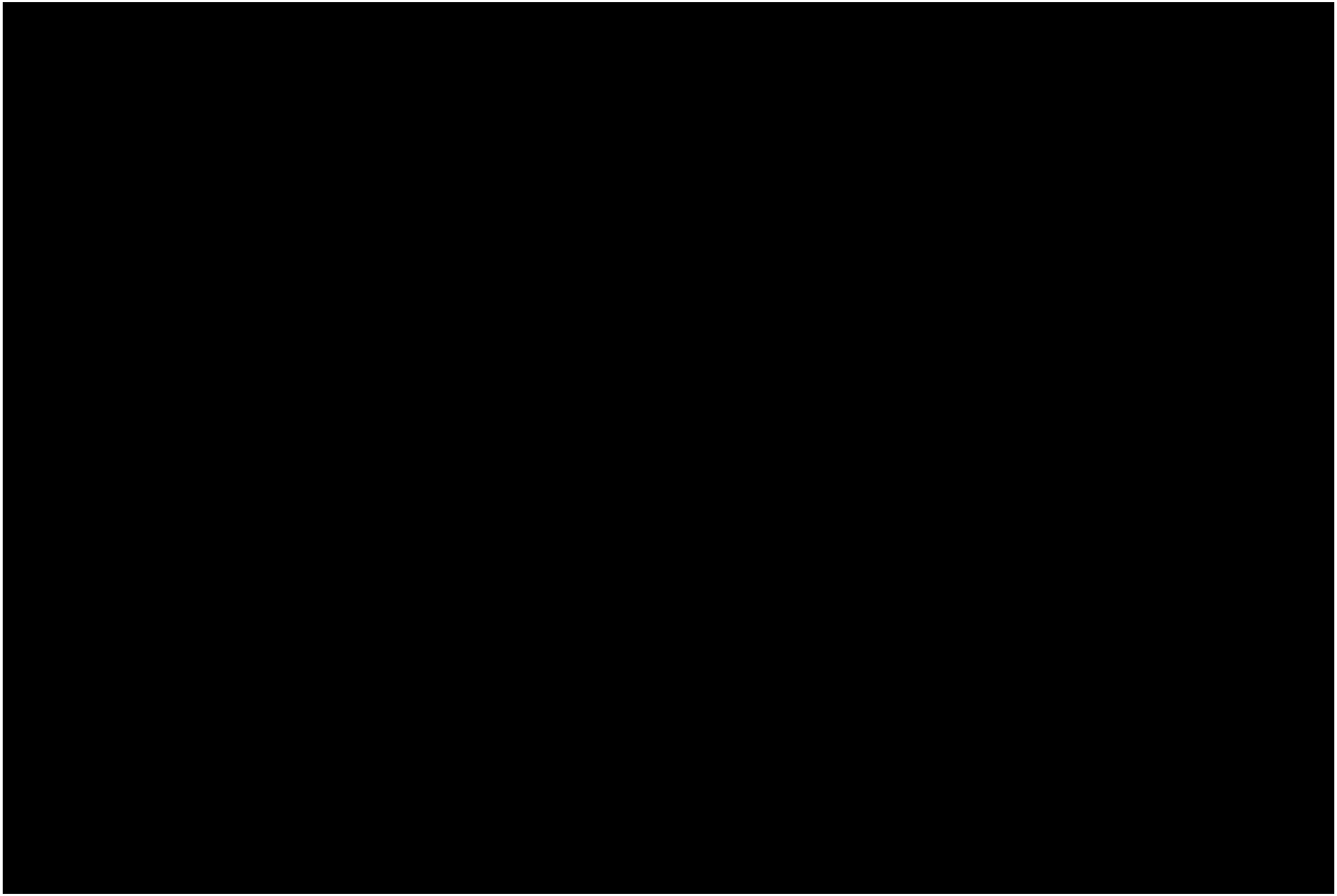
By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Ethics Committee procedures, instructions from Sun Pharmaceutical Industries, Inc. representatives, the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.











1. SYNOPSIS

Name of Sponsor/Company: Sun Pharmaceutical Industries, Inc.	
Name of Investigational Product: CTP-543	
Name of Active Ingredient: deuruxolitinib	
Title of Study: A Multicenter, Open-label, Extension Study to Assess the Long-Term Safety and Efficacy of CTP-543 in Adult Patients with Moderate to Severe Alopecia Areata	
Study Number: CP543.5002	
Study center(s): Multicenter; European Union	
Studied period (years): Estimated date first patient enrolled: September 2021 Estimated date last patient completed: July 2024	**Phase of development:** 3
Objectives: The overall objectives of the study are to evaluate long-term safety of CTP-543 and to assess long-term effects of CTP-543 on treating hair loss in adult patients with moderate to severe alopecia areata.	
Methodology: Patients with alopecia areata who previously participated in a qualifying Phase 3 clinical trial (study CP543.3001 or study CP543.3002) with CTP-543 and who complete the 24-week Treatment Period on Study Medication (active or placebo), have the opportunity to enroll in this open-label extension (OLE) study in which they will receive daily treatment with CTP-543. At the Week 52 visit, patients will be assessed for treatment success (Responders) defined as patients having an absolute SALT score of ≤20 at Week 52. These Responders will be eligible to continue in the OLE extension for up to a maximum of one additional year. Non-responders will complete the study at Week 52. Safety will be evaluated by clinical laboratory measurements, AEs and physical exams. SARS-CoV-2 testing will be performed at all visits. SALT assessments will be performed periodically for efficacy, as described in the Schedule of Events Tables (Table 1 and Table 2). **Study Design:** Patients who previously completed a qualifying CTP-543 clinical trial may participate in the OLE. Patients will provide written informed consent prior to completing any eligibility procedures for the OLE study. Following the Baseline visit, eligible patients were enrolled and study drug was dispensed. Initially, patients were assigned to receive daily treatment with CTP-543 at a dose of 8 mg BID or 12 mg BID according to the following criteria:	

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

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

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

At the Week 52 visit, patients will be assessed for treatment success (Responders) defined as patients having an absolute SALT score of ≤20. These Responders will continue in the OLE extension for one additional year. Non-responders will complete the study at Week 52. Additionally, patients should be withdrawn from the trial if, in the Investigator's opinion, continued study participation is undesirable or the risk-benefit profile has become unfavorable. Additional withdrawal criteria can be found in Section 7.3.

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

Serum pregnancy testing will be performed at all in-clinic visits. To minimize patient burden of additional clinic visits, urine pregnancy testing will be performed by the subject at home on Weeks 16, 24, 32, 40, 48 and 4-weeks post the final study visit. For responders, additional home pregnancy testing will be performed at Weeks 56, 64, 72, 80, 88, 96, 104 and 4-weeks post the final study visit. The test date and result will be documented in a patient diary and brought to each in-clinic study visit by the patient. Significant cytopenias or other hematologic abnormalities (Table 5) will be managed by severity through dose interruption or discontinuation, and signs and symptoms of infection will be closely monitored and treated promptly. Less significant changes in laboratory values may warrant clinical intervention and the Investigator should use his/her best clinical judgement when considering a dose interruption whether for singular or aggregate laboratory results outside of the normal range, or for other clinical signs, symptoms, or considerations that suggest dose interruption is in the best interest of the patient. Patients who experience intolerable symptoms during treatment may discontinue the study at any time. Patients may withdraw consent at any time.

Number of patients:

All patients who participated in a qualifying CTP-543 clinical trial and continue to meet eligibility criteria are eligible to participate.

Diagnosis and main criteria for inclusion:

Patients eligible for enrollment in this 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. Have completed a 24-week Treatment Period in a previously-qualifying CTP-543 clinical trial.
3. Female subjects are eligible to participate if at least one of the following conditions applies:

   a) Is a woman of childbearing potential (WOCBP) and using a medically highly effective form of birth control with a failure rate less than 1% per year from at least 4 weeks prior to Baseline until at least 30 days following last dose of study drug. Examples of medically highly effective birth control methods include:

      i. Combined (estrogen and progestogen containing) hormonal contraception (oral, patch, vaginal ring)
      ii. Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
      iii. Intrauterine device or intrauterine hormone-releasing system
      iv. Bilateral tubal occlusion
      v. Vasectomized partner (partner is the sole sexual partner of the WOCBP trial participant and the vasectomized partner has received medical assessment of the surgical success)
      vi. Sexual abstinence (reliable as refraining from heterosexual intercourse during the above-mentioned period)

   b) Is not a WOCBP:

      i. Premenopausal with one of the following:
         a. Documented hysterectomy;
         b. Documented bilateral salpingectomy;
         c. Documented bilateral oophorectomy.
      ii. Postmenopausal (cessation of menses for at least 12 months prior to screening)

      Postmenopausal is defined as no menses for 12 months without an alternative medical cause. In addition, a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm postmenopausal in women under 60 years old and not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment

4. Male participants must:
   a. Agree to use, with their partners, male contraception (condom) and one of the highly effective contraceptive methods listed in Inclusion Criterion 3, from Baseline until at least 90 days following last dose of study drug.
   b. Refrain from donating sperm during the study and for at least 90 days after the end of the study.

5. Willing to comply with the study visits and requirements of the study protocol.

Exclusion Criteria:

1. 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.
2. Females who are nursing, pregnant, or planning to become pregnant while in the study, and for 30 days after last dose of study medication.
3. Donation of blood at any point throughout the study and for 30 days after last dose of study medication.
4. Most recent hematologic parameters do not permit continued dosing; i.e., criteria for withholding IP have been met and have not recovered to values required to resume dosing.
5. Any medical (e.g. any prior history of thromboembolism), psychiatric, or social condition that is likely to unfavorably affect the risk-benefit of continued study participation, interfere with study compliance, or confound safety or efficacy assessments.

Investigational product, dosage and mode of administration:

CTP-543 (8 mg BID) tablets will be dosed orally according to the investigational drug product label.

Reference therapy, dosage and mode of administration:

N/A

Duration of treatment/Study participation:

Patients will receive study drug in this study for up to 52 weeks (non-responders) or a maximum of 108 weeks (responders).

Criteria for evaluation:

Safety:

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

Efficacy:

Hair regrowth and maintenance of hair growth will be assessed by SALT score over time.

Statistical methods:

All statistical methods are descriptive. No formal hypothesis will be tested. All confidence intervals, p-values, or any other inferential statistics provided will be exploratory in nature

Safety Analyses:

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

Efficacy Analyses:

Efficacy analyses will include all patients who receive study drug and have at least 1 post-baseline SALT assessment in this study. Relative change in SALT score overtime will be summarized descriptively by visit, as appropriate. Additional details for statistical methods will be provided in the Statistical Analysis Plan.

Table 1: Schedule of Events – (All Enrolled Subjects (Visit 1 – 9)

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

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

Table 2: Schedule of Events – Responders (Visit 10 – 16)

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

[1]Visit window is ± 3 days for Visits 10-16.
[2]Pregnancy testing will be performed every 4-weeks throughout study enrollment. As in-clinic visits are performed bi-monthly, subjects will perform in-home urine pregnancy tests at Week 56, 64, 72, 80, 88, 96, 104 and 4-weeks post the final study visit. The test date and result will be documented.
[3]In-home pregnancy testing window is ± 3 days
[4]Collected pre-dose, when possible.
[5]Includes fasted hematology, serum chemistry, SARS-CoV-2 testing, and lipids performed by the central lab.

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

LIST OF TABLES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 3: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AA	Alopecia Areata
BID	Twice daily dosing
CFR	Code of Federal Regulations
CTCAE	Common terminology criteria for adverse events
CYP3A4	Cytochrome P450 3A4
DMC	Data monitoring committee
DMP	Data Management Plan
EC	Ethics Committee
eCRF	Electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
ICF	Informed consent form
ICH	International Council for Harmonisation
IWRS	Interactive Web Response System
JAK	Janus kinase
LLN	Lower Limit of Normal
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
PCS	Potentially clinically significant
QD	Once daily dosing
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate (Fridericia's method)
SALT	Severity of Alopecia Tool
STAT	Signal transducers and activators of transcription
TB	Tuberculosis
TEAE	Treatment-emergent adverse events
ULN	Upper Limit of Normal
VAS	Visual Analog Scale

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 men and women, 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). Onset can occur at any age and affects both men and women over the course of their lifetime. Approximately 80% of alopecia areata patients experience the first episode of hair loss by 40 years of age and 40% by 20 years of age (Villasante Fricke, 2015). Alopecia areata can have a psychological impact with high rates of depression (Sellami, 2014) and anxiety reported, particularly in children and adolescents (Bilgic, 2013), and therefore, psychological counseling is often recommended as part of the standard of care (Al-Mutairi, 2011).

A cause for alopecia areata has not yet been identified, though as in other autoimmune disorders, genetic susceptibility and a wide array of environmental triggers are thought to be involved. Presently, treatments for alopecia areata include moderately effective intralesional corticosteroid injections or topicals, or aesthetic disguises such as makeup and wigs. Baricitinib (Olumiant®), a JAK kinase inhibitor, was recently approved by the US Food and Drug Administration (FDA) and the European Commission for treatment of adults with severe AA, demonstrating the utility of this class of molecule for alopecia areata.

4.2. 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.

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.

CTP-543 has been studied in patients with moderate to severe alopecia areata and at least 2 different doses have demonstrated significant hair regrowth over a 24-week treatment period. A Phase 2 dose-ranging clinical trial assessing the efficacy and safety of CTP-543 in moderate to severe AA patients was completed. 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 to 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 8 mg BID and 12 mg BID doses also produced significant results vs placebo when other analyses of SALT data were conducted as well as analyses of patient and clinician reported global impression.

In the pivotal phase 3, randomized, double-blind, placebo-controlled study CP543.3001 (THRIVE-AA1) evaluating the efficacy and safety of CTP-543 in adult subjects with moderate to severe AA, both CTP-543 8 mg BID and CTP-543 12 mg BID for 24 weeks resulted in a statistically significant proportion of subjects (29.6% and 41.5%, respectively; versus 0.8% on placebo) who achieved an absolute SALT score ≤20 at Week 24, a measure that is considered to be clinically meaningful to patients and physicians (Wyrwich et al., 2020). CTP-543 was generally well tolerated at both doses, with the safety profile consistent with that of other drugs of the same class.

Similarly, in the second pivotal phase 3, randomized, double-blind, placebo-controlled study CP543.3002 (THRIVE-AA2) evaluating the efficacy and safety of CTP-543 in adult subjects with moderate to severe AA, both CTP-543 8 mg BID and CTP-543 12 mg BID for 24 weeks resulted in a statistically significant proportion of subjects (33.0% and 38.3%, respectively; versus 0.8% on placebo) who achieved an absolute SALT score ≤20 at Week 24.

Therefore, this current study will assess the long-term safety of CTP-543 in patients with alopecia areata while continuing to evaluate the long-term effects on hair-regrowth, in patients who complete 24 weeks of treatment in the preceding study. In light of the known safety risks of the JAK class (see Section 8.1.1), patients who are non-responders after 52 weeks will be discontinued from the study. However, those patients who are responding with hair re-growth can continue to receive treatment, while being monitored from a benefit-risk perspective. Refer to the latest CTP-543 Investigator's Brochure for full details of the efficacy and safety data with CTP-543.

4.3. Nonclinical Information for CTP-543

A series of nonclinical studies were performed with CTP-543, which evaluated the *in vitro* pharmacokinetic (PK) and metabolism properties, safety pharmacology, toxicity/toxicokinetics, and genotoxicity. All safety pharmacology and toxicity 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 respective Investigator's Brochure.

4.4. Clinical Information for CTP-543

To-date, nine clinical studies with CTP-543 in healthy volunteers have been completed.

In patients with moderate to severe alopecia areata, seven clinical studies have been completed or are ongoing. Further information on all the completed and ongoing clinical studies, including results of completed studies, can be found in the current CTP-543 Investigator's Brochure.

Table 4: Clinical Trials with CTP-543 in Patients with Moderate to Severe Alopecia Areata

Study No. and Title	Phase	Country	No. of Subjects	Dosing Regimen	Status
Study CP543.2001: A Double-Blind, Randomized, Placebo Controlled Study to Evaluate the Safety and Efficacy of CTP-543 in Adult Patients with Moderate to Severe Alopecia Areata	2	United States	149 adult patients with moderate to severe alopecia areata 4 mg BID: 30 8 mg BID: 38 12 mg BID: 37 Placebo BID: 44	Cohort 1: 4 mg BID CTP-543 or matching placebo for 24 weeks Cohort 2: 8 mg BID CTP-543 or matching placebo for 24 weeks Cohort 3: 12 mg BID CTP-543 or matching placebo for 24 weeks	Completed
CP543.2002: A Randomized Parallel-Group Study to Evaluate the Efficacy and Tolerability of Two Dosing Regimens of CTP-543 in Adult Patients with Moderate to Severe Alopecia Areata	2	United States	57 adult patients with moderate to severe alopecia areata 8 mg BID: 29 16 mg QD: 28	CTP-543 dosed orally as tablets at doses of 8 mg BID or 16 mg QD for 24 weeks	Completed
CP543.2003: A Randomized Parallel-Group Study to Evaluate the Efficacy and Tolerability of Two Dosing Regimens of CTP-543 in Adult Patients with Moderate to Severe Alopecia Areata	2	United States Canada	66 adult patients with moderate to severe alopecia areata 12 mg BID: 34 24 mg QD: 32	CTP-543 dosed orally as tablets at doses of 12 mg BID or 24 mg QD for 24 weeks	Completed
CP543.2004: A Randomized Parallel-Group Study to Evaluate the Efficacy and Tolerability of Two Dosing Regimens of CTP-543 in Adult Patients with Moderate to Severe Alopecia Areata	2	United States	Approximately 317 adult patients with moderate to severe alopecia areata	Part A, Period 1 and Part B: 8 mg BID CTP-543 12 mg BID CTP-543 Part A, Period 2: 8 mg BID CTP-543 4 mg BID CTP-543 matching placebo	Ongoing
CP543.3001: 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	3	United States, Canada, Europe (select EU countries)	706 adult patients with moderate to severe alopecia areata	8 mg BID CTP-543 12 mg BID CTP-543 or matching placebo	Completed
CP543.3002: 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	3	United States, Canada, Europe (Poland, France, Spain,	517 adult patients with moderate to severe alopecia areata	8 mg BID CTP-543 12 mg BID CTP-543 or matching placebo	Completed

Study No. and Title	Phase	Country	No. of Subjects	Dosing Regimen	Status
		Germany, Hungary)			
CP543.5001: A Multicenter, Open-Label, Extension Study to Assess the Long-Term Safety and Efficacy of CTP-543 in Adult Patients with Moderate to Severe Alopecia Areata	2/3	United States Canada	Approximately 1,100*	CTP-543 dosed orally as tablets at doses of 8 mg BID or 12 mg BID** for up to 276 weeks	Ongoing

*In addition, eligible patients from Study CP543.2004 were eligible to enroll in this study following 24 weeks of treatment.
** Following implementation of urgent safety measures, only the 8 mg BID dose will be administered

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 Declaration of Helsinki, International Council for Harmonisation Guidelines, and local regulations governing the conduct of clinical studies.

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. Ethics Committee (EC)

The Ethics Committee (EC) will meet all regulatory authority requirements governing ECs according to local regulations (e.g., ICH E6 CFR, Title 21, Part 56). 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 will be submitted to the EC 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).

5.2. Written Informed Consent

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

The ICF, as specified by the clinical site's EC, must follow the Protection of Human Subjects regulations listed per local 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. The original signed consent form will be retained with the study records.

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

6. STUDY OBJECTIVES

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

6.1. Study Design and Method of Treatment Assignment

Patients with alopecia areata who previously participated in a qualifying Phase 3 clinical trial (CP543.3001 or CP543.3002) with CTP-543 and who complete a 24-week Treatment Period on Study Medication (active or placebo), have the opportunity to enroll in this open-label extension study. At the Week 52 visit, patients will be assessed for treatment success (Responders) defined as patients having an absolute SALT score of ≤20 at Week 52. These Responders will be eligible to continue in the OLE extension for up to a maximum of one additional year. Non-responders will complete the study at Week 52. Patients will provide informed consent prior to any baseline assessments being performed. Drug will be dispensed to patients following confirmation of eligibility.

Initially, patients were assigned to receive daily treatment with CTP-543 at a dose of 8 mg BID or 12 mg BID according to the following criteria:

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

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

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

At the Week 52 visit, patients will be assessed for treatment success (Responders) defined as patients having an absolute SALT score of ≤20 at Week 52. These Responders will be eligible to continue in the OLE extension for up to a maximum of additional year. Non-responders will complete the study at Week 52. Patients should be withdrawn from the trial if, in the Investigator's opinion, continued study participation is undesirable or the risk-benefit profile has become unfavorable. Additional withdrawal criteria can be found in Section 7.3.

On all Study Visit Days, every effort should be made to schedule study visits in the morning in order for patients to dose study drug in the clinic after clinical laboratory blood draws are completed.

Patient safety will be monitored throughout the trial. During the first 12 weeks of the Treatment Period, hematology, serum chemistry, and lipids will be conducted under fasted conditions every 4 weeks, followed by an assessment every 8 weeks thereafter through completion of the trial. Serum pregnancy testing will be performed at all in-clinic visits. To minimize patient burden of additional clinic visits, urine pregnancy testing will be performed by the subject at home on

Weeks 16, 24, 32, 40, 48 and 4-weeks post the final study visit. For responders, additional home pregnancy testing will be performed at Weeks 56, 64, 72, 80, 88, 96, 104, and 4-weeks post the final study visit. The test date and result will be documented in a patient diary and brought to each in-clinic study visit by the patient. SARS-CoV-2 testing will be performed at all visits. 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 (Section 8.1). Investigators should also monitor patients for possible signs, symptoms, or exposure to tuberculosis, including any travel to high-risk countries. In cases where TB infection or exposure is suspected, TB testing should be performed. Patients who experience intolerable symptoms during treatment may discontinue the study at the discretion of the Investigator. Patients may withdraw consent at any time. At each study visit, an assessment should also be undertaken for any changes in the physical exam, or symptoms such as pain, swelling or tenderness in leg(s), persistent breathing difficulties or shortness of breath, or severe headache, that are suggestive of an increased risk of thromboembolism. Patients must be withdrawn if they have a prior history of thrombotic event(s) or experience a thromboembolic event.

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

7. SELECTION AND WITHDRAWAL OF PATIENTS

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

7.1. Patient Inclusion Criteria

1. Written informed consent, and authorization for release and use of protected health information.
2. Have completed a 24-week Treatment Period in a previous qualifying CTP-543 clinical trial.
3. Female subjects are eligible to participate if at least one of the following conditions applies:
    a) Is a woman of childbearing potential (WOCBP) and using a medically highly effective form of birth control with a failure rate less than 1% per year from at least 4 weeks prior to Baseline until at least 30 days following last dose of study drug. Examples of medically highly effective birth control methods include:
        i. Combined (estrogen and progestogen containing) hormonal contraception (oral, patch, vaginal ring)
        ii. Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
        iii. Intrauterine device or intrauterine hormone-releasing system
        iv. Bilateral tubal occlusion
        v. Vasectomized partner (partner is the sole sexual partner of the WOCBP trial participant and the vasectomized partner has received medical assessment of the surgical success)
        vi. Sexual abstinence (reliable as refraining from heterosexual intercourse during the above-mentioned period)
    b) Is not a WOCBP:
        i. Premenopausal with one of the following:
            a. Documented hysterectomy;
            b. Documented bilateral salpingectomy;
            c. Documented bilateral oophorectomy.
        ii. Postmenopausal (cessation of menses for at least 12 months prior to screening)
        Postmenopausal is defined as no menses for 12 months without an alternative medical cause. In addition, a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm postmenopausal in women under 60 years old and not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment
4. Male participants must:

a. Agree to use, with their partners, male contraception (condom) and one of the highly effective contraceptive methods listed in Inclusion Criterion 5, from Baseline until at least 90 days following last dose of study drug.
b. Refrain from donating sperm during the study and for at least 90 days after the end of the study.

5. Willing to comply with the study visits and requirements of the study protocol.

7.2. Patient Exclusion Criteria

1. 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.
2. Females who are nursing, pregnant, or planning to become pregnant while in the study, and for 30 days after last dose of study medication.
3. Donation of blood at any point throughout the study and for 30 days after last dose of study medication.
4. Most recent hematologic parameters do not permit continued dosing; i.e., criteria for withholding IP have been met and have not recovered to values required to resume dosing.
5. Any medical (e.g. any prior history of thromboembolism), psychiatric, or social condition that is likely to unfavorably affect the risk-benefit of continued study participation, interfere with study compliance, or confound safety or efficacy assessments.

7.3. Patient Withdrawal Criteria

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

- Have a prior history of thrombotic event(s);
- Experience a thromboembolic event;
- Experience an intolerable adverse event, including but not limited to bone marrow related events characterized by protocol specified hematologic abnormalities, or a ≥ Grade 3 cardiac event, or a ≥ Grade 4 (other) adverse event (CTCAE v5.0 criteria) considered possibly related to study drug. Because laboratory abnormalities can occasionally occur that do not in themselves pose an unacceptable risk to subject safety (e.g., CK elevations with exercise, laboratory errors or artifacts), the occurrence of a ≥ Grade 4 laboratory abnormality, or any laboratory abnormality of concern to the Investigator, will be discussed with the Medical Monitor and a determination will be made, based on a reassessment of risk-benefit for the subject, whether the subject should discontinue randomized treatment. Documentation on the determination will be maintained in the study files;
- 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 when its use is unlikely to unfavorably alter the risk-benefit of subject participation or confound the study endpoints;

- Experience an adverse event of progressive multifocal leukoencephalopathy (PML) or skin cancer which are rare but potential risks of the drug;
- Do not follow guidelines specified in the protocol (i.e., is noncompliant with protocol procedures or study treatment administration);
- In the opinion of the Investigator, have any medically appropriate reason or significant protocol violation;
- Become pregnant;
- Have a serious adverse event associated with a SARS-CoV-2 infection;
- Are lost to follow up;
- Are, in the judgement of the Investigator, not exhibiting clear benefit following one full year of active treatment with CTP-543;
- In the opinion of the Investigator, feel that continued study participation is undesirable or the risk-benefit profile has become unfavorable.

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

7.3.1. Patient Withdrawal Procedures

A patient who prematurely discontinues study treatment/study participation should have all Early Termination Visit assessments performed (See Table 1 and Table 2).

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

Adverse events resulting in patient early termination will be followed to the satisfactory resolution and determination of outcome, as ascertained by the Investigator (and/or Sponsor, or its designee); See Section 10 Adverse Events. The data will be recorded on the appropriate eCRF.

7.4. Criteria for Study Termination

7.4.1. End of Trial

The end of the trial is defined as the date of the last visit of the last subject undergoing this trial. Within 90 days after the end of the clinical trial, the regular termination of the trial will be reported to the responsible ethics committee and competent authority according to national laws and regulations. If the trial has to be terminated early, this period shall be reduced to 15 days and the reasons clearly explained.

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

In the case of a negative change in the risk-benefit ratio, the study will not be continued even if adaptations to the maximum insured amount are requested.

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

8. DESCRIPTION OF STUDY TREATMENTS

8.1. Safety Criteria and Management for Stopping Doses

Patients who experience significant changes in their hematology laboratory values as described in Table 5 should have their dose interrupted; or be discontinued from the study based on the medical judgement of the Investigator. The Medical Monitor should be consulted whenever possible prior to decisions for dose interruption or patient discontinuation from the study.

Dose interruption requirements for hematologic abnormalities are provided below.

Table 5: Selected Hematologic Thresholds for Dose Interruption

Neutrophil Count	[redacted]
Less than 0.5 x 10^9/L	[redacted]
Between 0.5 and 1 x 10^9/L	[redacted]
Female Hemoglobin Level	[redacted]
Less than 10 g/dL	[redacted]
Male Hemoglobin Level	[redacted]
Less than 11.5 g/dL	[redacted]
Platelet Count	[redacted]
Less than 75 x 10^9/L	[redacted]
Greater than 750 x 10^9/L	[redacted] 600

Upon dose interruption, the parameters that triggered the interruption should be monitored at least weekly until recovery above the threshold for dosing resumption is achieved.

Any dose interruptions for a patient should be discussed with the Medical Monitor.

Patients who are discontinued from the study should undergo an Early Termination Visit per Section 7.3.1, Patient Withdrawal Procedures, and associated adverse events should follow the procedures described in Section 10, Adverse Events.

Hematology, serum chemistry, and lipid parameters will be assessed under fasted conditions every 4 weeks for the first 12 weeks of the Treatment, and every 8 weeks thereafter for the remainder of the study. Serum pregnancy testing will be performed at all in-clinic visits. To minimize patient burden of additional clinic visits, urine pregnancy testing will be performed by the subject at home on Weeks 16, 24, 32, 40, 48 and 4-weeks post the final study visit. For

responders, additional home pregnancy testing will be performed at Weeks 56, 64, 72, 80, 88, 96, 104, and 4-weeks post the final study visit. The test date and result will be documented in a patient diary and brought to each in-clinic study visit by the patient. Less significant changes in laboratory values may warrant clinical intervention and the Investigator should use his/her best clinical judgement when considering a dose interruption, whether for singular or aggregate laboratory results outside of the normal range, or for other clinical signs, symptoms, or considerations that suggest dose interruption is in the best interest of the patient. Prior to a dose interruption, the laboratory values of interest should be confirmed with repeat testing at an interval deemed appropriate by the Investigator (e.g., at the next protocol-defined visit or an Unscheduled Visit). Again, the Medical Monitor should be notified whenever possible prior to decisions for dose interruption.

8.1.1. Management of Risk with Janus Kinase (JAK) Inhibitors

On 23 January 2023, EMA's human medicines committee (CHMP) endorsed the measures recommended by the Pharmacovigilance Risk Assessment Committee (PRAC) to minimize the risk of serious side effects with approved Janus kinase (JAK) inhibitors used to treat several chronic inflammatory disorders. These recommendations were based on a review of available data, including the final results from a clinical trial of the JAK inhibitor Xeljanz (tofacitinib) and preliminary findings from an observational study involving Olumiant. These side effects include cardiovascular conditions, blood clots, cancer and serious infections. Janus kinase (JAK) inhibitors used to treat chronic inflammatory disorders are linked to a higher risk of major adverse cardiovascular events (MACE), venous thromboembolism (VTE), malignancy, serious infections and all-cause mortality.

As CTP-543 is an investigational product in the JAK inhibitor class of drugs, CTP-543 should be used with caution in patients with risk factors for blood clots in the lungs and in deep veins (venous thromboembolism, VTE), patients at increased risk of major cardiovascular problems (such as heart attack or stroke), those who smoke or have done so for a long time in the past and those at increased risk of cancer. Any patients presenting with an increased risk should be withdrawn per Section 7.3.

8.1.2. SARS-CoV-2 Dose Interruption Guidance

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 6: 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

Medical Monitor should be notified in case of a subject is diagnosed with monkeypox. Study drug should be interrupted during acute infection.

8.2. Treatment Compliance

At each scheduled study visit after enrollment, the Investigator or designee will interview the patient regarding treatment compliance and compare the number of dispensed versus returned study drug tablets.

8.3. Study Drug Materials and Management

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

8.3.1. Physical Description of Study Drug

CTP-543 are white, capsule-shaped tablets prescribed for oral administration.

8.3.2. Study Drug Packaging, Labeling, and Storage

CTP-543 tablets will be packaged and labeled by an appropriately qualified vendor. Details of the packaging, labeling and dispensing instructions can be found in the Pharmacy Manual.

The label(s) for the investigational product will include, at a minimum, Sponsor name, address and telephone number, the protocol number, investigational product name, dosage form, amount of investigational product per container, lot number, unique dosing bottle number, storage conditions, and required caution statements and/or regulatory statements, as applicable per local regulations.

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

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

8.3.3. Study Drug Preparation and Administration

No study drug preparation is required. Patients will be instructed to take study drug according to the study drug label. Patients should dose study drug in the clinic on all Study Visit Days after clinical laboratory blood draws are completed.

Study drug should be taken at approximately the same times each day, with water, and consistently with or without meals. If a dose is missed, the patient should skip the missed dose and resume dosing at the next scheduled dose. The patient should not take two doses at the same time. Deviations from prescribed dosing should be discussed at each visit for assessment of compliance and retraining when necessary.

8.3.4. Study Drug Return and Disposal

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

8.3.5. Study Drug Accountability

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

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

8.4. Concomitant Medications and Other Requirements for Continued Eligibility

All medications, including over-the-counter therapies (e.g., vitamins, herbal, and nutritional supplements) and vaccinations (including the SARS-CoV-2 vaccination), will be recorded in the patient's source documentation and documented in the eCRF.

Any change in medical history (including newly acquired risk factors for thromboembolism such as but not limited to: prolonged immobilization or surgery), adverse events, concomitant medications or physical exam findings that in the opinion of the investigator may lead to an increased risk of thromboembolism, should be evaluated for continuation of the subject in the study. The Medical Monitor should be consulted if, in the opinion of the investigator, the subject is at an increased risk for thromboembolism.

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. As subject and public health are paramount, SARS-CoV-2 vaccination should not be delayed or withheld for subjects already enrolled in this trial.

Knowledge about the vaccines and virus is continually growing. The Sponsor or the Medical Monitor 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 subject may be given at the discretion of the Investigator. Use of medications that are prohibited per protocol might

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.

[redacted]

Additionally, while enrolled in this study patients are not permitted to:

- Use adhesive wigs, other than banded perimeter wigs.
- Receive vaccinations for herpes zoster or any other live virus vaccine (except monkeypox vaccine, see the note below)

  NOTE: Live vaccines include, but are not limited to, the measles, mumps, and rubella (MMR) vaccine; intranasal flu vaccine; and Zostavax (but not Shingrix) for herpes zoster. Regarding monkeypox vaccine in the context of monkeypox outbreak as a Public Health Emergency of International Concern:

  > As an exception, if monkeypox vaccination is for the subject benefit, live attenuated vaccine can be given, following study drug dose interruption, in accordance with the international and national guidelines and in consultation with the medical monitor.

- Participate in another interventional clinical trial.

8.4.1. Continued Eligibility Beyond Initial 52-Weeks of Treatment

At the Week 52 visit, patients will be assessed for treatment response, defined as achieving a SALT score of ≤20 to determine their eligibility to continue treatment. Patients who meet responder criteria (SALT score of ≤20) will be eligible to continue to receive CTP-543 for an additional year. Patients who do not meet the defined criteria of SALT ≤20 will be deemed a non-responder and will complete the study at the Week 52 visit per the Schedule of Events (Table 1 and Table 2).

9. STUDY ASSESSMENTS AND PROCEDURES

The schedule of assessments and procedures is presented in Table 1 and Table 2 and should be referenced for details regarding the collection of each assessment at each visit. Any missed visits and associated assessments due to the COVID pandemic (e.g. site closures or travel restrictions) will be recorded on the e-CRF as COVID-related.

As the Baseline Visit for this study will occur on the same day as the End of Study Visit for the preceding clinical trial, assessments will not be repeated and results from the End of Study Visit will be carried over for this study.

9.1. Physical Examination

Complete physical exams will include vital signs, weight, an examination of all major organ systems, with an emphasis on assessing for active signs and symptoms of infection, exposure to tuberculosis, and skin examinations for skin cancers. Evaluation for progressive multifocal leukoencephalopathy (PML) symptoms such as facial droop, general weakness, clumsiness, trouble speaking, personality changes, memory problems, and vision changes will be assessed. Complete physical exams will be performed according to the Schedule of Events (Table 1 and Table 2).

Brief physical examinations will be performed according to the Schedule of Events (Table 1 and Table 2). Brief PE should focus on an evaluation of safety and include vital signs, weight, abdominal palpation, and head, eyes, ears, nose and throat assessment, assessing for active signs and symptoms of infection, exposure to TB, inquiry on changes to skin lesions and/or moles indicative of skin cancers, and an evaluation for progressive multifocal leukoencephalopathy (PML) as noted above.

At each study visit, an assessment should also be undertaken for any changes in the physical exam, or symptoms such as pain, swelling or tenderness in leg(s), persistent breathing difficulties or shortness of breath, or severe headache, that are suggestive of an increased risk of thromboembolism.

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 and remove his/her shoes before weight is measured.

9.2. Clinical Laboratory Assessments

Clinical laboratory assessments for hematology, serum chemistry, and lipids (Table 7), will be performed under fasted conditions every 4 weeks for the first 12 weeks then every 8 weeks thereafter as presented in the Schedule of Events (Table 1 and Table 2). Serum pregnancy testing will be performed at all in-clinic visits. To minimize patient burden of additional clinic visits, urine pregnancy testing will be performed by the subject at home on Weeks 16, 24, 32, 40, 48, and 4-weeks post the final study visit. For responders, additional home pregnancy testing will be performed at Weeks 56, 64, 72, 80, 88, 96, 104, and 4-weeks post the final study visit. The test date and result will be documented in a patient diary and brought to each in-clinic study visit by the patient.

Clinical laboratory samples should be collected at the beginning of each clinic visit. Every effort should be made to collect clinical laboratory samples prior to the first daily dose on all Study Visit Days.

The Investigator should indicate review of the laboratory reports throughout the study by signing and dating each report.

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

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

Table 7: Clinical Laboratory Assessments

Hematology	**Chemistry**	**Serum and Urine Pregnancy**
Complete blood count Absolute neutrophil count Absolute eosinophil count Platelet count White blood cell count with differential Absolute reticulocyte count Hemoglobin A1c	Alanine aminotransaminase Albumin Alkaline phosphatase Amylase Aspartate aminotransaminase Total bilirubin Direct bilirubin Indirect bilirubin Blood urea nitrogen Calcium Carbon dioxide Chloride Creatinine Creatine kinase Glucose Lipase Total protein Phosphorus Potassium Sodium Uric Acid	Human chorionic gonadotropin (females of childbearing potential only)
Lipids	**Other**	
Total cholesterol Low-density lipoprotein High-density lipoprotein triglycerides	SARS-CoV-2 testing	

9.3. Electrocardiogram

Twelve-lead electrocardiograms will be performed at the timepoints specified in the Schedule of Events (Table 1 and Table 2).

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

9.4. Severity of Alopecia Tool (SALT)

The SALT score was introduced as part of investigative guidelines published by the National Alopecia Areata Foundation (Olsen, 2004). The SALT is a measure of hair absence that quantifies the amount of scalp surface without hair in a pre-specified quadrant of the scalp (right side, top, left side, back), that is further summed after applying a quadrant-specific multiplier indicative of scalp surface area contribution, to provide an overall score of total hair loss. The SALT assessment will occur via live examination of the patient every 4 weeks for the first 12 weeks then every 8 weeks thereafter.

To reduce variability, one rater should perform the SALT assessment for the patient for the duration of the study. All investigators using the SALT should be trained prior to use. Please consult the associated SALT Manual for additional details regarding SALT scoring and training requirements for this study. An example of the SALT assessment tool is provided in Appendix 16.1.

9.5. Unscheduled Visit

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

10. ADVERSE EVENTS

10.1. Definition of Adverse Event

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

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

An adverse event reported after informed consent, but before the first dose of study drug (i.e., Day 1), will be considered a pretreatment adverse event and will be captured on the eCRF. Adverse events will be considered treatment-emergent if the onset is after the first dose of study drug or if an ongoing Adverse Event worsens after dosing is initiated.

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

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

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

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

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.

10.2. Evaluation of Adverse Events

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

10.2.1. Serious Adverse Event

A serious adverse event is an adverse event 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 and serious adverse event eCRF must be completed.

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

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

10.2.2. Severity/Intensity

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

The National Cancer Institute-Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 should be used to grade the severity/intensity of all events. These criteria will be provided in the Site Operations Manual. If a CTCAE criterion does not exist, the Investigator should grade the severity according to the following criteria:

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

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

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

10.2.3. Relationship to Study Drug

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

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

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

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

Unlikely Related: A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which

other drugs or concurrent or underlying disease provide plausible explanations (e.g., the patient's clinical condition, other concomitant treatments).

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

10.2.4. Duration

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

10.2.5. Action Taken

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

10.2.6. Outcome

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

10.3. Follow-Up

Adverse events, 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.

10.4. Pregnancy

The Sponsor must be informed within 24 hours upon learning that a patient, or male patient's partner, has become pregnant any time after the first dose of study drug until 30 days after the last dose of study drug. Prior to any data collection for a pregnant participant or a pregnant partner of a participant in study CP543.5002, written informed consent on the pregnant partner/participant information and consent form must be provided by the study participant or the partner of the participant, in accordance with local practice, law or regulation. Information about the follow-up of the pregnancy will be explained to the pregnant participant or the pregnant partner of a participant. A copy of the pregnant partner/participant information and consent form must be given to the patient, if applicable.

While pregnancy itself is not considered an AE or SAE, pregnancy reports will be processed in accordance with the same procedures set forth for non-expedited SAEs. 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 via a pregnancy notification. The Pregnancy Outcome eCRF should be used to report information regarding the status of the infant. No mandatory visits, tests, or specific assessments are required for this study. However, the Principal Investigator will liaise regularly with the health care provider of the participant or with the health care provider of the partner until termination of the pregnancy or until the birth of the child. Follow-up of the pregnancy will be scheduled by the study participant or the partner of the participant with their health care provider and conducted according to the standard of care. Standard of care is defined as a diagnostic and customary clinical treatment/practice process that a clinician chooses according to their clinical judgement for a certain type of illness, or clinical circumstance based on the clinical practice guidelines. The Clinical Research Organization (CRO) responsible for pharmacovigilance will contact the investigative site, advise them to follow the pregnancy, and query the site to report any complications during the pregnancy, or any adverse pregnancy outcomes.

The pregnancy eCRF pages are completed in EDC, and require the site report any clinical finding on prenatal testing. The obstetrical history is also collected. The Principal Investigator advises the participant to call the site to report any complications. In addition, the CRO pharmacovigilance group will query the site after the determined due date to obtain final pregnancy and newborn outcome.

Pregnancy cases are not considered closed until all data fields on the pregnancy report form are properly completed, including pregnancy outcome. Information on the outcomes of pregnancies will be reported along with all other safety data from the study in the final study report. In addition, a database of information relating to reported pregnancies across all CTP-543 studies will be maintained in order to include these data in any subsequent marketing application.

If pregnancy occurs in a female patient, then study drug should be discontinued immediately. If a female partner of a male patient taking investigational product becomes pregnant, the male patient taking the investigational product should notify the Investigator, and the pregnant female partner should be advised to call her healthcare provider immediately.

10.5. Recording Adverse Events

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

10.6. Reporting Adverse Events

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

10.6.1. Reporting Serious Adverse Events

The Investigator is required to notify the Sponsor, and the Sponsor's designated Drug Safety Unit, immediately, without undue delay, and no later than 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 EC.

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

10.6.2. Reporting Urgent Safety Issues

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

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

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

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

11. STATISTICAL METHODS

This section describes the rules, conventions, statistical analysis, and presentation of data for this study. Full details will be provided in the statistical analysis plan (SAP) for this study.

Revisions during the study may be made to accommodate protocol amendments and to make changes to adapt to unexpected issues in study execution that could affect planned analyses. A formal SAP for the analysis and presentation of data from this study will be prepared and issued before database lock. The SAP will provide a more technical and detailed description of the proposed data analysis methods and procedures. Deviations from the statistical analyses outlined in this protocol will be included in this plan; any further modifications will be noted in the clinical study report (CSR). All statistical analyses will be performed under oversight of the Sponsor.

All available data will be included in data listings and tabulations.

All data collected in this study will be presented using summary tables and patient data listings. Summary statistics for raw and change from Baseline data of continuous variables will minimally include n, mean, standard deviation (SD), minimum, median, and maximum. For categorical variables, frequencies and percentages will be presented. Graphical displays will be provided as appropriate.

Endpoints will be assessed using simple descriptive statistics.

11.1. Endpoints

11.1.1. Safety

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

11.1.2. Efficacy

Efficacy of CTP-543 will include all patients who receive study drug and have at least 1 post-treatment SALT assessment in this study. Relative change in SALT score over time will be summarized descriptively by visit, as appropriate.

11.2. Analyses

Efficacy will include all patients who receive study drug and have at least 1 post-treatment SALT assessment in this study. Safety will include all patients who receive study drug. Patients will be summarized according to study drug regimen received (i.e., as treated).

Data will be summarized by dosing regimen. All data for analysis will be listed by patient. Dosing regimens for summarization will be defined in SAP.

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

11.2.1. Disposition and Baseline Characteristics

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

Baseline characteristics will be summarized by dosing regimen for patients participating in the Treatment Period. Dosing regimens for summarization will be defined in SAP.

Medical history will be coded with the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Concomitant medications will be summarized by World Health Organization Drug Dictionary Anatomical-Therapeutic-Chemical classification and preferred term.

11.2.2. Study Drug Exposure

For each patient, the number of days of exposure to CTP-543 will be summed across the Treatment Period. The total number of days on study drug will exclude dose interruptions. The total number of days of exposure to CTP-543 by dose will be summarized with the mean, standard deviation, median, minimum, and maximum number of days.

11.2.3. Safety

All safety summaries will be descriptive with no statistical hypothesis testing and based on the Safety Population. All safety endpoints will be listed in by-patient data listings.

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

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

11.2.3.1. Adverse Events

Treatment-emergent adverse events (TEAEs) will be defined as any adverse event that occurs after administration of the first dose of study drug until completion of the study or the Early Termination Visit. The number and percentage of patients who report TEAEs will be summarized by system organ class and preferred term.

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

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

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

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

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

By-patient listings will be provided for any deaths, serious adverse events, and adverse events leading to discontinuation of treatment.

11.2.3.2. Clinical Laboratory

Clinical laboratory variables will be presented 3 ways. First, change from Baseline to each scheduled assessment will be summarized descriptively. Baseline will be defined as the laboratory value obtained before the first dose of study drug on Day 1.

Second, treatment-emergent potentially clinically significant (PCS) laboratory values will be identified. Potentially clinically significant values are defined as those that meet Grade 3 or Grade 4 toxicity criteria from the CTCAE criteria. Treatment-emergent PCS laboratory values are those in which the Baseline value is not PCS and the post-baseline value is PCS.

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

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

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

11.2.3.3. Vital Signs

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

Baseline will be defined as the last vital sign value obtained before the first dose of study drug on Day 1.

11.2.3.4. Electrocardiogram

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

12. REGULATORY CONSIDERATIONS

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

12.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Sponsor, its authorized representative, and Investigator abide by GCP, as described in ICH Guideline E6(R2) and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from the 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.

12.2. Sponsor's Responsibilities

The Sponsor or its designee is responsible for the following:

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

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

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

During the study, a monitor from Sun Pharmaceutical 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).

- Due to the COVID-19 pandemic and the possibility for site closures and/or travel restrictions, source data verification may be performed remotely to the degree allowed per local regulations.

  NOTE: If allowed per local regulations, remote source data verification will be instituted only during the COVID-19 pandemic. These are temporary measures that will be rescinded as soon as the rules governing the management of clinical trials during the COVID-19 pandemic are repealed.

- Record and report any protocol deviations.
- Confirm adverse events and serious adverse events have been properly documented on eCRFs and confirm any serious adverse events have been forwarded to the Sponsor and those serious adverse events that met criteria for reporting have been forwarded to the EC.

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

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

12.3. Investigator's Responsibilities

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

The Principal Investigator will ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, the study drug, and their study-related duties and functions. The Principal Investigator will maintain a list of sub-Investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

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

The Sponsor, or designee, should inform the 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 EC. A progress report will be sent to the EC and the protocol will be reviewed annually (e.g., re-approved) or more frequently, as required by the EC or local regulations.

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

The Sponsor or designee is responsible for notifying the EC/RA of the conclusion of the clinical study within 90 days of completion of the study, per the EU Directive. In cases where a study is

terminated early, notification must be made within 15 days of the early termination. The final study report must be submitted within 1 year after study completion.

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

12.4. Protocol Amendments

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

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 recent Regulatory Agency guidance, amendments to protocol defined criteria may be implemented without EC 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 EC notified within 5 days or per local regulations.

When, in the judgement of the chairman of the local 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.

12.5. Audits and Inspections

The Sponsor's Quality Assurance Unit (or representative) may conduct audits at the study site(s) or remotely. 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 inspect the Investigator during or after the study. The Investigator should contact the Sponsor immediately if this occurs, and must fully and reasonably cooperate with Regulatory inspections.

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

12.6. Quality Control and Quality Assurance

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

A quality control and quality assurance plan addressing aspects of the study that may impact data integrity or the protection of human subjects may be instituted for this study. Audit findings and follow-up will be documented as appropriate based on Sponsor Standard Operating Procedures.

In light of the COVID-19 pandemic, risk-based approaches to patient safety will be instituted, as applicable and per local regulations. Compliance with Good Clinical Practice (GCP) will be maintained and risks to patient safety and data integrity will be maintained.

13. DATA HANDLING AND RECORDKEEPING

13.1. Confidentiality

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

Submission of this protocol and any other necessary documentation to the EC is expressly permitted, 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.

13.2. Patient Data Protection

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

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

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

13.3. Data Collection

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

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

13.4. Case Report Form Completion

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

13.5. Database Management, Data Clarification, and Quality Assurance

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

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

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

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

13.6. Inspection of Records

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

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

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

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

Source document verification is not a substitute for clinical study monitoring, the purpose of which is to ensure that the protocol has been followed correctly, the eCRF has been fully and accurately completed, source document verification has been carried out, and the study timelines and enrollment goals and requirements have been met. In light of the COVID-19 pandemic, source document verification may occur remotely, as applicable, and in accordance with local regulations. Additional detail on remote source document verification will be provided in the study plans.

13.7. Retention of Records

For all trials in which the clinical trial data are used to support a marketing authorization, per Directive 2003/63/EC (amending Directive 2001/83/EC), study records will be retained for at least 15 years after completion or discontinuation of the trial or at least two years after the granting of the last marketing authorization in the European Union (when there are no pending or contemplated marketing applications in the EU) or for at least two years after formal discontinuation of clinical development of the investigational product, whatever is the longest.

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, they shall inform the Sponsor. The relevant records shall be transferred to a mutually agreed upon designee.

14. PUBLICATION POLICY

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

15. LIST OF REFERENCES

First Author (Year)	Citation
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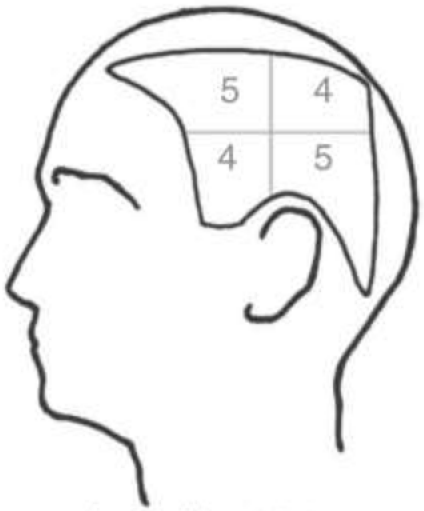
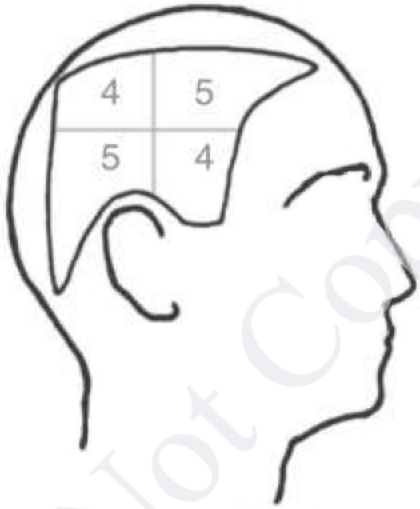
16. APPENDICES

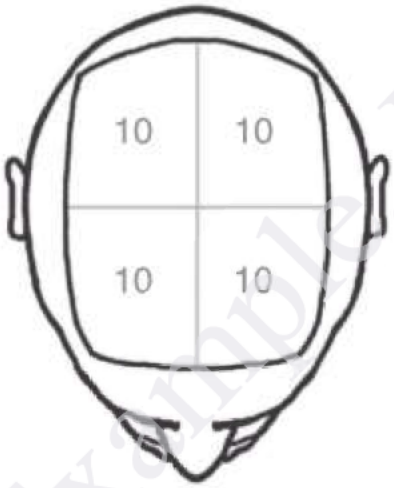
16.1. Severity of Alopecia Tool (SALT)



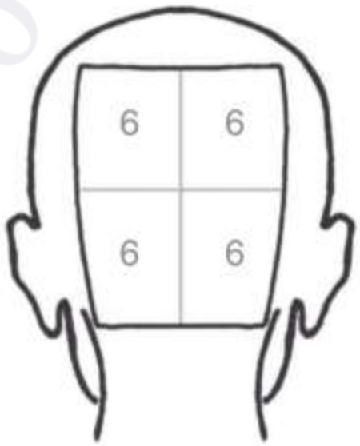
Left side: 18%



Right side: 18%



Top: 40%



Back: 24%

Olsen/Canfield

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