Official title: A Phase II, Randomized, Double Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Efficacy and Safety of AS012 in Subjects with Non-segmental Vitiligo

Document: Study Protocol

NCT number: NCT04487860

Document date: 20-May-2022

CONFIDENTIAL

A PHASE II, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED DOSE-RANGING STUDY TO EVALUATE THE EFFICACY AND SAFETY OF AS012 IN SUBJECTS WITH NON-SEGMENTAL VITILIGO

CLINICAL STUDY PROTOCOL

Protocol Number: AS012-20-01

[redacted]

Protocol Version Date: May 20, 2022

Study Managing Lead: [redacted]

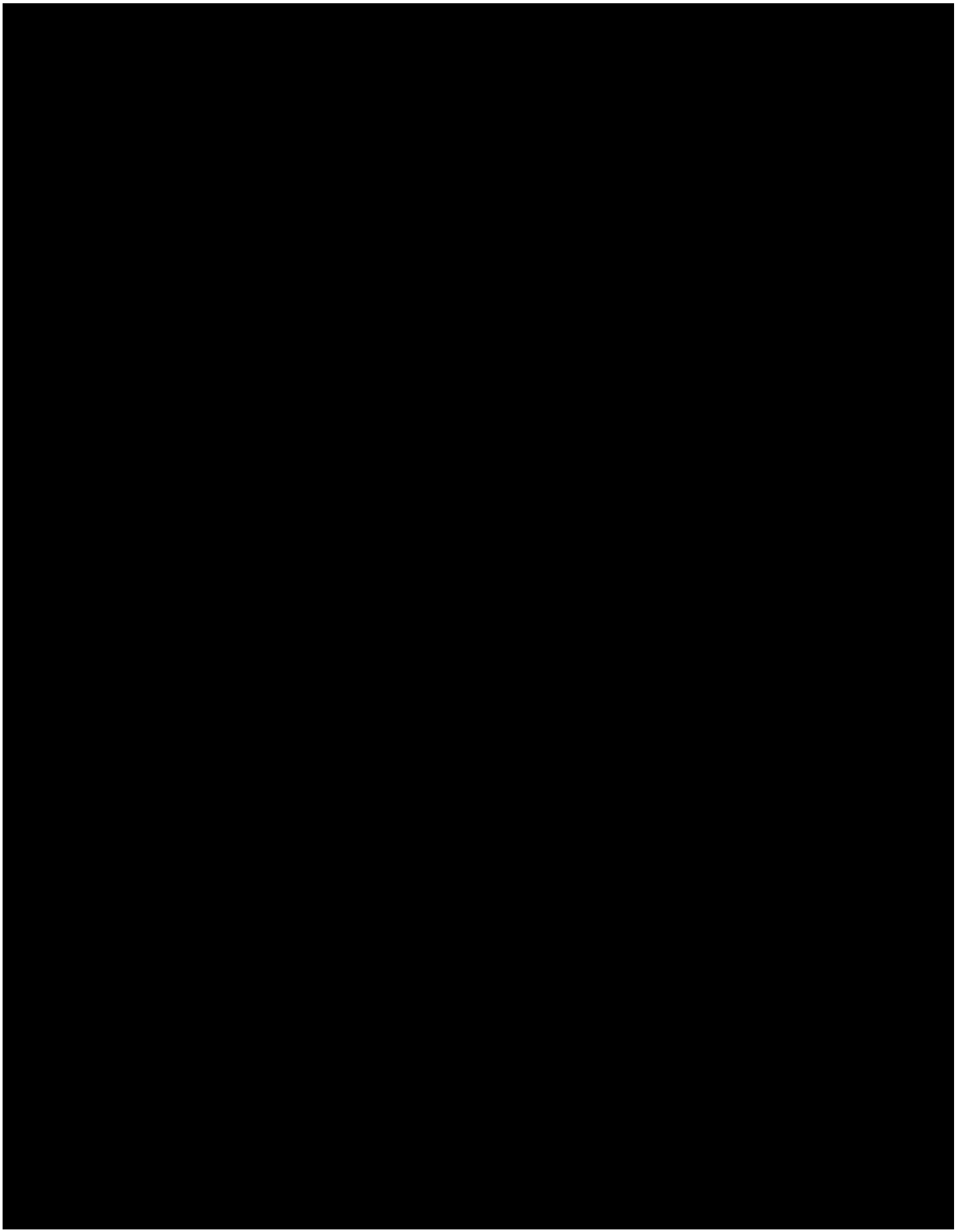
[redacted]

Sponsor: [redacted]

Developmental phase of study: II

PROTOCOL APPROVAL:

[redacted]



PRINCIPAL INVESTIGATOR AGREEMENT

I have carefully read and understand the foregoing protocol AS012-20-01 “A PHASE II, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED DOSE-RANGING STUDY TO EVALUATE THE EFFICACY AND SAFETY OF AS012 IN SUBJECTS WITH NON-SEGMENTAL VITILIGO” and agree that it contains all the necessary information for conducting this study safely. I will conduct this study in strict accordance with this protocol, ICH guidelines for Good Clinical Practice, the Code of Federal Regulations and local regulatory guidelines. I will attempt to complete the study within the time designated.

I will ensure that the rights, safety and welfare, of Subjects under my care are protected. I will ensure control of the drugs under investigation in this study.

I will provide copies of the protocol and all other study-related information supplied by the Sponsor to all personnel responsible to me who participate in the study. I will discuss this information with them to assure that they are adequately informed regarding the drug and conduct of the study.

I agree to keep records on all Subject information (case report forms, shipment and drug return forms and all other information collected during the study) and drug disposition in accordance with FDA regulations.

I will not enroll any Subjects into this protocol until IRB approval and Sponsor approval are obtained.

Principal Investigator	**Signature, Date**

TABLE OF CONTENTS

[redacted]

LIST OF ABBREVIATIONS

AE	Adverse Event
ALC	Absolute Lymphocyte Counts
ALT	Alanine aminotransferase
a.m.	ante meridiem, 00:00 -11:59
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
[redacted]	[redacted]
CI	Confidence Interval
CFR	Code of Federal Regulations
eCRF	Electronic Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
dl	Deciliter
DLQI	Dermatology Life Quality Index
DM	Data Management
EC	Ethics Committee
ECG	Electrocardiography
ED	Early Discontinuation
EDC	Electronic Data Capture
e.g.	exempli gratia, “for example”, “such as”
EoS	End-of-Study
EOT	End of Treatment
[redacted]	[redacted]
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma Glutamyltransferase
hCG	Human Chorionic Gonadotropin
HEENT	Head, Eyes, Ears, Nose and Throat
HDL	high-density lipoproteins
HIV	Human immunodeficiency virus
HR	Heart rate
IA	Interim Analysis
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IFN	Interferon
ICH	International Council on Harmonization
ID	Identification
IRB	Institutional Review Board
IUD	Intrauterine Device
ICH	International Conference on Harmonization
INR	International Normalized Ratio
IND	Investigational New Drug
IP	Investigational Product
IRT	Interactive Response Technology
ITT	Intent To Treat
[redacted]	[redacted]
JAK	Janus kinase
LDL	Low-density Lipoproteins
MedDRA	Medical Dictionary For Regulatory Activities
[redacted]	[redacted]
mL	Milliliter
MM	Medical Monitor
Mm Hg	millimeter of mercury
NCE	New Chemical Entity
NOAEL	No Observed Adverse Effect Level
[redacted]	[redacted]

[redacted]

OTC	Over the Counter
p.m.	post meridiem, 12:00-23.59
[redacted]	[redacted]
PL	Placebo
[redacted]	[redacted]
PT	Prothrombin time
PGA	Physician Global Assessment
PUVA	psoralen and ultraviolet A
QD	once a day
QT	QT Interval (the time from the start of the Q wave to the end of the T wave)
QTcF	QT corrected Fridericia's formulas
RBC	Red Blood Cells
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
[redacted]	[redacted]
SUSAR	Suspected Unexpected Serious Adverse Reactions
T4	Serum Free Thyroxine
Tmax	Time Of Maximal Concentration
$T_{1/2}$	Half-Life
TID	three times a day
Tmax	Time to Maximum Plasma Concentration
TSH	Thyroid Stimulating Hormone
UPT	Urine Pregnancy Test
[redacted]	[redacted]
VASI	Vitiligo Area Scoring Index
[redacted]	[redacted]
VES	Vitiligo Extent Score
[redacted]	[redacted]
VIPs	Vitiligo Impact Patient Scale
U.S.A.	United States of America
ULN	Upper Limit Of Normal
UV-B	type B ultraviolet
WBC	White Blood Cell
WHO	World Health Organization

STUDY SYNOPSIS

Protocol Number: AS012-20-01

Title of Study: A PHASE II, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED DOSE-RANGING STUDY TO EVALUATE THE EFFICACY AND SAFETY OF AS012 IN SUBJECTS WITH NON-SEGMENTAL VITILIGO

[redacted]

Investigational Products: AS012 Tablets [redacted]

Control: Placebo of AS012 product

Treatment Duration: The study treatment period will last for 52 weeks

Dose and Mode of Administration: Subjects will take three tablets three times a day, approximately every 8 hours, in the morning, in the afternoon, and in the evening according to a randomization scheme [redacted]

Objectives:

Primary Objective:

- To evaluate the efficacy of different doses of AS012 compared to placebo in subjects with non-segmental vitiligo at Week 24 by evaluating the response using Vitiligo Area Score Index (VASI) scale

Secondary Objectives:

- [redacted]
- To assess the efficacy of different doses of AS012 by using the Physician Global Assessment (PGA), Vitiligo Extent Score (VES) [redacted]
- To assess the effect of AS012 on quality of life, as measured by Dermatology Life Quality Index (DLQI) and Vitiligo Impact Patient scale (VIPs) [redacted]

[redacted]

Design: Subjects in this randomized, double-blind, placebo controlled, parallel-group, multiple-center study will be assigned to treatment with the investigational products or placebo control according to a randomization scheme:

- **Part I*:** 24 weeks: Subjects will be randomized to Placebo, [redacted] or [redacted] AS012 in 3:3:1:3:1 ratio (approximately first 55% of enrolled subjects) or in 1:1:3:1:3 (approximately remaining 45% enrolled subjects).
  **Part I includes week 24 assessments*
- **Part II:** week 24 to week 52: Subjects initially randomized to placebo will be re-randomized to [redacted] AS012 in 1:1 ratio. Subjects originally randomized to AS012 doses will remain on their assigned dosing regimen until the end of Part II (week 52).
- **Part III:** week 52 to week 64: After week 52 (or early termination of study treatment prior to week 52), the study treatment will be stopped and all subjects will enter the follow-up period to monitor safety and tolerability for 12 weeks following last dose of study treatment.

[redacted]

Clinical Evaluations will be performed at:

Visit 1: Screening Visit (Week ≥ -4 / Day -28 to -1);
Visit 2: Baseline Visit (Week 1 / Day 1);
Visit 3: Interim Visit (Week 4 / Day 29 ± 3 Days);
Visit 4: Interim Visit (Week 12 / Day 85 ± 3 Days);
Visit 5: Interim Visit (Week 16 / Day 113 ± 3 Days);
Visit 6: Interim Visit (Week 20 / Day 141 ± 3 Days);
Visit 7: Interim Visit (Week 24 / Day 169 ± 3 Days);
Visit 8: Interim Visit (Week 28 / Day 197 ± 3 Days);
Visit 9: Interim Visit (Week 36 / Day 253 ± 3 Days);
Visit 10: Interim Visit (Week 44 / Day 309 ± 3 Days);
Visit 11: Interim Visit (Week 48 / Day 337 ± 3 Days);
Visit 12: End of Treatment Visit (Week 52 / Day 365 ± 3 Days);
Visit 13: Follow-up Visit (Week 64 / Day 449 ± 3 Days);

Subjects will be admitted into the study after informed consent has been obtained. An Unscheduled Visit is allowed at any time, for any reason, if in the Principal Investigator's opinion it is warranted. If a Subject is discontinued from the study during an Unscheduled Visit, the Unscheduled Visit will be referred to as an Early Discontinuation Visit. For all the subjects who discontinue the study prior to Visit 7 all efforts should be made to conduct a visit at, or close to week 24 to collect focused area assessments. Regardless of the reason, Subjects discontinued from IP prior to the end of study will be required to complete the End of Study (EoS) assessment within 2 weeks after the last dose.

Study Population:

Inclusion Criteria

1. Males and non-pregnant non-lactating females ≥ 18 years of age providing written informed consent prior to any study-related procedures;
[redacted]
3. Diagnosis of generalized, non-segmental vitiligo confirmed by physical examination by investigator

   Note: Stable (without new patches ≥ 1 year) or unstable (with new patches for the last 1 year) vitiligo is acceptable for the enrollment in the study. The stability of the condition will be recorded at the screening and will be used for the treatment stratification.
4. Vitiligo at Screening and Baseline with:
   - [redacted]
   - VASI score of ≥ 4
5. Female Subjects of childbearing potential (excluding women who are premenarchal, surgically sterilized (by hysterectomy) or postmenopausal for at least 1 year), in addition to having a negative urine pregnancy test, must be willing to use an acceptable form of birth control during the study from the day of the first dose administration to 90 days after the last administration of study drug. For the purpose of this study the following are considered acceptable methods of birth control: oral or injectable contraceptives, contraceptive patches, [redacted] (stabilized for at least 3 months), [redacted] (vaginal contraceptive), [redacted] (contraceptive implant), double barrier methods (e.g. condom and spermicide), intrauterine device (IUD), tubal ligation, Essure or abstinence with a 2nd acceptable method of birth control should the Subject become sexually active. Subjects on hormonal contraception must be stabilized on the same type for at least three months prior to enrolment in the study and must not change the method during the study. A sterile sexual partner is NOT considered an adequate form of birth control.

6. All male Subjects must agree to use accepted methods of birth control with their partners, from the day of the first dose administration to 90 days after the last administration of study drug. Abstinence is an acceptable method of birth control. Female partners should use an acceptable method of birth control as described in the above Item Number 5.
7. Willing to refrain from using all study prohibited medications during the treatment period
8. Willing and able to understand and comply with the requirements of the protocol, including attendance at the required study visits.

Exclusion Criteria

[redacted]

2. Segmental vitiligo, focal, or mixed vitiligo
3. Subjects who have high risk of suicidality at the Screening and Baseline assessments based on Investigator's judgment [redacted]
8. History of alcohol or drug abuse in the previous 2 years
9. Consumption of excessive amounts of alcohol (greater than 2 drinks per day) or use drugs of abuse (including, but not limited to, cannabinoids, cocaine and barbiturates)

[redacted]

[redacted]

13. Subjects who were submitted to melanocyte transfer;

[redacted]

23. Previous enrolment in this study
24. The subject or a family member is among the personnel of the investigational site or Sponsor designee staff directly involved with this trial.
25. Subjects who are members of the same household with subjects participating or previously enrolled in this study

Number of Subjects:

Approximately 320 subjects will be enrolled in the study in a 1:1:1:1:1 ratio [redacted]

[redacted]

Randomization and re-randomization will be stratified by stability of disease (stable vs. non-stable) [redacted]

Criteria for Evaluation:

Following assessments will be performed by the investigator according to the schedule of assessments:

Efficacy:

- Physician Global Assessment (PGA), [redacted] Vitiligo Area and Scoring Index (VASI), [redacted] Vitiligo Extent Score (VES), [redacted]
- Subjects will be asked to complete DLQI, [redacted] Vitiligo Impact Patient Scale (VIPs), [redacted]
- [redacted].

Safety:

- Vital signs
- Physical examination
- Monitoring of all adverse events (AEs)
- Laboratory assessments: Thyroid function Hematology, Clinical chemistry, Lipid Profile, Urinalysis, Pregnancy test, Coagulation profile, Serology at screening: HIV antibodies, HBsAg, HCV antibodies.
- ECG
- Chest X-ray (if not done in last 6 months)
- Columbia-Suicide Severity Rating Scale (C-SSRS)

[redacted]

Study Endpoints:

Primary:

- Mean change from baseline in VASI score at Week 24

Key Secondary:

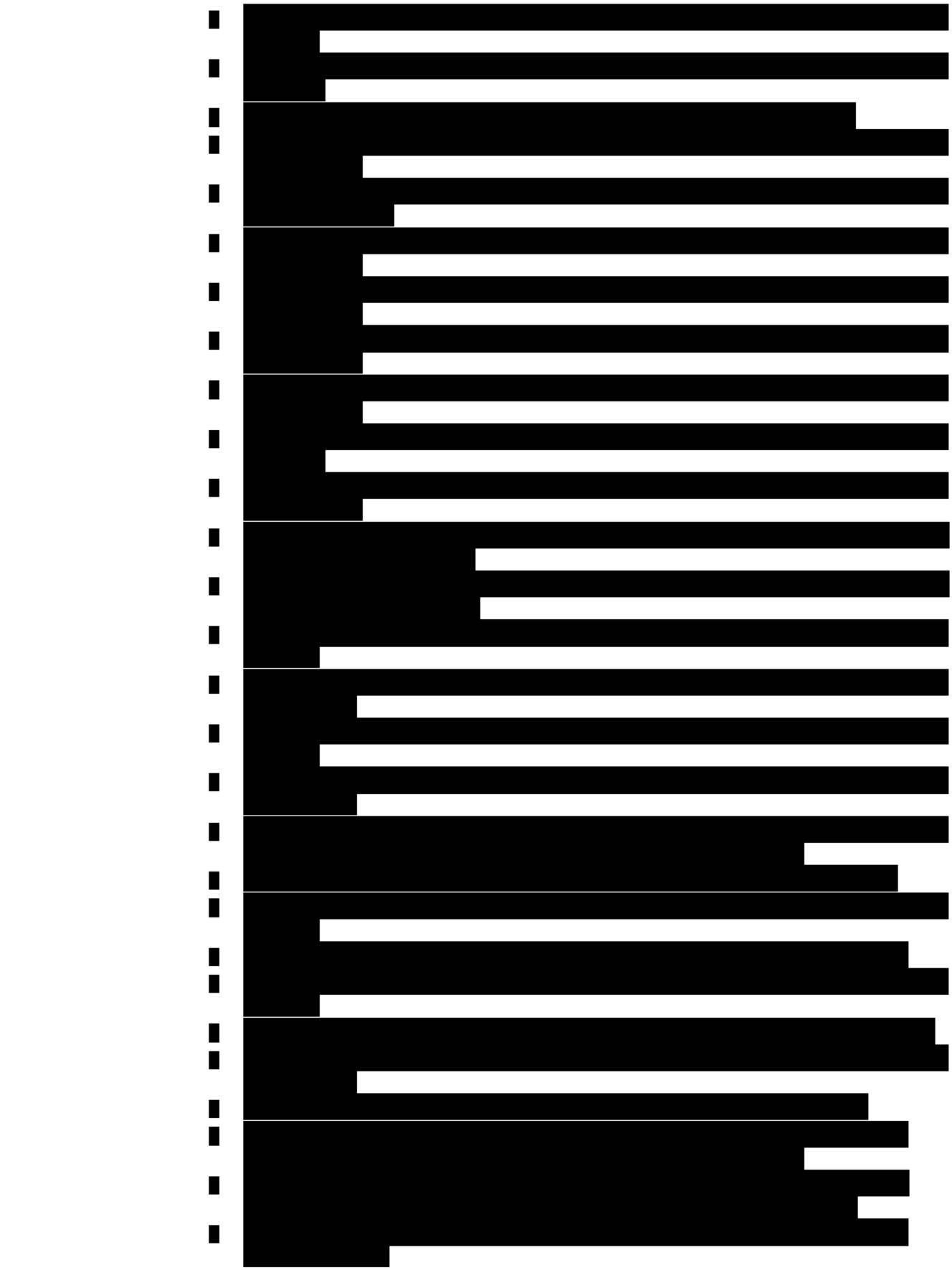
- Mean change from baseline in VES at Week 24.

[redacted]

- Mean change, from baseline, in VIPs at Week 24

[redacted]

[redacted]




PGA score
Week 52
DLQI at
Week 52

[redacted]

Statistical Methods:

The primary efficacy endpoint will be evaluated using the Intent-to-Treat (ITT) Population. The primary endpoint method of analysis will use an Analysis of Covariance (ANCOVA) model to compare change from baseline in VASI score results between treatment arms at Week 24. The ANCOVA model will include fixed effects for treatment, stability of disease (stable vs. non-stable), [redacted] baseline VASI score as a covariate. Point estimates and 95% confidence intervals (CI) will be obtained for the difference between each active dose *versus* placebo.

Missing VASI data at Week 24 will be addressed in the model using multiple imputation methods. Sensitivity analyses will be included to investigate the impact of missingness, and will include a completer analysis without imputation, as well as imputation based on placebo scores. Type I error (alpha, α) will be preserved in the primary efficacy analysis by use of a closed test step-down approach. Beginning with the highest dose, pairwise comparisons to placebo will be made until a non-significant result at the alpha (α) 0.05 level is reached, at which time testing will stop.

Secondary efficacy variables will be analyzed similarly, however without using multiple imputation methods.

Summary of Subjects who terminate prematurely

Reasons for premature termination will be summarized by treatment group.

Concomitant medication

The start and stop date of concomitant medication use during the study will be provided in the data set in addition to the reason for the medication use.

Safety Analyses

Safety analyses will be conducted on the Safety Population. Safety Incidence of all adverse events reported during the study will be summarized by treatment group, severity and relationship to study drug.

Summary of Subjects who Screen Fail

Reasons for removal of subjects during screening will be summarized.

1. INTRODUCTION AND BACKGROUND

Vitiligo is an acquired pigmentary disorder of skin and mucous membranes, manifesting as expanding depigmented lesions, related to selective loss of melanocytes. Prevailing theories of the pathogenesis of vitiligo include an immune hypothesis, a neural-mediated hypothesis, and a "self-destruct" hypothesis. While a specific cause for vitiligo has not been definitively proven, it is likely that the loss of epidermal and follicular melanocytes in vitiligo may be the result of several different pathogenic mechanisms.[1]

Vitiligo affects about 1% of world population. Some precipitating factors for this disease include physical and emotional stress, mechanical trauma, and exposures to chemicals such as phenol derivatives. Autoimmune diseases, especially of thyroid origin, are more common in patients with vitiligo. A study has shown that more than 50% of the patients with vitiligo report suffering some kind of social discrimination.[2]

Recent developments in vitiligo research have shown that:

- Vitiligo is an autoimmune skin disease mediated by CD8+ T cells that kill melanocytes in the epidermis
- T-cell recruitment to the skin requires Interferon (IFN)-γ and IFN-γ –induced chemokines secreted from keratinocytes.
- Chemicals found in common household products can induce or exacerbate vitiligo through induction of melanocyte stress.
- Melanocyte stem cell reservoirs are often protected within hair follicles in patients with vitiligo and are responsible for re-pigmentation of the skin after treatment.

To date, there are no approved treatments specifically for vitiligo. Patients are treated with a variety of modalities, many of which must be repeated for long periods of time to show any effect. Some of the treatments are administered or performed only in doctors' offices or hospital clinics, which may be located far from the patient's home, thus making access to therapy difficult for some patients.

[redacted]

The current study is a Phase II dose ranging study to assess the efficacy and safety of AS012 in treatment of non-segmental vitiligo.

2. OBJECTIVES

The objectives of this study are as follows:

Primary Objective:

- To evaluate the efficacy of different doses of AS012 compared to placebo in subjects with non-segmental vitiligo at Week 24 by evaluating the response using Vitiligo Area Score Index (VASI) scale.

Secondary Objectives:

- [redacted]
- To assess the efficacy of different doses of AS012 by using the Physician Global Assessment (PGA), Vitiligo Extent Score (VES), [redacted]

- [redacted]
- [redacted]
- To assess the effect of AS012 on quality of life, as measured by Dermatology Life Quality Index (DLQI) and Vitiligo Impact Patient scale (VIPs) [redacted]

[redacted] each of the

[redacted]

3. STUDY OVERVIEW

Subjects in this randomized, double-blind, placebo controlled, parallel-group, multiple-center study will be assigned to treatment with the investigational products or placebo control according to a randomization scheme.

- **Part I*:** 24 weeks: Subjects will be randomized to Placebo, [redacted] or [redacted] AS012 in 3:3:1:3:1 ratio (approximately first 45% of enrolled subjects) or in 1:1:3:1:3 (approximately remaining 55% enrolled subjects).
  **Part I includes week 24 assessments*
- **Part II:** week 24 to week 52: Subjects initially randomized to placebo will be re-randomized to [redacted] AS012 in 1:1 ratio. Subjects originally randomized to AS012 doses will remain on their assigned dosing regimen until the end of Part II (week 52).
- **Part III:** week 52 to week 64: After week 52 (or early termination of study treatment prior to week 52), the study treatment will be stopped and all subjects will enter the follow-up period to monitor safety and tolerability for 12 weeks following last dose of study treatment.

[redacted]

Clinical Evaluations will be performed at:

Visit 1: Screening Visit (Week ≥ -4 / Day -28 to -1);
Visit 2: Baseline Visit (Week 1 / Day 1);
Visit 3: Interim Visit (Week 4 / Day 29 ± 3 Days);
Visit 4: Interim Visit (Week 12 / Day 85 ± 3 Days);
Visit 5: Interim Visit (Week 16 / Day 113 ± 3 Days);
Visit 6: Interim Visit (Week 20 / Day 141 ± 3 Days);
Visit 7: Interim Visit (Week 24 / Day 169 ± 3 Days);
Visit 8: Interim Visit (Week 28 / Day 197 ± 3 Days);
Visit 9: Interim Visit (Week 36 / Day 253 ± 3 Days);
Visit 10: Interim Visit (Week 44 / Day 309 ± 3 Days);
Visit 11: Interim Visit (Week 48 / Day 337 ± 3 Days);
Visit 12: End of Treatment Visit (Week 52 / Day 365 ± 3 Days);
Visit 13: Follow-up Visit (Week 64 / Day 449 ± 3 Days);

Subjects will be admitted into the study after informed consent has been obtained. An Unscheduled Visit is allowed at any time, for any reason, if in the Principal Investigator's opinion it is warranted. If a Subject is discontinued from the study during an Unscheduled Visit, the Unscheduled Visit will be referred to as an Early Discontinuation Visit. For all the subjects who discontinue the study prior to Visit 7 all efforts should be made to conduct a visit at, or close to week 24 to collect focused area assessments. Regardless of the reason, subjects discontinued from IP prior to the end of study will be required to complete the End of Study (EoS) assessment within 2 weeks after the last dose.

[redacted].

Randomization and re-randomization will be stratified by stability of disease (stable vs. non-stable) [redacted]

The assigned Investigational Product will be administered orally three tablets three times a day, in the morning, in the afternoon, and in the evening according to a randomization scheme. Subjects will be required to use diaries to document the date of study treatments, any missed treatments and the occurrence of all adverse events.

The duration of each Subject's participation in the study will be approximately 64 weeks (449 days).

If the Principal Investigator determines that the Subject's condition has worsened to the degree that it is unsafe for the Subject to continue in the study (e.g. an increase in VASI score from baseline by ≥ 25%), the Subject may be discontinued from the study as a treatment failure and the Subject may be treated using the standard care.

4. STUDY POPULATION

4.1 Number of Subjects

Approximately 320 subjects will be enrolled in the study in a 1:1:1:1:1 [redacted]

The number of subjects contributed by a site will not exceed approximately 10% of total study population unless approved by the Sponsor. Approximately 192 subjects will be enrolled in US sites and approximately 128 subjects will be enrolled in sites in India.

4.2 Inclusion Criteria

1. Males and non-pregnant non-lactating females ≥ 18 years of age providing written informed consent prior to any study-related procedures.

[redacted]

3. Diagnosis of generalized, non-segmental vitiligo confirmed by physical examination by investigator

   Note: Stable (without new patches ≥ 1 year) or unstable (with new patches for the last 1 year) vitiligo is acceptable for the enrollment in the study. The stability of the condition will be recorded at the screening and will be used for the treatment stratification.

4. Vitiligo at Screening and Baseline with:

   [redacted]

   - VASI score of ≥ 4 [redacted]

5. Female Subjects of childbearing potential (excluding women who are premenarchal, surgically sterilized (by hysterectomy) or postmenopausal for at least 1 year), in addition to having a negative urine pregnancy test, must be willing to use an acceptable form of birth control during the study from the day of the first dose administration to 90 days after the last administration of study drug. For the purpose of this study the following are considered acceptable methods of birth control: oral or injectable contraceptives, contraceptive patches, [redacted] (stabilized for at least 3 months), [redacted] (vaginal contraceptive), [redacted] (contraceptive implant), double barrier methods (e.g. condom and spermicide), IUD, tubal ligation, Essure or abstinence with a 2nd acceptable method of birth control should the Subject become sexually active. Subjects on hormonal contraception must be stabilized on the same type for at least three months prior to enrolment in the study and must not change the method during the study. A sterile sexual partner is NOT considered an adequate form of birth control.

6. All male Subjects must agree to use accepted methods of birth control with their partners, from the day of the first dose administration to 90 days after the last administration of study drug. Abstinence is an acceptable method of birth control. Female partners should use an acceptable method of birth control as described in the above Item Number 5.

7. Willing to refrain from using all study prohibited medications during the treatment period

8. Willing and able to understand and comply with the requirements of the protocol, including attendance at the required study visits.

4.3 Exclusion Criteria

[redacted]

2. Segmental vitiligo, focal, or mixed vitiligo.
3. Subjects who have high risk of suicidality at the Screening and Baseline assessments based on Investigator's judgment [redacted]

[redacted]

8. History of alcohol or drug abuse in the previous 2 years
9. Consumption of excessive amounts of alcohol (greater than 2 drinks per day) or use drugs of abuse (including, but not limited to, cannabinoids, cocaine and barbiturates)

[redacted]

[redacted]

[redacted]

13. Subjects who were submitted to melanocyte transfer;

[redacted]

23. Previous enrolment in this study.
24. The subject or a family member is among the personnel of the investigational site or Sponsor designee staff directly involved with this trial.
25. Subjects who are members of the same household with subjects participating or previously enrolled in this study

4.4 Prohibited Medications, Procedures, and Activities

Medication necessary for the health and well-being of the subject are permitted provided the subject has been at a stable dose for 30 days prior to screening/baseline. The use of any medication that could affect the course of vitiligo is prohibited during the entire study period. Subjects will be advised to refrain from making any significant change in the use of consumer products during the study (including moisturizers, new brands of make-up, creams, ointments, lotions, and powders) applied on or near the affected area.

The following are prohibited during this study**:**

1. Use of new or changes in use of hormonal contraceptives
2. Minocycline
3. Phototherapy (e.g. UV-B light phototherapy, PUVA therapy, tanning salon, home-administered UVB), or excessive exposure to the sun
4. Herbal preparations for the treatment of vitiligo [e.g. Rubia cordifolia (manjistha or majith) and Psoralea coryfolia (bakuchi or bavanchi)
5. Oral or injectable corticosteroids
6. Biologic agents
7. Immunosuppressive agents (e.g. e.g. Methotrexate, Azahioprine, cyclosporine, 6-thiouganine, mercaptopurine, mycophenolate mofetil, hydroxyurea, tacrolimus)
8. JAK inhibitors

4.5 Precautions

If a reaction suggesting Subject's condition has worsened to the degree that it is unsafe for the Subject to continue in the study, the Principal Investigator should assess the Subject's condition as soon as possible (i.e., during an Unscheduled Visit) and determine whether treatment should be discontinued. If the Subject is discontinued from the study during an Unscheduled Visit, the visit will be referred to as an Early Discontinuation Visit.

4.6 Subject Disposition and Discontinuation

Investigators are urged to enroll only those eligible Subjects who are likely to complete the entire study and who are willing to comply with the protocol-specified procedures. It is the right and duty of the investigator to interrupt the treatment of any Subject whose health or well-being may be threatened by continuation in this study, or who may be experiencing unmanageable factors that may interfere with the study procedures and/or the interpretation of study results. Such Subjects should be withdrawn from the study rather than continued under a modified regimen.

Subjects will be removed from the study for any of the following reasons:

- If the Subject withdraws his or her consent for any reason;
- If the Subject's condition has worsened to the degree that the Principal Investigator feels it is unsafe for the Subject to continue in the study;
- If the Subject's drug code is unblinded (on a case-by-case basis in consultation with the MM);
- If an adverse event occurs for which the Subject desires to discontinue treatment or the Principal Investigator determines that it is in the Subject's best interest to be discontinued;
- If there is a significant protocol violation;
- If the Subject is lost to follow-up;
- If the Subject becomes pregnant;
- If the Subject becomes a prisoner or become involuntarily incarcerated;
- Any other reason that may affect the outcome of the study or the safety of Subjects
- Termination of the study by the IRB; or
- Termination of the study by the Sponsor.

Additional reasons for Subjects to be removed from the study:

- More than 14 consecutive days of non-compliance to study medication i.e. subjects who have missed all doses for more than 14 consecutive days

Medical Monitor/Sponsor notification is required before removing subjects for any of the reasons noted above.

A significant protocol violation is defined as any Subject or Investigator activity that could have possibly interfered with the therapeutic administration of the treatment or the precise evaluation of

treatment efficacy.

The reasons for a Subject discontinuation will be documented. Data, in addition to the reason for discontinuation and the date of removal, will be documented.

Before a Subject is considered to be lost to follow-up, the Principal Investigator will document all (at least three) attempts to reach the Subject twice by telephone and will send a certified follow-up letter.

In the event that a Subject discontinues from the study at any time due to an adverse event, the reason for discontinuation, the nature of the event and its clinical course must be fully documented. For such a Subject, the Principal Investigator must strive to follow the Subject until the adverse event has resolved, becomes clinically insignificant, is stabilized or the Subject is lost to follow-up. Should a serious adverse event be noted, procedures stated in Section 10.3 must be followed.

Subjects who drop out after randomization will not be replaced.

5. SAFETY AND TOLERABILITY EVALUATIONS

5.1 Medical History

A complete medical history will be obtained for the Subject's current and past medical conditions. Significant medical history should include, but not be limited to, evidence of hypertension, lipid disorders, obesity (BMI >/= 30 as per the Metropolitan Index), heart attack, stroke, congestive heart failure, kidney disease, auto immune disease and gestational diabetes. Significant surgical history should include, but not be limited to, removal of blockage from an artery and gallbladder removal.

5.2 Physical Examination

The investigator, sub-investigator or appropriately delegated designee, (Physician's Assistant, Advanced Registered Nurse Practitioner, and Registered Nurse as per local regulations) will perform a physical examination, prior to the Subject starting study drug and at the end of treatment.

The physical examination will include, at a minimum, examination of the Subject's general appearance, comprehensive skin examination, HEENT (head, eyes, ears, nose and throat), heart, lungs, musculoskeletal system, neurological system, lymph nodes, abdomen and extremities.

Height and weight will be measured without shoes.

At the study visits 1, 2, 6, 10, 11, 12, and 13 (Screening, Baseline, and study weeks 20, 44, 48, 52, and 64) the Subject's body weight will also be measured while the Subject is lightly clothed (e.g., no coat or shoes).

5.3 Vital Signs

Vital signs, including blood pressure, pulse rate*, respiratory rate and oral body temperature, will be documented at every visit. Vital signs will be measured after the Subject has rested in a seated or supine position for at least 5 minutes.

* *Pulse rate will be measured once by counting the number of heart beats over 60 seconds (the pulse rate should not be extrapolated after counting for part of 60 seconds).*

5.4 Pregnancy Test

All female Subjects of childbearing potential will undergo serum beta-hCG at Screening. A urine pregnancy test will be performed during all Visits.

All female Subjects are considered to be of childbearing potential unless they are premenarchal, have been surgically sterilized (by hysterectomy) or have been postmenopausal for at least 1 year. Tubal ligation is not considered equivalent to female sterilization. Women with a history of tubal ligation are still considered females able to become pregnant and must complete a urine pregnancy test. Women of childbearing potential, in addition to having a negative urine pregnancy test, must be willing to use an acceptable form of birth control during the study from the day of the first dose administration to 90 days after the last administration of study drug. For the purpose of this study the following are considered acceptable methods of birth control: oral or injectable contraceptives, contraceptive

patches, [redacted] (contraceptive implant), double barrier methods (e.g. condom and spermicide), IUD, tubal ligation, Essure or abstinence with a 2nd acceptable method of birth control should the Subject become sexually active. A sterile sexual partner is NOT considered an adequate form of birth control. Subjects on hormonal contraception must be stabilized on the same type for at least three months prior to enrollment in the study and must not change the method during the study. Subjects who had used hormonal contraception and stopped must have stopped no less than three months prior to the study.

5.5 Laboratory Assessments

A central laboratory will be used for all assessments unless noted otherwise. Unscheduled laboratory assessments can be performed at discretion of the investigator in response to AEs. The laboratory assessments include:

Thyroid function*: at study visits 1, 7 and 12 (screening and weeks 24 and 52) a blood sample will be collected for free T4 and TSH testing.

***Hematology*:** at all study visits a blood sample will be collected for total and differential WBC count, Absolute Neutrophil count (ANC), Absolute Lymphocyte count (ALC), Platelet count, Hemoglobin, Hematocrit.

Lipid profile: at the study visits 1, 2, 7, and 12 (Screening and study weeks 1, 24, and 52) a blood sample will be collected for LDL, HDL and total cholesterol and Triglycerides testing. The test does not need to be repeated at study visit 2 if the screening assessment (visit 1) was performed within 2 weeks of visit 2.

***Clinical chemistry*:** at all study visits a blood sample will be collected for sodium, potassium, chloride, calcium, magnesium, bicarbonate, phosphate, blood urea nitrogen, random glucose, albumin, total protein, alkaline phosphatase, creatinine, ALT, AST, gamma glutamyltransferase (GGT), total bilirubin, conjugated bilirubin testing.

***Coagulation profile*:** at the study visits 1, 2, 7 and 12 (Screening and study weeks 24, and 52) a blood sample will be collected for PT and INR testing. The test does not need to be repeated at study visit 2 if the screening assessment (visit 1) was performed within 2 weeks of visit 2.

Serology: at Screening visit a blood sample will be collected for: HIV antibodies, HBsAg, and HCV antibodies testing.

Serum pregnancy test: at Screening visit a blood sample will be collected for serum beta-hCG testing.

The following tests will be performed at a clinic site:

Urinalysis dipstick: at the study visits from 1 to 12 (Screening and study weeks 1 to 52) a urine sample will be collected for pH, specific gravity, protein, glucose, ketones, and blood testing. The test does not need to be repeated at study visit 2 if the screening assessment (visit 1) was performed within 2 weeks of visit 2.

Microscopic exam may be performed at the local or central laboratory at the discretion of the investigator if the dipstick is positive (i.e. trace or above).

Urine Pregnancy Test: at all study visits a urine sample will be collected in women of childbearing potential and the results of all pregnancy tests (positive or negative) will be documented.

A positive result should be confirmed by a different brand of UPT. A confirmed positive urine pregnancy test during the treatment periods of the study requires immediate interruption of study treatment and the subject must be discontinued from the study.

** for Hematology, Chemistry, Thyroid function, and Coagulation profile the labs that were abnormal and clinically significant at EOT are needed at safety follow-up visit*

Chest X-ray (posteroanterior view): before Baseline visit a chest X-ray should be evaluated for concurrent medical condition or uncontrolled, clinically significant systemic disease. A chest X-ray and/or it's report is acceptable if performed within the past 6 months and available at a site.

5.6 Concomitant Medications

Concomitant medications, including the use of non-drug treatments/therapies, in addition to the reason for the medication use, will be assessed at baseline and at each subsequent study visit. The start and stop date of concomitant medication use during the study should be provided in the data set in addition to the reason for the medication use.

A record of concomitant medications taken by the Subject is to be obtained using generic name, if known, with the corresponding indication. The medications to be recorded will include prescription and over-the-counter (OTC) medications and dietary supplements. All medications taken on a regular basis, including acetaminophen, should be recorded.

5.7 Adverse Events (AEs)

Any AEs reported after signing Informed Consent should be reported. An adverse event is defined as any untoward medical occurrence (sign, symptom or abnormal laboratory finding) regardless of severity in a Subject or clinical-trial Subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. All adverse events, whether observed by an Investigator or Study Coordinator or reported by the Subject, whether related to study drug or not related to study drug, shall be documented on Subject records, together with details, i.e. date of onset, description of the AE, the duration and intensity of each episode, the action taken, the relationship to the investigational product and the degree of severity, the seriousness, date of resolution, and the outcome.

5.8 Columbia-Suicide Severity Rating Scale (C-SSRS)

Subject will not be eligible to participate in the study if at Screening Subject responded “yes” within the last 12 months to Questions 4 or 5 in the suicidal ideation section, or any positive response in the behavioral section of the Columbia Suicide Severity Rating Scale (C-SSRS). [redacted]

5.9 ECG

Digital ECG devices will be used to record 12-lead ECGs at the Screening visit to confirm the subject’s eligibility criteria as well as at the study visits 4, 7, 9, end of treatment and post treatment follow up (study weeks 12, 24, 36, 52, and 64). To avoid impacting results and quality of data, ECG should be done before other invasive or stressful procedures.

The following ECG parameters will be obtained directly from the computerized 12-lead ECG recordings: rhythm, ventricular rate, P-R interval (the portion of the ECG between the onset of the P wave and the QRS complex), R-R interval, QRS duration and QT. QTcF will be calculated according to the Fridericia formula.

5.10 Treatment Interruption Guidance for AEs

The treatment period should not be extended beyond 52 weeks due to missed doses or treatment interruption periods. Subjects whose condition worsens (e.g. an increase in VASI score from baseline by ≥ 25%, or development of allergic reactions or the development of other potentially serious drug reactions) should be re-evaluated by the Investigator and management reconsidered.

Study drug dosing may be temporarily suspended in the event of:

- Clinically important laboratory abnormalities
- Other inter-current illnesses or major surgery or AE related or unrelated to the study treatment

A decision to discontinue IP and/or to resumption of study treatment after temporary discontinuation due to illness, AE or laboratory abnormality should be discussed with the Medical Monitor. The Investigator may suspend study treatment at any time, without consultation with the medical monitor if the urgency of the situation requires immediate action and if this is determined to be in the subject’s best interest. Medical Monitor should be contacted as soon as possible in any case of IP discontinuation.

The subject shall be discontinued from the study if more than 2 temporary interruptions are needed for these reasons. The maximum allowable duration for each of a temporary discontinuation of the study drug will be 14-day time period.

6 STUDY EVALUATIONS

6.1 Efficacy

Efficacy assessments should be performed by the investigator or a designee who is appropriately trained and experienced in the assessment of vitiligo patients.

Preferably a single qualified Investigator or designee at each clinical site will perform focused area assessments (PGA, VASI, VES,) for each Subject at each visit from the beginning to the end of the Subject's participation to maintain consistency; however, only up to two qualified Investigators or designees may perform evaluations of efficacy for a single Subject, if necessary. **All efforts should be made to have the same evaluator at Baseline (Visit 2) and Week 24 (Visit 7)**.

PGA, assessment should be done (in the listed order) by the investigator before performing other efficacy assessments and after obtaining the subject questionnaires.

Subjects who worsen beyond their scores at baseline will be described in the safety evaluation.

The inter-rater reliability and validity for VASI, , and VES will be performed at Baseline and at EoT by approximately 5 sites with approximately 50 subjects.

6.1.1 Dermatology Life Quality Index (DLQI)[9]

subjects will be asked to complete a questionnaire to measure how much the skin problem has affected subject's life over the past week. :

6.1.3 Vitiligo Impact Patient Scale (VIPs)[10]

subjects will be asked to complete) questionnaire to assess the burden experienced by individuals affected by.

[redacted]

6.1.9 Physician Global Assessment (PGA)[18]

[redacted] the investigator will perform an average assessment of all vitiligo lesions. The static PGA determines vitiligo extend at a single point in time, without taking the baseline disease condition into consideration. [redacted]

6.1.10 Vitiligo Area and Scoring Index (VASI)[11]

At Screening and Baseline, to be eligible for inclusion in the study, Subjects must have a definite clinical diagnosis of vitiligo with VASI score ≥ 4) as an overall assessment of all vitiligo lesions.

[redacted] the investigator will perform vitiligo scoring using VASI. The VASI produces a numeric score that can range from 0 to 100, with higher VASI scores denoting poorer the disease state. [redacted] Approximately 5 sites will be designated to perform VASI at Baseline and EoT by two independent assessors to test reliability and validity of the instrument.

[redacted]

6.1.13 Vitiligo Extent Score (VES)[17]

[redacted] the investigator will assess subject's extent of vitiligo. [redacted]

The VES instrument is based on clinical pictures that mimic the natural distribution of vitiligo [redacted]

7 STUDY VISITS (SEE STUDY VISIT SCHEDULE)

At all visits the efficacy assessments have to be performed in the order per instructions below:

- AE will be evaluated before application of any assessment questionnaire
- the patient-rated questionnaires like DLQI, [redacted], VIPs, [redacted] must be completed prior to the Investigator assessments*

  only at a screening visit the patient rated questionnaires can completed after the investigator assessments
- Physician Global assessment (PGA) for vitiligo, [redacted] must be completed prior to other efficacy assessments (VASI, [redacted] VES)

Note: changes in study visit schedules, missed visits, or subject discontinuations may lead to missing information (e.g., for protocol-specified procedures). It is important to capture specific information in the subject records that explains the basis of the missing data, including the relationship to COVID-19, for missing protocol-specified information (e.g., from missed study visits or study discontinuations due to COVID-19).

7.1 Visit 1: Screening Visit (Week ≥ -4 / Day -28 to -1)

Potential subjects will be screened during a 4-week period prior to randomization. CRO/Sponsor's approval is required on a case-by-case basis for an extension of the Screening Period to obtain all test results and to re-screen a subject. Re-screening is allowed once per subject; all assessments should be repeated using a new screening number. The new informed consent/assent is not required, unless an amended or revised informed consent/assent is introduced during the study.

The following procedures will be performed at Screening:

1. **Written informed consent will be obtained**. Subjects must have provided IRB approved written informed consent. Subjects will be given the approved ICF describing the study and any risks associated with participation. The Subject will be allowed as much time as needed to read and understand the information presented in the consent form. Appropriate study personnel will be available to answer any questions the Subject might have regarding the study or study-related procedures. If the Subject chooses to participate in the study, he or she will be asked to sign and date the consent form and will be provided with a copy for his or her records. The ICF must be signed by the Subject before any protocol assessments can be undertaken. Subjects participating [redacted] the study, or those having skin biopsies taken, will be asked to sign a separate informed consent form in addition to the main study consent.
2. Demographics will be collected, including date of birth, gender, race and ethnicity.
3. A compliance with applicable inclusion and exclusion criteria will be reviewed. (See Sections 4.2, 4.3)
4. After confirming the eligibility, the Subject will be assigned a screening number.
5. A complete medical history will be obtained for the Subject's current and past medical conditions, including a complete list of current and past (within the previous 30 days) medications. Significant medical history should include, but not be limited to, evidence of hypertension, lipid disorders, obesity*, heart attack, stroke, congestive heart failure, kidney disease, and auto immune disease and gestational diabetes. Significant surgical history should include, but not be limited to, removal of blockage from an artery and gallbladder removal. (See Section 5.1)

   * Obesity = BMI ≥30 (as defined by Metropolitan Life Insurance Company Chart)
6. A urine pregnancy test will be conducted for all females of childbearing potential (see Section 5.4)
7. A physical examination will be performed. At a minimum, the physical examination will include the following: height, weight, assessment of general appearance, comprehensive skin

examination, HEENT, heart, lungs, musculoskeletal system, lymph nodes, neurological systems, abdomen, and extremities. (See Section 5.2)

8. Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated or supine position for at least 5 minutes before vital signs are obtained. (See Section 5.3)
9. Chest X-ray (if not done in last 6 months) be performed or scheduled with an external expert (See Section 5.5)
10. A urinalysis dipstick will be performed and evaluated (See Section 5.5)
11. Any AEs occurred after signing Informed Consent should be reported (See Section 5.7)
12. A query for Columbia-Suicide Severity Rating Scale (C-SSRS) will be performed (See Section 5.8)
13. A 12-lead electrocardiogram (ECG) will be performed (See Section 5.9)
14. The occurrence of all AEs will be assessed and documented following the procedures in Sections 5.7, 10.1, and 10.3.

[redacted]

18. Vitiligo Area and Scoring Index (VASI) will be evaluated. To be included in the study, subjects must have vitiligo with VASI score 4 or higher [redacted]

[redacted]

20. Vitiligo Extent Score (VES) will be evaluated. [redacted]
21. Blood samples will be collected for Thyroid function, Hematology, Chemistry, Coagulation profile, Lipid Profile, Serology, and Serum pregnancy test for women of childbearing potential (See Section 5.5) Blood sampling should be done after other applicable criteria for subject's eligibility have been confirmed.
22. The following will be dispensed during Screening visit:
    - A diary card to record health changes and concomitant medication
23. Visit 2 (Study Day 1) will be scheduled and the Subject will be instructed to bring the Subject diary with him or her to this visit. [redacted]

7.2 Visit 2: Baseline Visit (Week 1 / Day 1)

[redacted]

<u>If the Screening assessment was completed more than 2 weeks prior:</u>

1. A physical examination will be performed. At a minimum, the physical examination will include the following: height, weight, assessment of general appearance, comprehensive skin examination, HEENT, heart, lungs, musculoskeletal system, lymph nodes, neurological systems, abdomen, and extremities. (See Section 5.2)
2. A urinalysis dipstick will be performed and evaluated (See Section 5.5)
3. A blood sample(s) will be collected for Coagulation and Lipid Profile (See Section 5.5)

The following procedures will be performed at Baseline:

4. Compliance with the inclusion and exclusion criteria, including results of laboratory evaluations and chest X-ray will be reviewed.
5. A medical history will be updated with any changes of the Subject's health since the previous study visit. (See Section 5.1)
6. A urine pregnancy test will be conducted for all females of childbearing potential (see Section 5.4)
7. After confirming the eligibility, the Subject will be randomized and assigned a number using Interactive Response Technology (IRT). (see Section 8.5)
8. The use of concomitant medications since the previous study visit will be documented and assessed. (See Section 5.6)
9. The Subject's diary provided at the previous visit will be collected and reviewed.
10. Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated or supine position for at least 5 minutes before vital signs are obtained. (See Section 5.3)
11. A blood sample(s) will be collected for Hematology, Chemistry, Coagulation profile and Lipid Profile (Coagulation profile and Lipid Profile need not be repeated at baseline if these assessments for screening visit are performed within 2 weeks prior to the Visit 2) (See Section 5.5)

[redacted]

15. Subjects will be instructed to take the study drug with approximately 240 mL (8 oz.) of water. Tablets should be swallowed intact and not chewed or crushed. (See Section 8.6)
16. The occurrence of all AEs will be assessed and documented following the procedures in Sections 5.7, 10.1, and 10.3.
17. A query for Columbia-Suicide Severity Rating Scale (C-SSRS) will be performed (See Section 5.8)

[redacted]

19. Subject Reported Assessments will be collected for:
    - Dermatology Life Quality Index (DLQI) [redacted]
    - Vitiligo Impact Patient Scale (VIPs) [redacted]
20. Focused Area Assessments will be performed for:
    - Physician Global Assessment (PGA) [redacted]
    - [redacted]
    - Vitiligo Area and Scoring Index (VASI) will be evaluated. To be included in the study, subjects must have vitiligo with VASI score 4 or higher [redacted]

      At designated sites VASI will be performed by two independent assessors to test reliability and validity

- [redacted]
- [redacted]
- Vitiligo Extent Score (VES) will be evaluated. [redacted]

21. The following will be dispensed:
    - The IP kit assigned for Visit 2 by IRT
    - A diary card with instructions and to record health changes and concomitant medication
22. Visit 3 (Study Day 29 ± 3 Days) will be scheduled and the Subject will be instructed to bring the Study Product (used, unused, and partially used) and Subject diary with him or her to this visit.

7.3 Visit 3: Interim Visit (Week 4 / Day 29 ± 3 Days)

The following procedures will be performed at Visit 3:

1. Results of laboratory evaluations will be reviewed
2. The Subject's diary provided at the previous visit will be reviewed.
3. A urine pregnancy test will be conducted for all females of childbearing potential (see Section 5.4)
4. The use of concomitant medications since the previous study visit will be documented and assessed. (See Section 5.6)
5. Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated or supine position for at least 5 minutes before vital signs are obtained. (See Section 5.3)
6. A urinalysis dipstick will be performed and evaluated at a site (See Section 5.5)
7. A blood sample will be collected for Hematology and Chemistry (See Section 5.5)
8. The occurrence of all AEs will be assessed and documented following the procedures in Sections 5.7, 10.1, and 10.3.
9. Visit 4 (Study Day 85 ± 3 Day) will be scheduled and the Subject will be instructed to bring the Study Product (used, unused, and partially used) and Subject diary with him or her to this visit. [redacted]
10. A phone call will be scheduled at the study week 8 to collect information on the study drug use, health changes and concomitant medication

7.4 Visit 4: Interim Visit (Week 12 / Day 85 ± 3 Days)

[redacted]

The following procedures will be performed at Visit 4:

1. Results of laboratory evaluations will be reviewed
2. A urine pregnancy test will be conducted for all females of childbearing potential (see Section 5.4)

[redacted]

3. The use of concomitant medications since the previous study visit will be documented and assessed. (See Section 5.6)
4. The Subject's diary provided at the previous visit will be collected and reviewed.
5. The returned study drugs will be counted
6. Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated or supine position for at least 5 minutes before vital signs are obtained. (See Section 5.3)
7. A urinalysis dipstick will be performed and evaluated (See Section 5.5)
8. A blood sample(s) will be collected for Hematology and Chemistry (See Section 5.5)

[redacted]

10. Subjects will be instructed to take the study drug with approximately 240 mL (8 oz.) of water. Tablets should be swallowed intact and not chewed or crushed. (See Section 8.6)
11. The occurrence of all AEs will be assessed and documented following the procedures in Sections 5.7, 10.1, and 10.3.
12. A 12-lead electrocardiogram (ECG) will be performed (See Section 5.9)

[redacted]

14. Focused Area Assessments will be performed for:
    - [redacted]
    - Vitiligo Area and Scoring Index (VASI) will be evaluated. To be included in the study, subjects must have vitiligo with VASI score 4 or higher [redacted]
    - [redacted]
    - [redacted]
    - [redacted]
15. The following will be dispensed:
    - The IP kit assigned for Visit 4 by IRT
    - A diary card with instructions and to record health changes and concomitant medication
16. Visit 5 (Study Day 113 ± 3 Days) will be scheduled and the Subject will be instructed to the Subject diary with him or her to this visit.

7.5 Visit 5: Interim Visit (Week 16 / Day 113 ± 3 Days)

The following procedures will be performed at Visit 5:

1. Results of laboratory evaluations will be reviewed
2. The Subject's diary provided at the previous visit will be reviewed.
3. A urine pregnancy test will be conducted for all females of childbearing potential (see Section 5.4)

4. The use of concomitant medications since the previous study visit will be documented and assessed. (See Section 5.6)
5. Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated or supine position for at least 5 minutes before vital signs are obtained. (See Section 5.3)
6. A urinalysis dipstick will be performed and evaluated (See Section 5.5)
7. A blood sample will be collected for Hematology and Chemistry (See Section 5.5)
8. The occurrence of all AEs will be assessed and documented following the procedures in Sections 5.7, 10.1, and 10.3.
9. Visit 6 (Study Day 141 ± 3 Day) will be scheduled and the Subject will be instructed to bring the Subject diary with him or her to this visit.

7.6 Visit 6: Interim Visit (Week 20 / Day 141 ± 3 Days)

The following procedures will be performed at Visit 6:

1. Results of laboratory evaluations will be reviewed
2. The Subject's diary provided at the previous visit will be reviewed.
3. A urine pregnancy test will be conducted for all females of childbearing potential (see Section 5.4)
4. The use of concomitant medications since the previous study visit will be documented and assessed. (See Section 5.6)
5. A physical examination will be performed. At a minimum, the physical examination will include the following: weight, assessment of general appearance, comprehensive skin examination, HEENT, heart, lungs, musculoskeletal system, lymph nodes, neurological systems, abdomen, and extremities. (See Section 5.2)
6. Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated or supine position for at least 5 minutes before vital signs are obtained. (See Section 5.3)
7. A urinalysis dipstick will be performed and evaluated at a site (See Section 5.5)
8. A blood sample will be collected for Hematology and Chemistry (See Section 5.5)
9. The occurrence of all AEs will be assessed and documented following the procedures in Sections 5.7, 10.1, and 10.3.
10. Visit 7 (Study Day 169 ± 3 Day) will be scheduled and the Subject will be instructed to bring the Study Product (used, unused, and partially used) and Subject diary with him or her to this visit. [redacted]

7.7 Visit 7: Interim Visit (Week 24 / Day 169 ± 3 Days)

[redacted]

The following procedures will be performed at Visit 7:

1. Results of laboratory evaluations will be reviewed
2. A urine pregnancy test will be conducted for all females of childbearing potential (see Section 5.4)

3. The use of concomitant medications since the previous study visit will be documented and assessed. (See Section 5.6)
4. The Subject's diary provided at the previous visit will be collected and reviewed.
5. The returned study drugs will be counted
6. Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated or supine position for at least 5 minutes before vital signs are obtained. (See Section 5.3)
7. A urinalysis dipstick will be performed and evaluated (See Section 5.5)
8. A blood sample(s) will be collected for Thyroid function, Hematology, Chemistry, Coagulation profile, and Lipid Profile (See Section 5.5)

[redacted]

12. Subjects will be instructed to take the study drug with approximately 240 mL (8 oz.) of water. Tablets should be swallowed intact and not chewed or crushed. (See Section 8.6)
13. The occurrence of all AEs will be assessed and documented following the procedures in Sections 5.7, 10.1, and 10.3.
14. A 12-lead electrocardiogram (ECG) will be performed (See Section 5.9)

[redacted]

16. Subject Reported Assessments will be collected for:
    - [redacted]
    - Vitiligo Impact Patient Scale (VIPs) ([redacted]
    - [redacted]
17. Focused Area Assessments will be performed for:
    - [redacted]
    - [redacted]
    - [redacted]
    - Vitiligo Area and Scoring Index (VASI) will be evaluated. To be included in the study, subjects must have vitiligo with VASI score 4 or higher [redacted]
    - [redacted]
    - [redacted]
    - Vitiligo Extent Score (VES) will be evaluated. ([redacted]
18. The following will be dispensed:
    - The IP kit assigned for Visit 7 by IRT
    - A diary card with instructions and to record health changes and concomitant medication

[redacted]

19. Visit 8 (Study Day 197 ± 3 Days) will be scheduled and the Subject will be instructed to bring the Subject diary with him or her to this visit.

7.8 Visit 8: Interim Visit (Week 28 / Day 197 ± 3 Days)

The following procedures will be performed at Visit 8:

1. Results of laboratory evaluations will be reviewed
2. The Subject's diary provided at the previous visit will be reviewed.
3. A urine pregnancy test will be conducted for all females of childbearing potential (see Section 5.4)
4. The use of concomitant medications since the previous study visit will be documented and assessed. (See Section 5.6)
5. Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated or supine position for at least 5 minutes before vital signs are obtained. (See Section 5.3)
6. A urinalysis dipstick will be performed and evaluated (See Section 5.5)
7. A blood sample will be collected for Hematology and Chemistry (See Section 5.5)
8. The occurrence of all AEs will be assessed and documented following the procedures in Sections 5.7, 10.1, and 10.3.
9. Visit 9 (Study Day 253 ± 3 Day) will be scheduled and the Subject will be instructed to bring the Study Product (used, unused, and partially used) and Subject diary with him or her to this visit. [redacted]
10. A phone call will be scheduled at the study week 32 to collect information on the study drug use, health changes and concomitant medication

7.9 Visit 9: Interim Visit (Week 36 / Day 253 ± 3 Days)

[redacted]

The following procedures will be performed at Visit 9:

1. Results of laboratory evaluations will be reviewed
2. A urine pregnancy test will be conducted for all females of childbearing potential (see Section 5.4)
3. The use of concomitant medications since the previous study visit will be documented and assessed. (See Section 5.6)
4. The Subject's diary provided at the previous visit will be collected and reviewed.
5. The returned study drugs will be counted
6. Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated or supine position for at least 5 minutes before vital signs are obtained. (See Section 5.3)
7. A urinalysis dipstick will be performed and evaluated (See Section 5.5)
8. A blood sample(s) will be collected for Hematology and Chemistry (See Section 5.5)

[redacted]

10. Subjects will be instructed to take the study drug with approximately 240 mL (8 oz.) of water. Tablets should be swallowed intact and not chewed or crushed. (See Section 8.6)

[redacted]

11. The occurrence of all AEs will be assessed and documented following the procedures in Sections 5.7, 10.1, and 10.3.
12. A 12-lead electrocardiogram (ECG) will be performed (See Section 5.9)

[redacted]

14. Focused Area Assessments will be performed for:

[redacted]

- Vitiligo Area and Scoring Index (VASI) will be evaluated. To be included in the study, subjects must have vitiligo with VASI score 4 or higher [redacted]

[redacted]

15. The following will be dispensed:
    - The IP kit assigned for Visit 9 by IRT
    - A diary card with instructions and to record health changes and concomitant medication
16. Visit 10 (Study Day 309 ± 3 Days) will be scheduled and the Subject will be instructed to bring the Subject diary with him or her to this visit.
17. A phone call will be scheduled at the study week 40 to collect information on the study drug use, health changes and concomitant medication

7.10 Visit 10: Interim Visit (Week 44 / Day 309 ± 3 Days)

The following procedures will be performed at Visit 10:

1. Results of laboratory evaluations will be reviewed
2. The Subject's diary provided at the previous visit will be reviewed.
3. A urine pregnancy test will be conducted for all females of childbearing potential (see Section 5.4)
4. The use of concomitant medications since the previous study visit will be documented and assessed. (See Section 5.6)
5. A physical examination will be performed. At a minimum, the physical examination will include the following: weight, assessment of general appearance, comprehensive skin examination, HEENT, heart, lungs, musculoskeletal system, lymph nodes, neurological systems, abdomen, and extremities. (See Section 5.2)
6. Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated or supine position for at least 5 minutes before vital signs are obtained. (See Section 5.3)

7. A urinalysis dipstick will be performed and evaluated (See Section 5.5)
8. A blood sample will be collected for Hematology and Chemistry (See Section 5.5)
9. The occurrence of all AEs will be assessed and documented following the procedures in Sections 5.7, 10.1, and 10.3.
10. Visit 11 (Study Day 337 ± 3 Day) will be scheduled and the Subject will be instructed to bring the Study Product (used, unused, and partially used) and Subject diary with him or her to this visit.

7.11 Visit 11: Interim Visit (Week 48 / Day 337 ± 3 Days)

The following procedures will be performed at Visit 11:

1. Results of laboratory evaluations will be reviewed
2. The Subject's diary provided at the previous visit will be collected and reviewed.
3. The returned study drugs will be counted
4. A urine pregnancy test will be conducted for all females of childbearing potential (see Section 5.4)
5. The use of concomitant medications since the previous study visit will be documented and assessed. (See Section 5.6)
6. A physical examination will be performed. At a minimum, the physical examination will include the following: weight, assessment of general appearance, comprehensive skin examination, HEENT, heart, lungs, musculoskeletal system, lymph nodes, neurological systems, abdomen, and extremities. (See Section 5.2)
7. Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated or supine position for at least 5 minutes before vital signs are obtained. (See Section 5.3)
8. A urinalysis dipstick will be performed and evaluated (See Section 5.5)
9. A blood sample will be collected for Hematology and Chemistry (See Section 5.5)
10. The occurrence of all AEs will be assessed and documented following the procedures in Sections 5.7, 10.1, and 10.3.
11. The following will be dispensed:
    - The IP kit assigned for Visit 11 by IRT
    - A diary card with instructions and to record health changes and concomitant medication
12. Visit 12 (Study Day 365 ± 3 Day) will be scheduled and the Subject will be instructed to bring the Study Product (used, unused, and partially used) and Subject diary with him or her to this visit. [redacted]

7.12 Visit 12: End of Treatment Visit (Week 52 / Day 365 ± 3 Days)

[redacted]

The following procedures will be performed at Visit 12:

1. Results of laboratory evaluations will be reviewed
2. A urine pregnancy test will be conducted for all females of childbearing potential (see Section 5.4)
3. The use of concomitant medications since the previous study visit will be documented and assessed. (See Section 5.6)

4. The Subject's diary provided at the previous visit will be collected and reviewed.
5. The returned study drugs will be counted
6. A physical examination will be performed. At a minimum, the physical examination will include the following: weight, assessment of general appearance, comprehensive skin examination, HEENT, heart, lungs, musculoskeletal system, lymph nodes, neurological systems, abdomen, and extremities. (See Section 5.2)
7. Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated or supine position for at least 5 minutes before vital signs are obtained. (See Section 5.3)
8. A urinalysis dipstick will be performed and evaluated (See Section 5.5)
9. A blood sample(s) will be collected for Thyroid function, Hematology, Chemistry, Coagulation profile, and Lipid Profile (See Section 5.5)

[redacted]

12. Subjects will be instructed to take the study drug with approximately 240 mL (8 oz.) of water. Tablets should be swallowed intact and not chewed or crushed. (See Section 8.6)
13. The occurrence of all AEs will be assessed and documented following the procedures in Sections 5.7, 10.1, and 10.3.
14. A 12-lead electrocardiogram (ECG) will be performed (See Section 5.9)

[redacted]

16. Subject Reported Assessments will be collected for:
    - Dermatology Life Quality Index (DLQI) [redacted]
17. Focused Area Assessments will be performed for:
    - Physician Global Assessment (PGA) [redacted] in the study, subjects must have vitiligo with VASI score 4 or higher [redacted]

      At designated sites VASI will be performed by two independent assessors to test reliability and validity
    - [redacted]

[redacted]

[redacted]

19. The following will be dispensed:
    - A diary card with instructions and to record health changes and concomitant medication
20. Follow-Up Visit 13 (Study Day 449 ± 3 Days) will be scheduled and the Subject will be instructed to bring the Subject diary with him or her to this visit.

7.13 Follow-up Visit/EoS (Week 64 / Day 449 ± 3 Days) or within 2 weeks after last dose for discontinued subjects

The following procedures will be performed at Follow-Up Visit 13:

1. Results of laboratory evaluations will be reviewed
2. A urine pregnancy test will be conducted for all females of childbearing potential (see Section 5.4)
3. The use of concomitant medications since the previous study visit will be documented and assessed. (See Section 5.6)
4. The Subject's diary provided at the previous visit will be collected and reviewed.
5. A physical examination will be performed. At a minimum, the physical examination will include the following: weight, assessment of general appearance, comprehensive skin examination, HEENT, heart, lungs, musculoskeletal system, lymph nodes, neurological systems, abdomen, and extremities. (See Section 5.2)
6. Vital signs (blood pressure, pulse, respiratory rate and oral body temperature) will be documented. Subjects must remain in a seated or supine position for at least 5 minutes before vital signs are obtained. (See Section 5.3)
7. A blood sample(s) will be collected, if needed, for Thyroid function, Hematology, Chemistry, Coagulation profile, and Lipid Profile that were abnormal and clinically significant at Visit 12 (EOT) (See Section 5.5)

[redacted]

)

10. The occurrence of all AEs will be assessed and documented following the procedures in Sections 5.7, 10.1, and 10.3.
11. A 12-lead electrocardiogram (ECG) will be performed (See Section 5.9)

[redacted]

14. Focused Area Assessments will be performed for:
    - [redacted]
    - Vitiligo Area and Scoring Index (VASI) will be evaluated. To be included in the study, subjects must have vitiligo with VASI score 4 or higher [redacted]
    - [redacted]

[redacted]

[redacted]

7.14 Phone call on use of study drug (Weeks 8, 32, and 40)

Phone calls will be scheduled at the study weeks 8, 32, and 40 to collect information on the study drug use, health changes and concomitant medication

7.15 Unscheduled Visits and Early Discontinuation Visit

An Unscheduled Visit is allowed at any time, for any reason, if in the Principal Investigator's opinion it is warranted. If the Unscheduled Visit is due to an AE, the Principal Investigator will determine whether additional visits are needed.

If a Subject is discontinued from the study during an Unscheduled Visit, the Unscheduled Visit will be referred to as an Early Discontinuation Visit:

1. A urine pregnancy test will be conducted for all females of childbearing potential (see Section 5.4)
2. The use of concomitant medications since the previous study visit will be documented and assessed. (See Section 5.6)
3. The occurrence of all AEs will be assessed and documented following the procedures in Sections 5.7, 10.1, and 10.3

Additional assessments may be performed per the Investigator's decision.

For all the subjects who discontinue the study prior to Visit 7 all efforts should be made to conduct a visit at, or close to week 24 to collect focused area assessments. Regardless of the reason, Subjects discontinued from IP prior to the end of study will be required to complete the End of Study (EoS) assessment within 2 weeks after the last dose.

If the Subject's condition has worsened to the degree that it is unsafe for the Subject to continue in the study, the Subject may be discontinued from the study as treatment failure and a standard of care treatment may be advised at the Principal Investigator's discretion.

8 INVESTIGATIONAL PRODUCT

8.1 Description

All study medications will be dispensed by and returned to a qualified dispenser designated by the Principal Investigator. The investigational product will be dispensed only from the institution(s) approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

The Investigational Product will be supplied by the Sponsor. The following treatments will be self-administered or administered by the Subject's caregiver during this study.

Investigational Products:	AS012 Tablets [redacted]
Control:	Placebo of AS012 product

8.2 Storage Conditions

All study products should be stored in a limited access area, between 15°C and 30°C (59°F and 86°F), protect from bright light.

8.3 Packaging and Labeling

In order to maintain the study blind the randomization schedule will be generated by a third party. Randomization will be performed according to a computer-generated randomization scheme. Only

one Subject number will be assigned to each Subject. The Subject will maintain the same number throughout the study. The Investigational Product will be provided in identically labeled and packaged such that neither the Subject nor any Investigator can identify the treatment.

Each container will be labeled with a two-part, double blind label and will display the following text: "content statement, protocol number, subject number, instructions for use and storage, Sponsor's name, an investigational use statement and warnings: "Keep out of reach of children". Part 2 of the label will contain a **sealed copy of the randomization scheme** (as a scratch off portion of the product label). This label should be detached from the container **prior to dispensing to the Subject and retained at the study site**, to be opened in case of medical emergency only. Where possible, the Medical Monitor should be contacted before breaking the blind for any Subject. The Sponsor must be notified in the event the blind is broken.

To maintain the study blind the labels for IP boxes and bottles will include the same content description "Placebo and/or Active [redacted] AS012 Tablets".

8.4 Treatment Assignment

The subject number will correspond to a computer-generated randomization schedule assigning that number to one of the study treatment groups in Part I. The randomization scheme will be generated that the Placebo, [redacted] or [redacted] AS012 are assigned in a 3:3:1:3:1 or in 1:1:3:1:1 ratio. The randomization ratio will be changed after enrolling of approximately 55% of subjects.

In Part II (week 24 to week 52) subjects initially randomized to placebo will be re-randomized to [redacted] AS012 in 1:1 ratio. Subjects originally randomized to AS012 doses will remain on their assigned dosing regimen until the end of Part II (week 52). At the study visits 2, 4, 7, 9, and 11 the IP kit number will be assigned to each subject using Interactive Response Technology (IRT).

8.5 Randomization

At visit 2 the subject will be randomized to one of five treatment groups and the subject number will be assigned by an Interactive Response Technology (IRT). At visit 7 the active treatment will be reassigned for the Placebo group by IRT. Randomization and re-randomization will be stratified by stability of disease (stable vs. non-stable) [redacted] IRT using global data across all sites.

At visits 2, 4, 7, 9, and 11 the IP kit number corresponding to the subject's treatment group will be assigned by IRT using kit numbers available at a site.

8.6 Administration of Investigational Product

Individual doses will be provided in identically packaged bottles. Bottles will be dispensed at study visits 2, 4, 7, 9, and 11 (Baseline and study weeks 12, 24, 36, and 48.

Each Subject will also receive written study instructions, which detail the proper administration method of the Investigational Product and general study instructions. At scheduled visits 2, 4, 7, 9, and 12 (Baseline and study weeks 12, 24, 36, and 52) the study product will be administered under a supervision of the study site personnel.

[redacted]

Tablets should be swallowed intact and not chewed or crushed. The doses should be taken with approximately 240 mL (8 oz.) of water between meals, approximately one hour after and before meals.

Investigational Product will be used for 365 consecutive days.

Subjects will be required to use diaries to document the date and time of doses, any missed doses and the occurrence of all adverse events.

At each visit during the study, the Investigator or designee should review proper use of the Investigational Product.

In case of vomiting within 30 minutes of taking a dose, the dose shall be repeated. The dose shall not be repeated if vomiting occurs more than 30 minutes after ingestion. If vomiting recurs no new doses should be taken and the subject should contact the site for instructions.

Missed doses:

The dose will be skipped if the subjects realizes more than 2 hours after the scheduled time-point. All missed doses should be entered by the subject in the patient diary.

More than 14 consecutive days of non-compliance to study medication (i.e. subjects who have missed all doses for more than 14 consecutive days) will result in subject's discontinuation from the study.

8.7 Assessment of Compliance

Compliance with scheduled use of Investigational Product will be determined from the Subject's diary. Subjects will be instructed to bring their daily diary and used and unused study drug containers at all scheduled visits or Early Discontinuation Visit to allow for tablet count and compliance checks. Subjects will also be asked to record in a daily diary the date and time at which they took the study drug. In addition, Subjects will be instructed to document all AEs on the diary.

If the subject does not return the Diary, Subject-reported dosing compliance will be recorded in the source notes and will be used to derive compliance between those visits.

For scheduled visits greater than 4 weeks apart, subjects will be called (at w8, w32, w40) and asked about compliance with study drug.

8.8 Investigational Product Accountability

It is the responsibility of the Principal Investigator to ensure that the current disposition of the Investigational Product is maintained at each study site where Investigational Product is inventoried and dispensed. When a drug shipment is received at a study site, the Principal Investigator or the Principal Investigator's Designee must inventory the drug and sign the receipt form provided with the shipment. The receipt form should be emailed as per instructions provided on the receipt. A copy of the receipt should remain at the site.

The Investigator will not supply study test articles to any person not enrolled in this study, or to any physician or scientist except those named as sub-investigators.

A Drug Accountability Log will assist study site staff in maintaining inventory records of study drug.

Subjects must return used, partially used or unused Investigational Product so that any remaining drug supplies can be accounted for and noted in the Drug Accountability Log.

8.9 Return of Clinical Supplies

All used and unused containers of Investigational Product may be returned to the Drug Shipping Facility for destruction or be destructed at the site after study close-out and final drug accountability is reconciled.

9. STATISTICAL METHODS

9.1 Scientific and Statistical Considerations of the Study Design

This study to assess the efficacy and safety of AS012 in the treatments of non-segmental vitiligo is designed based on recommendations provided by the FDA in PIND 147209 Guidance Meeting (03/05/2020, Reference ID 4571020) regarding the scope and design of studies for this new product.

9.1.1 Rationale for Dose Selection

This will be the first study conducted with AS012 in the setting of a well-controlled clinical trial, assessing a range of doses. Previously conducted pilot study was a non-comparative trial in a small number of subjects [redacted]. The proposed doses are considered safe and appropriate based on the pre-clinical toxicology studies conducted to date. In the genotoxicity studies, AS012 showed no mutagenic potential.

9.1.2 Rationale for the Use of Comparator

A placebo control arm is included to demonstrate that the investigational products are active and as a parameter that the study is sufficiently sensitive to detect differences between products. However, to ensure that patients in the placebo arm receive treatment, they will be re-randomized at Week 24 to receive either [redacted]

9.2 Sample Size Rationale

The study will randomize approximately 320 subjects into 5 treatment arms (n=approximately 64 subjects per arm) in a 1:1:1:1:1 ratio. The sample size assumes a drop-out rate of about 20%, with 52 evaluable subjects per treatment arm at the time of analysis. The study is powered at 85%, and assumes a two-sample Z-test with equal variances, two-sided alpha (α) of 0.05, a Baseline VASI mean of 15.7 and standard deviation of 8.9 (Hamzavi et al, 2004) and an improvement at Week 24 of 35% (Δ 5.50) for AS012 versus an improvement for placebo of 10% (Δ 1.56), for a mean treatment difference of 3.94. Since the correlation between Baseline and Week 24 VASI scores is expected to be >0.5, the standard deviation of the difference is conservatively estimated at 70% of the Baseline SD, or 6.4. Randomization will be stratified by stability of disease (stable vs. non-stable) [redacted] With a total of six possible stratification levels, 52 evaluable subjects per treatment arm ensures at least 8 subjects per stratification level.

9.3 Blinding and Unblinding Procedures

In order to maintain the study blind the randomization schedule will be generated by a third party. Randomization will be performed according to a computer-generated randomization scheme. The placebo and tablets for all strengths of AS012 look alike which ensures blinding. The Investigational Product will be provided in identically labeled and packaged such that neither the Subject nor any Investigator can identify the treatment. The Drug Labeling, Packaging and Shipping facility will hold the randomization code throughout the conduct of the study in order to minimize bias. A sealed copy of the randomization scheme (as a scratch off portion of the product label attached to the drug accountability page) will be retained at the study site. In the event of an emergency, the Subject-specific treatment may be identified; however, every effort should be made to maintain the blind. Where possible, the Medical Monitor should be contacted before breaking the blind for any subject. The Sponsor must be notified in the event the blind is broken.

The treatment assignments will remain blinded until the final database is closed.

If Suspected Unexpected Serious Adverse Reactions (SUSAR) requires unblinding by a Regulatory Agency, a designated member of the Sponsor's safety team will be un-blinded on case-by-case basis by receiving the randomization directly from the study unblinded statistical consultant.

The bioanalytical team will analyse the samples collected from all subjects, including samples from subjects assigned to placebo to ease the selection of samples and avoid releasing the randomization code.

9.4 Significance Level

Tests for superiority over placebo for the primary and the key secondary end-point will be conducted via a straight step-down approach in the order of highest to lowest dose to preserve the overall Type I error rate of 0.05.

9.5 Datasets to be Analyzed

Three analysis populations will be used in the analysis of the clinical data:

1. A Safety Population subject is any individual who was randomized into the study and dispensed study drug.
2. The ITT Population includes all randomized subjects regardless of whether they received the investigational product.

[redacted]

Additionally, the Screen Fail subjects will be summarized, including reasons for removal.

9.6 Demographics and Baseline/Randomization Characteristics

Demographic and baseline/randomization characteristics will be summarized descriptively by treatment group for the ITT, [redacted] and Safety Populations.

9.7 Safety Assessment

Safety Assessments will include vital signs, physical examination, adverse events (AEs), laboratory tests, ECG monitoring, chest X-ray (if not done in last 6 months) and Columbia-Suicide Severity Rating Scale (C-SSRS).

The safety of AS012 will be evaluated by:

- Incidence, seriousness and severity of all adverse events
- Shifts from baseline in hematology and laboratory tests
- Change from baseline in ECG parameters; Frequencies and percentages of ECG findings

The extent of exposure will be summarized using descriptive statistics. No inferential analyses are planned.

Incidence of all adverse events reported during the study will be summarized using the Medical Dictionary For Regulatory Activities (MedDRA) dictionary by System Organ Class and Preferred Term, by treatment group, severity, and relationship to study drug.

An AE is considered treatment emergent if it was not present prior to the first dose of treatment or, if it was present, it worsened in severity or treatment attribution.

Safety analyses will be performed on the Safety Population. All safety data will be listed by treatment and subject in data listings. AEs will also be summarized by actual dose at time of onset of the AE to account for possible dose reductions over the course of the study.

9.8 Efficacy Assessment

Primary endpoints:

- Mean change, from baseline, in VASI score at Week 24

Key Secondary endpoint:

- Mean change, from baseline, in VES at Week 24.

[redacted]

- Mean change, from baseline, in VIPs at Week 24

Other Secondary endpoints:

[redacted]

[redacted]

- [redacted]
- Proportion of subjects achieving a PGA score of "no involvement" (score 0) or "limited extent" (score 1) with at least 2-point reduction from baseline, at [redacted] Week 52.
- Mean change, from baseline, in DLQI at [redacted] Week 52.
- Incidence and severity of Adverse Event (AE)

[redacted]

Efficacy Analysis

The primary efficacy endpoint will be evaluated using the Intent-to-Treat (ITT) Population. The primary endpoint method of analysis will use an Analysis of Covariance (ANCOVA) model to compare change from baseline in VASI score results between treatment arms at Week 24. The ANCOVA model will include fixed effects for treatment, stability of disease (stable vs. non-stable), [redacted] baseline VASI score as a covariate. Point estimates and 95% confidence intervals will be obtained for the difference between each active dose versus placebo.

Missing VASI data at Week 24 will be addressed in the model using multiple imputation methods.

Secondary efficacy variables will be analyzed similarly, however without using multiple imputation methods.

Sensitivity Analyses

Sensitivity analyses will be included to investigate the impact of missingness, and will include a completer analysis without imputation, as well as imputation based on placebo scores. Type I error (alpha, α) will be preserved in the primary efficacy analysis by use of a closed test step-down approach. Beginning with the highest dose, pairwise comparisons to placebo will be made until a non-significant result at the alpha (α) 0.05 level is reached, at which time testing will stop.

Interim Analysis (IA)

No formal Interim Analysis will be performed for this study.

Part I analysis will include all safety and efficacy assessments conducted at week 24. Analysis outputs will be generated when the last subject has completed 24 weeks of study participation, and may include results for all available visits/data. After Part I database lock, subject-level unblinded information will be confined to a designated unblinded study team. A separate document/SAP will provide further details related to unblinding of personnel. A designated list of blinded and unblinded study personnel shall be maintained. Part I analysis subject-level data will not be provided to the site staff and the blinded study team.

An additional unblinded analysis could be undertaken at a subsequent time (e.g. after last patient completed week 36/52 visit) by the unblinded study team to assess the efficacy if required based on the sponsor's discretion. If such an analysis is planned to be undertaken the details would be discussed in SAP.

Final Analysis

The final study database will be locked following last patient last visit at Week 64, once all subject data have been cleaned and all coding of terms (AE, Concomitant Medications, Medical History) has been finalized. Investigational sites, subjects, and study team members directly involved in study activities will remain blinded to study treatment assignments until the database lock. The unblinded subject-level data will be provided to the PI at the end of the study.

9.9 Concomitant Medication

The start and stop date of concomitant medication use during the study will be provided in the data listings in addition to the reason for the medication use.

9.10 Summary of Subjects who terminate prematurely

Reasons for premature termination will be summarized by treatment group.

[redacted]

[redacted]

10. ADVERSE EVENTS

10.1 Reporting of Adverse Events

Any untoward medical occurrence in a Subject or clinical-trial Subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Any adverse event associated with the use of a drug in humans, whether or not considered product-related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action. Reporting an adverse event does not necessarily reflect a conclusion that the product caused or contributed to the adverse event.

All adverse events, whether observed by an Investigator or Study Coordinator or reported by the Subject, whether related to study drug or not related to study drug, shall be documented in the Subject records, together with details, i.e., date of onset, description of the AE, the duration and intensity of each episode, the action taken, the relationship to the Investigational Product and the degree of severity, the seriousness, date of resolution, and the outcome.

In the completed and on-going studies for AS012, based on the safety data review, no safety signals were noted till date.

The Principal Investigator must strive to follow the Subject until the adverse event has resolved, becomes clinically insignificant, is stabilized or the Subject is lost to follow-up. The Principal Investigator must immediately report to the Contract Research Organization, by telephone and follow-up in writing, all study drug discontinuations due to adverse events.

Assessment of Severity

The intensity or severity of an adverse event (AE) is characterized as:

- Mild: an AE that is easily tolerated
- Moderate: an AE sufficiently discomforting to interfere with daily activity
- Severe: an AE that prevents normal daily activities

Relationship to Study Medication

The relationship is characterized as:

- Not Related: This applies to any AE that is clearly not related to use of the study drug.
- Possible: This means the association of the AE with the study drug is unknown; however, a relationship between drug and event cannot be ruled out.
- Probable: There is a reasonable temporal relationship between the use of the study drug

[redacted]

and the AE. Based upon the Principal Investigator's clinical experience, the association of the event with the study drug seems likely.

- Definite: The AE occurs following the application of the study drug and it cannot be reasonably explained by any known characteristics of the Subject's clinical state, environmental or toxic factors or other modes of therapy administered to the Subject. It disappears or decreases upon discontinuation of the study drug and reappears on a re-challenge of the investigational product.

10.2 Pregnancy

Female Subjects of childbearing potential must have been using and must agree to continue to use accepted methods of birth control, throughout the study. All female Subjects are considered to be of childbearing potential unless they are premenarchal, have been surgically sterilized or have been postmenopausal for at least 1 year. Tubal ligation is not considered equivalent to female sterilization. Women with a history of tubal ligation are still considered females able to become pregnant and must complete a urine pregnancy test. Alternatively, any of the following methods of birth control are acceptable: oral or injectable contraceptives, contraceptive patches, Depo-Provera® (stabilized for at least 3 months), NuvaRing® (vaginal contraceptive), Implanon™ (contraceptive implant), double barrier methods (e.g. condom and spermicide), IUD, tubal ligation, Essure or abstinence with a 2nd acceptable method of birth control should the Subject become sexually active. Prior to study enrollment women of child bearing potential must be advised of the importance of avoiding pregnancy during study participation.

A negative result of a pregnancy test having a minimum sensitivity of at least 50mIU/ml for hCG should be obtained, prior to study participation, at Visit 1. Pregnancy testing will also be performed at every study visit and the results of all pregnancy tests (positive or negative) will be documented.

If following initiation of study treatment, it is subsequently discovered that a study Subject is pregnant or may have been pregnant at the time of Investigational Product exposure, the Investigational Product will be permanently discontinued. The Principal Investigator must immediately notify the CRO of this event.

Protocol-required procedures for study discontinuation and follow-up must be performed on the Subject. Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the Principal Investigator must report to the sponsor follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants should be followed for a minimum of eight weeks after birth.

10.3 Serious Adverse Events

An **Adverse Event or Suspected Adverse Reaction** is considered ''serious'' if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life threatening adverse event; (Note: the term "life-threatening" as used here refers to an event in which the Subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.)
- In-Subject hospitalization or prolongation of existing hospitalization

  (A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health or if the hospitalization is clearly not associated with an AE (e.g., hospitalization due to social / logistic reason) are not to be considered as SAEs)
- A persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Any "other" important medical event

Important medical events that may not result in death, be life-threatening or require hospitalization may be considered Serious Adverse Events when, based on appropriate medical judgment, they may

jeopardize the Subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Regardless of the above, any additional adverse events, which the Principal Investigator considers significant, should be immediately reported to the Contract Research Organization.

SAE reporting by the Investigator - US:

Any Serious Adverse Event, whether deemed drug-related or not, must be reported by the Investigator to the Contract Research Organization (CRO) within 24 hours after the Principal Investigator or Study Coordinator becomes aware of its occurrence. The Principal Investigator or the Principal Investigator's Designee must complete a Serious Adverse Event (SAE) Form and email it to the Contract Research Organization, along with the subject's Adverse Events, Medical History, and Concomitant Medications Log within 24 hours of notification of the event.

The Principal Investigator or the Principal Investigator's Designee must be prepared to supply the following information:

a. Principal Investigator Name and Site Number
b. Subject I.D. Number
c. Subject initials and date of birth
d. Subject Demographics
e. Clinical Event
   1) Diagnoses and Description
   2) Date of onset
   3) Severity
   4) Treatment
   5) Medical records, hospitalization/discharge records
   6) Relationship to study drug
   7) Action taken regarding study drug
f. **If the AE was Fatal or Life-threatening**
   1) Cause of death (whether or not the death was related to study drug)
   2) Autopsy findings (if available)
   3) Death Certificate

The Principal Investigator must provide a follow-up written report within **5 calendar days** of reporting the event to the CRO. The written report must contain a full description of the event and any sequelae. Subjects who have had an SAE must be followed clinically until all parameters (including laboratory) have either returned to normal or are stabilized. The Investigator must also report follow-up information if it becomes known to the Investigator.

SAE reporting by the Investigator - India:

Any AE considered serious by the investigator or sub-investigator or which meets the aforementioned criteria is subjected for expedited reporting.

SAEs will be reported by the investigator to Contract Research Organization (CRO), Central Licensing Authority [Central Drugs Standard Control Organization (CDSCO)] and Ethics Committee within 24 hours of its occurrence. SAE details to CRO should be sent to:

[redacted]

[redacted]

In case investigator fails to report any SAE within the stipulated period, he/she shall have to furnish the reason for the delay to the satisfaction of the Licensing authority along with the report of the SAE.

The report of any serious adverse event after due analysis, shall be forwarded by the investigator to the central licensing authority, the chairperson of the ethics committee and the head of institution where the study has been conducted within 14 days of occurrence of SAE.

Subjects who have had SAEs must be followed clinically until all parameters (including laboratory) have either:

- Recovered: Fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first study related activity after the subject signed the informed consent.
- Recovering: The condition is improving and the subject is expected to recover from the event. This term should only be used when the subject has completed the study.
- Recovered with sequelae: As a result of the AE, the subject suffered persistent and significant disability/incapacity (e.g. became blind, deaf, paralyzed). Any AE recovered with sequelae should be rated as an SAE.
- Fatal
- Unknown: This term should only be used in cases where the subject is lost to follow-up

The Investigator must also report follow-up information if it becomes known to the Investigator.

SAE reporting by the CRO:

The CRO must notify the [redacted] Study Manager and Investigational New Drug (IND) Sponsor Drug Safety Department **within 24 hours** of the initial notification of the event. Documentation should be sent to Taro's SAE Coordinator and IND Sponsor Drug Safety listed below:

[redacted] must receive any follow-up **within 24 hours** of receipt by CRO.

[redacted] will submit detailed report of any serious adverse event to CDSCO, Ethics Committee and head of the institution (study site) within 14 days of its occurrence.

Ethics committee will send its review report to CDSCO for any serious adverse event within 30 days of its occurrence.

10.4 Suspected Unexpected Serious Adverse Reactions (SUSARs)

An **Adverse Event or Suspected Adverse Reaction** is considered a SUSAR if it is serious, unexpected, and suspected. Prior to reporting to the applicable Regulatory Authorities, the IND Sponsor will evaluate the available evidence and to judge the likelihood that the drug actually caused the adverse event. The SUSAR must be reported to FDA within 15 days, or if fatal or life threatening, within 7 days, by the IND Sponsor. The IND Sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event. Additionally, potential Hy's law cases will be reported as SUSARs.

The applicable Regulatory Authorities shall be notified by Sponsor Safety Physician of any SUSAR, as per local Regulatory Authorities guidelines and timeframe specified as per local regulation.

All participating Investigators, IEC/IRB and other stakeholders shall be notified of any SUSAR by CRO's Medical Monitor as per local regulatory requirement.

10.5 Post-study Events

Any AE/SAE that occurs up until the follow-up visit, or if the follow-up visit does not occur within the defined time window, then 4 weeks post the end of treatment visit or 4 weeks post the last dose of study drug for subjects with early discontinuation, should be reported and included in the safety analysis of the study.

Any AE/SAE which occurs past this date will be reported if it is considered related to study drug by the Investigator.

11. ETHICS

This study will be conducted in accordance with the ethical principles that have their origin in the current Declaration of Helsinki and will be consistent with International Council on Harmonisation Good Clinical Practice (ICH GCP) and applicable regulatory requirements. The study will be conducted in compliance with the protocol.

The rights, safety and well-being of the study Subjects are the most important considerations and should prevail over interests of society and science.

11.1 Informed Consent

The Principal Investigator must ensure that Subjects are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical studies in which they volunteer to participate. The principles of Informed Consent, according to FDA Regulations and ICH GCP will be followed. A copy of the proposed consent form must be submitted to the IRB, together with the protocol, for approval. Prior to beginning of the study, the Principal Investigator must have the IRB's written approval of the written informed consent form and any other information to be provided to Subjects.

Informed consent will be obtained from all Subjects using the following procedure: Subjects must have provided IRB approved written informed consent. Prior to initiating screening for the study, Subjects will be given the approved ICF describing the study and any risks associated with participation. The Subject will be allowed as much time as needed to read and understand the information presented in the consent form. Appropriate study personnel will be available to answer any questions the Subject might have regarding the study or study-related procedures. If the Subject chooses to participate in the study, he or she will be asked to sign and date the consent form and will be provided with a copy for his or her records. The ICF must be signed by the Subject before any protocol assessments can be undertaken. Each Subject's signed informed consent must be kept on file by the Principal Investigator.

Audio-video (AV) consent in India:
As per, DCGI regulation (G.S.R. 611 (E), Dated 31st July 2015) AV recording of the informed consent process is mandatory for vulnerable subjects participating in clinical trials of new chemical entity (NCE) or new molecular entity (NME). Consequently, for patients aged ≥65 years, AV recording of the consent process will be done.

11.2 Institutional Review Board

Before study initiation, the Principal Investigator must have written and dated approval from the IRB for the protocol, consent form, Subject recruitment materials and any other written information to be provided to Subjects.

Any changes to the protocol as well as a change of the Principal Investigator, which is approved by the Sponsor, must also be approved by the site's IRB and documentation of this approval provided to the Sponsor/designee. Records of the IRB review and approval of all documents pertaining to this study must be kept on file by the Principal Investigator and are subject to inspection during or after completion of the study. All SAEs must also be reported to the IRB.

Periodic status reports must be submitted to the IRB at least annually, as well as notification of completion of the study and a final report within one (1) month of study completion or discontinuation. A copy of all reports submitted to the IRB must be sent to the Sponsor/designee.

The Principal Investigator will ensure that an IRB that complies with the requirements set forth in 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the proposed clinical study.

11.3 Subject Confidentiality

The monitor(s), the auditor(s), IRB/IEC, and the regulatory authority(ies), will be granted direct access to the Subject's original medical records for verification of the clinical trial procedures and/or data, without violating the confidentiality, to the extent permitted by the applicable laws and regulations and that by signing a written informed consent form, the Subject or the Subject's legally acceptable representative is authorizing such access.

The identifying the Subject will be kept confidential and, to the extent permitted by the applicable laws and regulations, will not be made publicly available. If the results of the trial are published, the Subject's identity will remain confidential.

12. DOCUMENTATION

12.1 Site Regulatory Documents Required for Initiation

The following documents will be received by the CRO from US sites prior to the initiation of the study:

1. Completed and signed FDA Form 1572
2. Current curricula vitae, signed and dated for the Principal Investigator and each Sub-Investigator named in the FDA Form 1572 (current within 2 years)
3. Current medical licenses of the Principal Investigator and Sub-Investigators named in FDA Form 1572
4. Documentation of IRB approval of this study protocol, Principal Investigator and informed consent form
5. Current IRB membership list or roster
6. A copy of the protocol agreement page signed by the Principal Investigator
7. Non-disclosure Agreements for the Principal Investigator and Sub-Investigators named in FDA Form 1572
8. Financial Disclosure Statement for the Principal Investigator and each Sub-Investigator named in FDA Form 1572.
9. Statement of Non-Debarment

12.2 Maintenance and Retention of Records

It is the responsibility of the Principal Investigator to maintain a comprehensive and centralized filing system of all relevant documentation.

Copies of all pertinent records will be retained by the Principal Investigator for at least two years following final approval of the drug and/or notification from the Sponsor. These regulatory documents should be retained for a longer period if required by local regulatory authorities. These records include documents pertaining to the receipt and return of drug supplies, IRB, informed consent, source documents. No documents shall be transferred from the site or destroyed without first notifying the Sponsor. If the Principal Investigator withdraws from the study, the records shall be transferred to a mutually agreed upon designee. Notice of such transfer will be given in writing to the Sponsor.

The Principal Investigator is required to prepare and maintain adequate and accurate case histories

designed to document all observations and other data pertinent to the investigation on each individual treated with the Investigational Product or entered as a control in the investigation.

12.3 Data Collection and Reporting

Data for individual Subjects will be collected on source documents. The data management system will be Electronic Data Capture (EDC). The Investigator and his/her study site personnel will be responsible for transferring data to the eCRFs. The Investigator is required to verify that all of the requested information is accurately recorded in the eCRFs. All information requested in the eCRFs needs to be supplied, including subject identification, date(s), assessment values, etc., and any omission or discrepancy will require explanation. All information on eCRFs must be traceable to source documents.

Source documents such as the clinic chart are to be maintained separately from the eCRF in order to allow data verification. Because of the potential for errors, inaccuracies and illegibility in transcribing data into eCRFs, originals of laboratory and other test results must be kept on file. Source documents and copies of test results must be available at all times for inspection by the study monitor. The following should also be available for review:

1. Subject Screening Log – reflecting the reason any Subject screened for the study was found to be ineligible
2. Delegation of Authority / Study Personnel Signature Log – all site personnel will be listed along with their responsibilities and signatures; to be maintained at the site throughout the study
3. Monitoring Log – the date and purpose of all monitoring visits by the Sponsor/Designee will be documented
4. Enrollment Log – documenting Subject initials and start and end dates for all Subjects enrolled
5. Drug Inventory/Packing Slip – reflecting the total amount of drug shipped to the site and received and signed for by the Principal Investigator
6. Drug Accountability Log – reflecting the total amount of Investigational Product dispensed to and returned by each Subject
7. Informed Consent Form and Assent Form – which must be available for each Subject and be verified for proper documentation

The study monitor will be responsible for reviewing and verifying the data recorded in the eCRFs, utilizing the original source documentation and will query discrepant findings. The Investigator and study site personnel will be responsible for answering all queries. All queries issued by the data management personnel will be answered by site personnel and verified by the monitor.

Electronically generated data like laboratory results, ECG results etc. could be directly integrated with or transferred to the clinical database.

The CRO will have an independent CRA(s) and MM to monitor the cardiac monitoring and targeted safety lab data. The access to related data will be restricted to other CRO members and Sponsor.

12.4 Primary Source Documents

The Principal Investigator must maintain primary source documents supporting significant data for each Subject's medical notes. These documents, which are considered "source data", should include documentation of:

- Demographic information
- Evidence supporting the diagnosis/condition for which the Subject is being studied
- General information supporting the Subject's participation in the study
- General history and physical findings
- Hospitalization or Emergency Room records (if applicable)
- Each study visit by date, including any evaluations, relevant findings/notes by the Principal Investigator(s), occurrence (or lack) of adverse events and changes in medication usage, including the date the study drug commenced and completed.

- Any additional visits during the study
- Any relevant telephone conversations with the Subject regarding the study or possible adverse events
- An original, signed informed consent form or assent form for study participation

The Principal Investigator must also retain all Subject specific printouts/reports of tests/procedures performed as a requirement of the study.

12.5 Study Monitoring

The study will be monitored by a representative of the Contract Research Organization to assess compliance with ICH-GCP and applicable regulations. The Principal Investigator will be visited by a monitor prior to the study and at regular intervals during the course of the study. These visits are for the purposes of verifying adherence to the protocol.

The study monitor will review the informed consent/assent forms and verify eCRF entries by comparing them with the source documents (hospital/clinic/office records) that will be made available for this purpose. The monitor will review the maintenance of regulatory documentation and drug accountability. The monitor will review on a regular basis the progress of the study with the Principal Investigator and other site personnel.

eCRF sections may be monitored during these visits. At the end of the study, a closeout monitoring visit will be performed. Monitoring visits will be arranged in advance at a mutually acceptable time with site personnel. Sufficient time must be allowed by the site personnel for the monitoring of eCRFs and relevant source documents. The Study Coordinator and/or Principal Investigator should be available to answer questions or resolve data clarifications. Adequate time and space for these visits should be made available by the Principal Investigator.

12.6 Audits and Inspections

During the course of the study and/or after it has been completed, one or more site visits may be undertaken by auditors as authorized representatives of the Sponsor. The purpose of the audit is to determine whether or not the study is being conducted and monitored in compliance with the protocol, recognized GCP guidelines and all applicable regulations.

Additionally, the study may be inspected by regulatory agencies. These inspections may take place at any time during the course of the study and/or after it has been completed.

THE INVESTIGATOR MUST NOTIFY THE CONTRACT RESEARCH ORGANIZATION and SPONSOR PROMPTLY OF ANY INSPECTIONS SCHEDULED BY REGULATORY AUTHORITIES, AND PROMPTLY FORWARD COPIES OF INSPECTION REPORTS TO THE SPONSOR.

12.7 Modifications to the Protocol

The procedures defined in the protocol will be carefully reviewed to ensure that all parties involved with the study fully understand the protocol. In order to ensure the validity of the data, no violations from the protocol, with minimal exceptions, may be made unless the issue is broad enough to warrant revision of the protocol. Such revisions must be submitted to and have documented approval from the Sponsor and the IRB prior to implementation.

The only circumstance in which an amendment may be initiated without prior IRB approval is to eliminate apparent immediate hazards to a Subject or Subjects. However, the Principal Investigator must notify the Sponsor immediately and the IRB within 5 working days after implementation.

All protocol violations will be reported on the protocol violation log and included in the study reports. A protocol violation is defined as any change, deviation, or departure from the study design or procedures of research project that is NOT approved by the IRB prior to its initiation or implementation, OR deviation from standard operating procedures, Good Clinical Practices (GCPs), federal, state or local regulations.

12.8 Completion of Study

The Principal Investigator is required to sign the eCRFs and all other relevant data and records to the Contract Research Organization.

The Principal Investigator is expected to submit a final report to the IRB and the Sponsor within one (1) month of study completion or discontinuation.

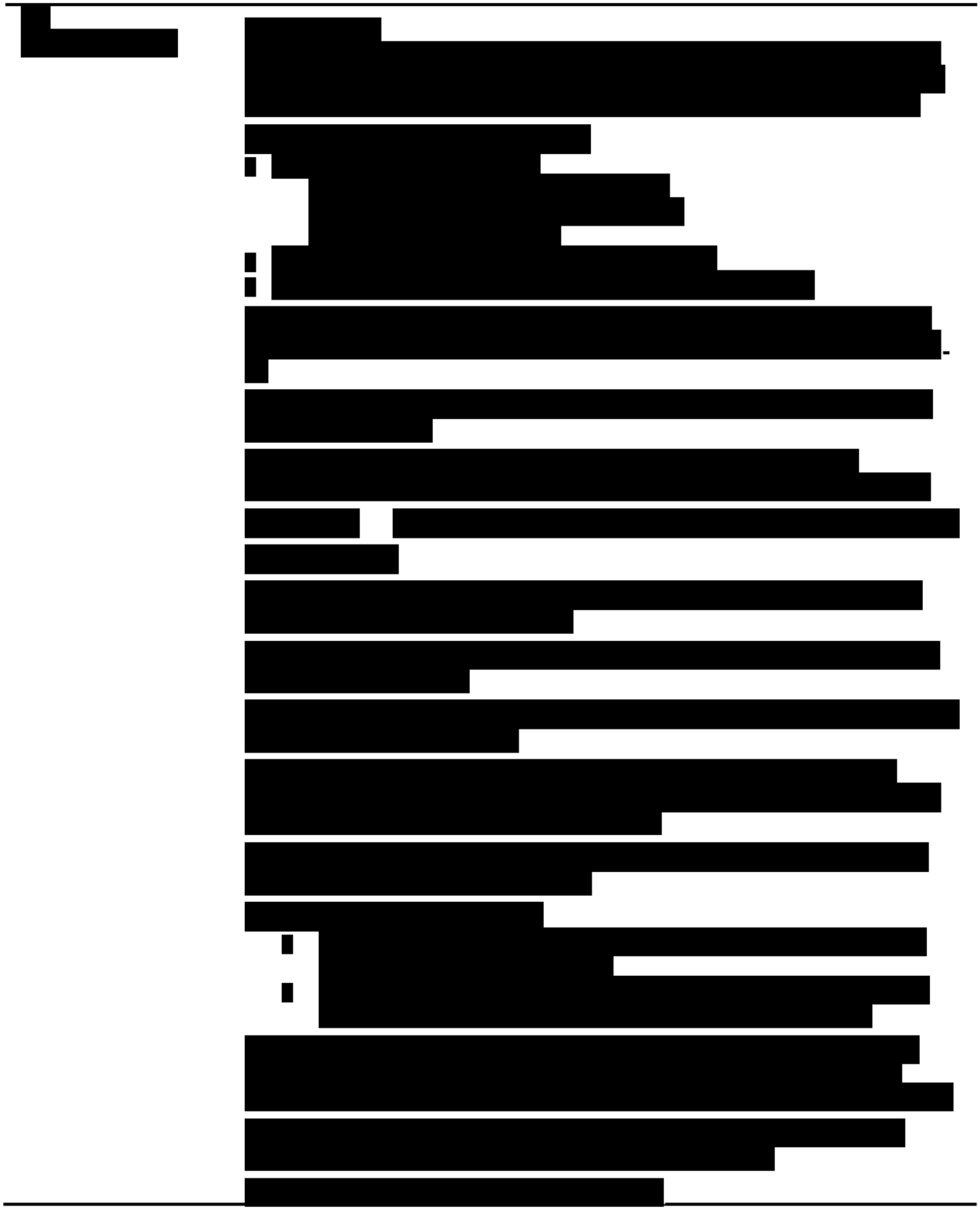
13. REFERENCES

1. Frisoli ML, Harris JE. Vitiligo: Mechanistic insights lead to novel treatments. J Allergy Clin Immunol 2017;140: 654-62
2. Steiner D, et al. Vitiligo. An. Bras Dermatol. 2004; 79(3): 335-351
3. Adebajo, AC, et al. Hypoglycaemic constituents of Stachytarpheta cayennensis leaf. Planta Med 2007 (3): 241-50
4. Froelich S. et al. Phenylethanoid glycosides from Stachytarpheta cayennensis (Rich.) Vahl, Verbenaceae, a traditional antimalarial medicinal plant. Revista Brasileira de Farmacognosia 2008:18(4) 517-20
5. Schapoval, EE, et al. Antiinflammatory and antinociceptive activities of extracts and isolated compounds from Stachytarpheta cayennensis. J Ethnopharmacol. 1998; 60(1) 53-9
6. Report 1: Effect of ACHE´s new treatment on αCD3/CD28-induced IFNγ secretion and proliferation in CD8+T cells. Executor: Draconis Pharma. Sponsor: AchéLaboratórios S/A. 2014
7. Report 2: Analysis of the new compounds generated during the acid hydrolysis of ipolamiide and evaluation of their efficacy. Executor: Draconis Pharma. Sponsor: AchéLaboratórios S/A. 2015
8. Niu C and Aisa H. Upregulation of Melanogenesis and Tyrosinase Activity: Potential Agents for Vitiligo. Molecules 2017, 22, 1303.
9. Lee Ai. Recent progress in melasma pathogenesis. Pigment Vell Melanoma Res 2015; 28:648-660.
10. Khaitan BK, Kathuria S, Ramam M. A descriptive study to characterize segmental vitiligo. Indian J Dermatol Venereol Leprol. 2012;78(6):715-21
11. Hamzavi I et al. Parametric modeling of narrowband UV-B phototherapy for vitiligo using a novel quantitative tool: The Vitiligo Area Scoring Index. Arch Dermatol 2004 Jun; 140:677-83
12. Njoo MD, Das PK, Bos JD, Westerhof W. Association of the Köbner phenomenon with disease activity and therapeutic responsiveness in vitiligo vulgaris. Arch Dermatol. 1999;135(4):407-13
13. Phan NQ, Blome C, Fritz F, Gerss J, Reich A, Ebata T, Augustin M, Szepietowski JC, Ständer S. Assessment of pruritus intensity: prospective study on validity and reliability of the visual analogue scale, numerical rating scale and verbal rating scale in 471 patients with chronic pruritus. Acta Derm Venereol. 2012;92(5):502-7
14. van Geel N, Lommerts J, Bekkenk M, Wolkerstorfer A, Prinsen C, Eleftheriadou V, Taı¨eb A, Picardo M, Ezzedine K and Speeckaert R: Development and Validation of the Vitiligo Extent Score (VES): an International Collaborative Initiative. Journal of Investigative Dermatology (2016) 136(5): 978-984.
15. Tour SK, Thomas KS, Walker DM et al. Survey and online discussion groups to develop a patient-rated outcome measure on acceptability of treatment response in vitiligo. BMC Dermatol 2014; 14:10.
16. Batchelor JM, Tan W, Tour S, Yong A, Montgomery AA, Thomas KS. Validation of the Vitiligo Noticeability Scale: a patient-reported outcome measure of vitiligo treatment success. Br J Dermatol. 2016;174(2):386-394.
17. van Geel N, Lommerts JE, Bekkenk MW, Prinsen CA, Eleftheriadou V, Taieb A, Picardo M, Ezzedine K, Wolkerstorfer A, Speeckaert R; international Vitiligo Score Working Group. Development and validation of a patient-reported outcome measure in vitiligo: The Self Assessment Vitiligo Extent Score (SA-VES). J Am Acad Dermatol. 2017;76(3):464-471.
18. van Geel N, Wolkerstorfer A, Ezzedine K, Pandya AG, Bekkenk M, Grine L, Van Belle S, Lommerts JE, Hamzavi I, Harris JE, Eleftheriadou V, Esmat S, Kang HY, Kumarasinghe P, Lan

CE, Parsad D, Raboobee N, Flora Xiang L, Suzuki T, Prinsen CA, Taieb A, Picardo M, Speeckaert R; participants of the Rome International VGICC /VIS Workshop. Validation of a physician global assessment tool for vitiligo extent: Results of an international vitiligo expert meeting. Pigment Cell Melanoma Res. 2019;32(5):728-733

19. DLQI Website University of Cardiff.

    Available at: http://sites.cardiff.ac.uk/dermatology/quality-of-life/dermatology-quality-of-life-index-dlqi (last accessed on 08 Jun 2020)
20. Camille Salzes1, Sophie Abadie2, Julien Seneschal1,3, Maxine Whitton4, Jean-Marie Meurant5, Thomas Jouary6, Fabienne Ballanger1, Franck Boralevi1, Alain Taieb1,3, Charles Taieb7 and Khaled Ezzedine. The Vitiligo Impact Patient Scale (VIPs): Development and Validation of a Vitiligo Burden Assessment Tool. Journal of Investigative Dermatology (2016) 136, 52-58
21. Speeckaert R, Lambert J van Geel N. Clinical Significance of Serum Soluble CD Molecules to Assess Disease Activity in Vitiligo. JAMA Dermatol. 2016;152(11):1194–1200
22. Harris JE, et al. A mouse model of vitiligo with focused epidermal depigmentation requires IFN-γ for autoreactive (CD8+) T cell accumulation in the skin. J Invest Dermatol, 2012; 132(7):1869-1876
23. Speeckaert R, Lambert J van Geel N. Clinical Significance of Serum Soluble CD Molecules to Assess Disease Activity in Vitiligo. JAMA Dermatol. 2016;152(11):1194–1200
24. Speeckaert R, Speeckaert M, S. De Schepper, van Geel N. Autoimmunity Reviews 16 (2017) 937–945
25. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ (last accessed on 08 Jun 2020)

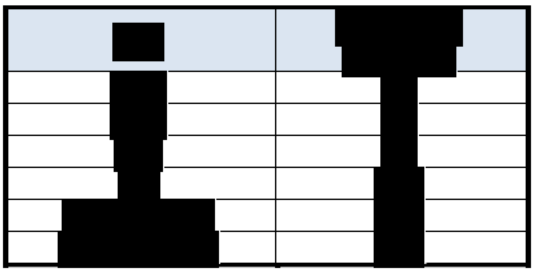


[redacted]

[redacted]

[redacted]

[redacted]



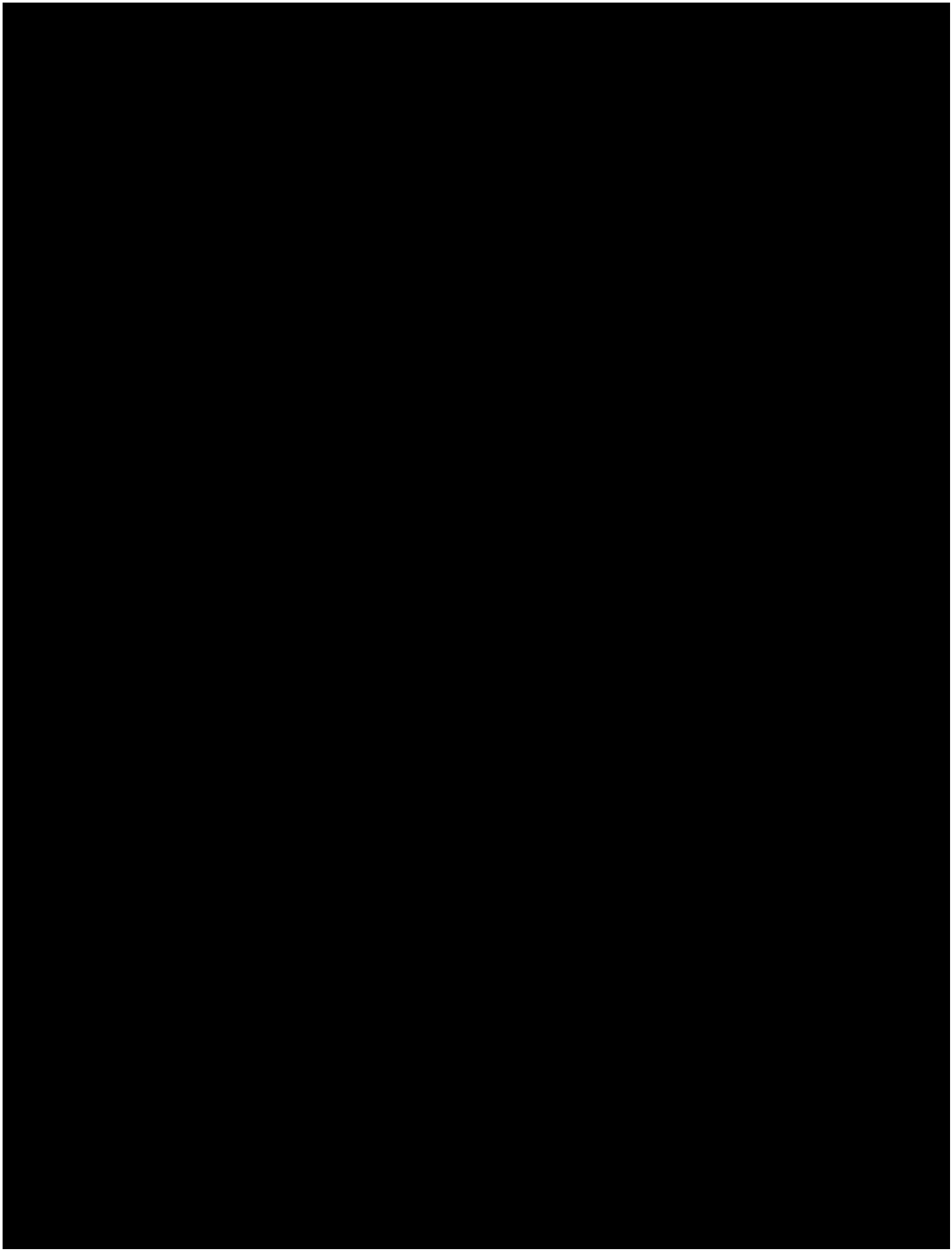
[redacted]

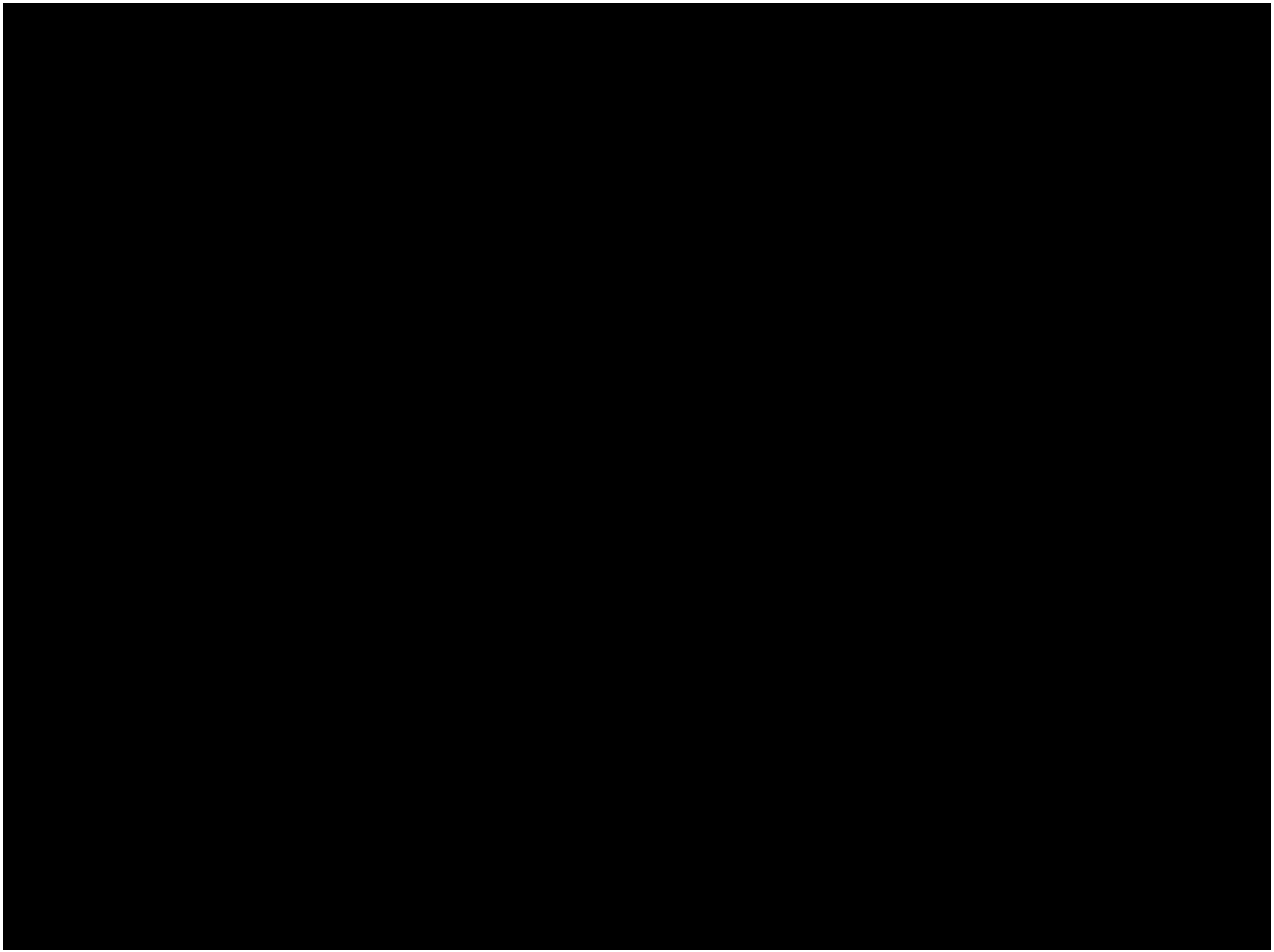
APPENDIX IV: VITILIGO AREA SCORING INDEX (VASI) SOURCE DOCUMENT

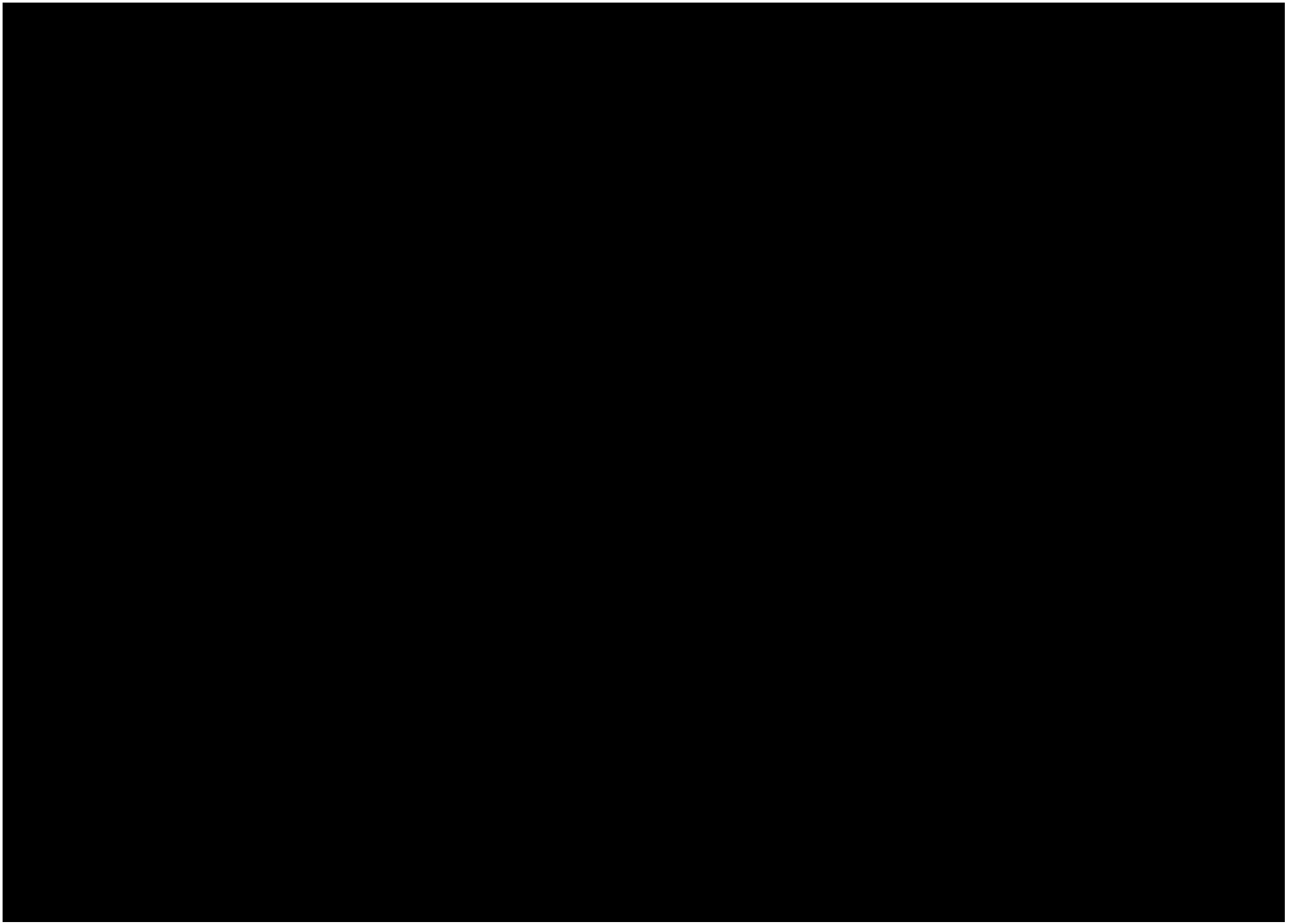
The total VASI score is calculated as follows (to be performed programmatically by DM):

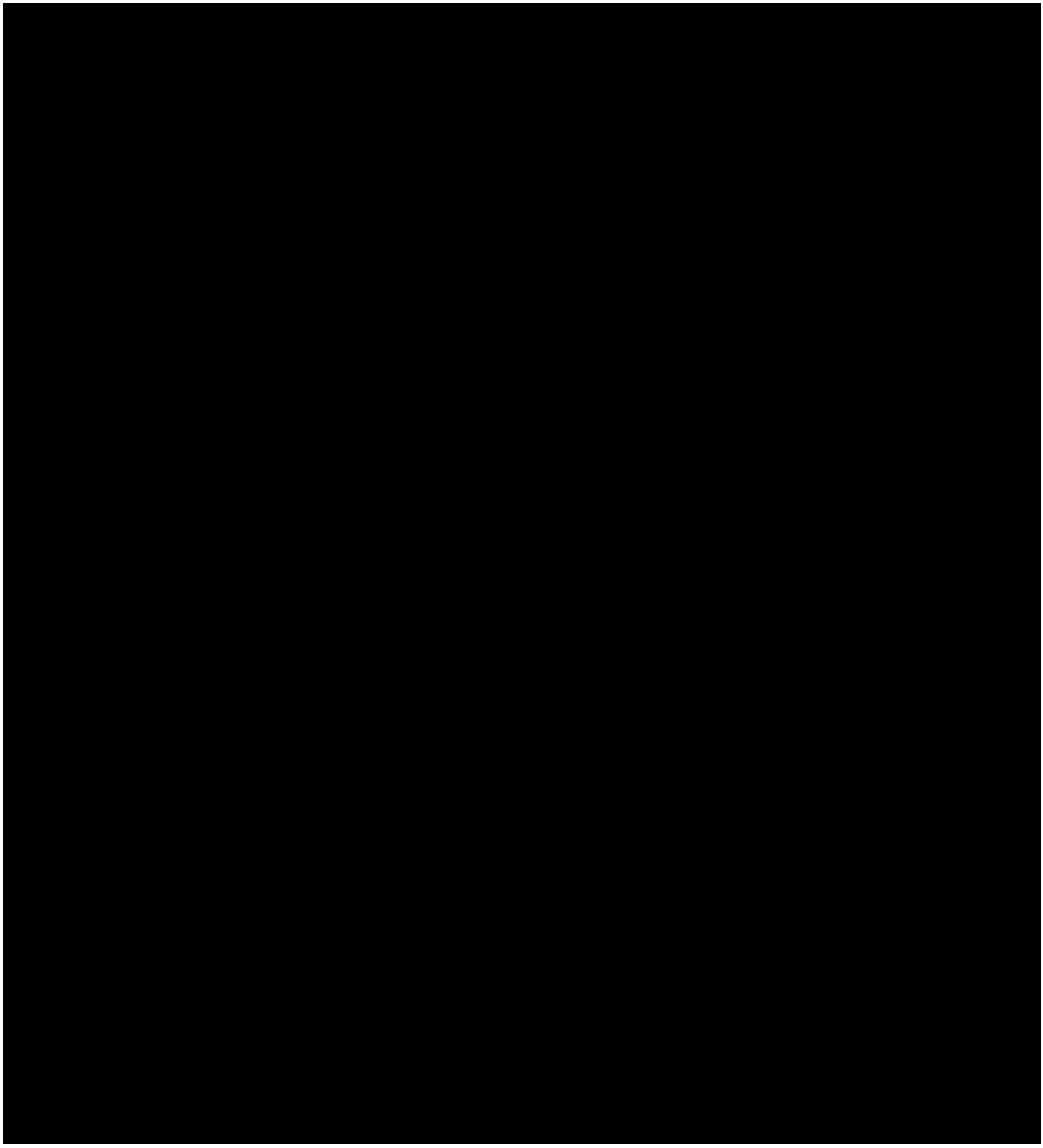
Area	Surface (hands units)	Residual depigmentation*	Total
Hands	x	=	
Upper Extremities *excludes hands; includes axillae*	x	=	
Trunk	x	=	
Lower Extremities *excludes feet; includes inguinal areas and buttocks*	x	=	
Feet	x	=	
	Total VASI Score (sum of above)	=	

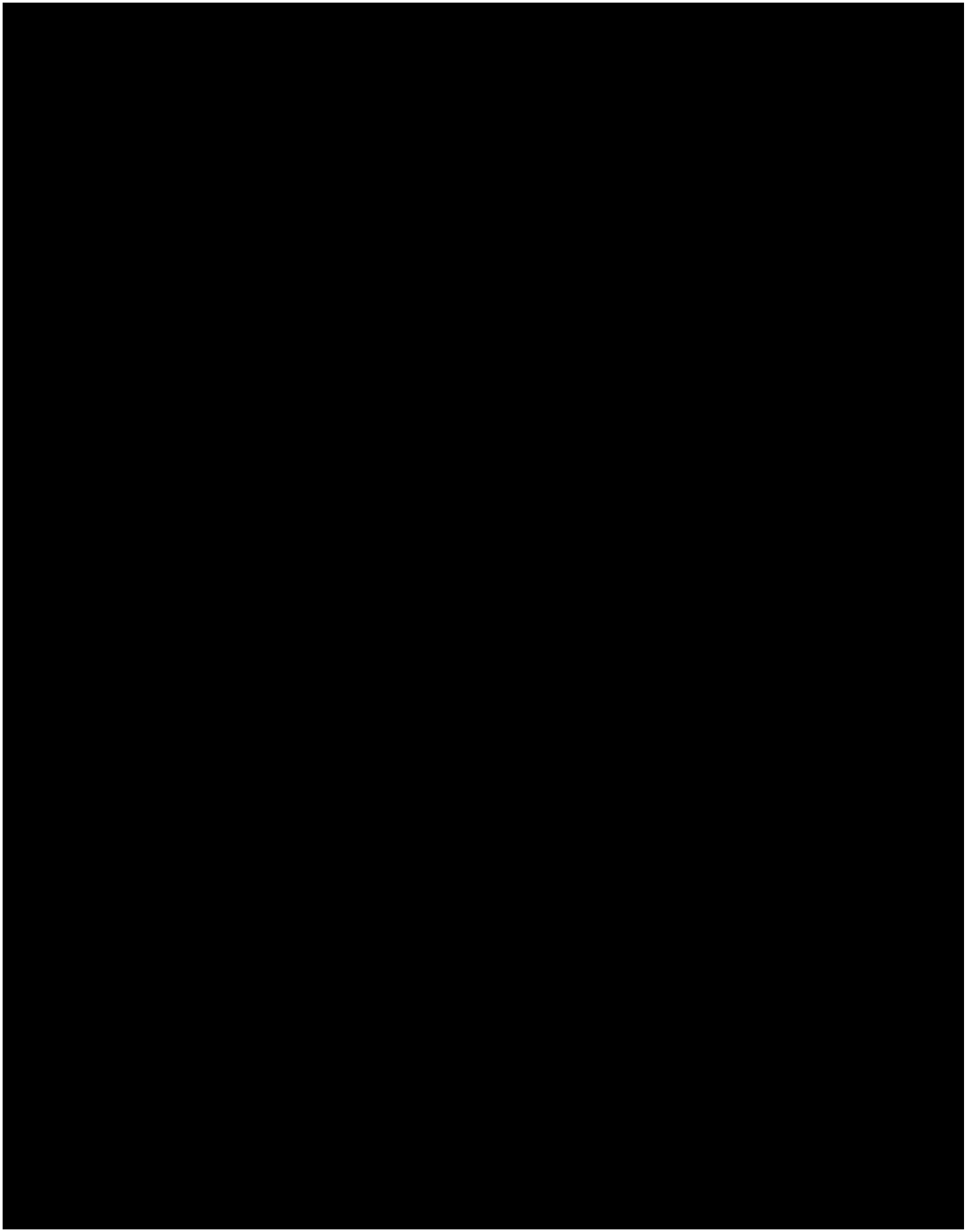
One hand unit encompasses the palm plus the volar surface of all digits, is approximately 1% of the total body surface area.











APPENDIX XIV: COLUMBIA SUICIDE SEVERITY RATING SCALE (C-SSRS)

1. C-SSRS SCREENING

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Screening

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

[redacted]

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Past X Months

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?
Yes ☐ No ☐

If yes, describe:

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan.
Have you actually had any thoughts of killing yourself?
Yes ☐ No ☐

If yes, describe:

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it."*
Have you been thinking about how you might do this?
Yes ☐ No ☐

If yes, describe:

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?
Yes ☐ No ☐

If yes, describe:

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?
Yes ☐ No ☐

If yes, describe:

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.

Most Severe Ideation: _____ _____

Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day
_____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous
_____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts
_____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply
_____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply
_____

SUICIDAL BEHAVIOR

(Check all that apply, so long as these are separate events; must ask about all types)

Past X Years or Lifetime

Actual Attempt:

A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt.

Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.

Have you made a suicide attempt?

Have you done anything to harm yourself?

Have you done anything dangerous where you could have died?

What did you do?

Did you_____ as a way to end your life?

Did you want to die (even a little) when you_____?

Were you trying to end your life when you _____?

Or did you think it was possible you could have died from_____?

Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)? (Self-Injurious Behavior without suicidal intent)

If yes, describe:

Yes ☐ **No** ☐

Total # of Attempts: _____

Has subject engaged in Non-Suicidal Self-Injurious Behavior?

Yes ☐ **No** ☐

Interrupted Attempt:

When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).*

Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt.

Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.

Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?

If yes, describe:

Yes ☐ **No** ☐

Total # of interrupted: _____

Aborted Attempt:

When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.

Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?

If yes, describe:

Yes ☐ **No** ☐

Total # of aborted: _____

Preparatory Acts or Behavior:

Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note).

Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?

If yes, describe:

Yes ☐ **No** ☐

Suicidal Behavior:

Suicidal behavior was present during the assessment period?

Yes ☐ **No** ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

2. C-SSRS BASELINE

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer.

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice, *pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements [redacted]

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.

Lifetime: Time He/She Felt Most Suicidal

1. Wish to be Dead
Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up.
Have you wished you were dead or wished you could go to sleep and not wake up?

If yes, describe:

Yes ☐ **No** ☐

2. Non-Specific Active Suicidal Thoughts
General, non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan.
Have you actually had any thoughts of killing yourself?

If yes, describe:

Yes ☐ **No** ☐

3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."*
Have you been thinking about how you might do this?

If yes, describe:

Yes ☐ **No** ☐

4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan
Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."*
Have you had these thoughts and had some intention of acting on them?

If yes, describe:

Yes ☐ **No** ☐

5. Active Suicidal Ideation with Specific Plan and Intent
Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out.
Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?

If yes, describe:

Yes ☐ **No** ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal.

Most Severe Ideation: _____ _____

Type # (1-5) ***Description of Ideation***

Most Severe

Frequency
How many times have you had these thoughts?
(1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day

____

Duration
When you have the thoughts, how long do they last?
(1) Fleeting - few seconds or minutes
(2) Less than 1 hour/some of the time
(3) 1-4 hours/a lot of time
(4) 4-8 hours/most of day
(5) More than 8 hours/persistent or continuous

____

Controllability
Could/can you stop thinking about killing yourself or wanting to die if you want to?
(1) Easily able to control thoughts
(2) Can control thoughts with little difficulty
(3) Can control thoughts with some difficulty
(4) Can control thoughts with a lot of difficulty
(5) Unable to control thoughts
(0) Does not attempt to control thoughts

____

Deterrents
Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?
(1) Deterrents definitely stopped you from attempting suicide
(2) Deterrents probably stopped you
(3) Uncertain that deterrents stopped you
(4) Deterrents most likely did not stop you
(5) Deterrents definitely did not stop you
(0) Does not apply

____

Reasons for Ideation
What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?
(1) Completely to get attention, revenge or a reaction from others
(2) Mostly to get attention, revenge or a reaction from others
(3) Equally to get attention, revenge or a reaction from others and to end/stop the pain.
(4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling)
(0) Does not apply

____

SUICIDAL BEHAVIOR

(Check all that apply, so long as these are separate events; must ask about all types)

Lifetime

Actual Attempt:

A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt.

Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred.

Have you made a suicide attempt?
Have you done anything to harm yourself?
Have you done anything dangerous where you could have died?
What did you do?
Did you_____ as a way to end your life?
Did you want to die (even a little) when you_____?
Were you trying to end your life when you _____?
Or did you think it was possible you could have died from_____?
Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)? (Self-Injurious Behavior without suicidal intent)

If yes, describe:

Yes ☐ No ☐

Total # of Attempts _____

Has subject engaged in Non-Suicidal Self-Injurious Behavior? Yes ☐ No ☐

Interrupted Attempt:

When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*.

Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt.

Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so.

Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?

If yes, describe:

Yes ☐ No ☐

Total # of interrupted _____

Aborted Attempt:

When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.

Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?

If yes, describe:

Yes ☐ No ☐

Total # of aborted _____

Preparatory Acts or Behavior:

Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note).

Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?

If yes, describe:

Yes ☐ No ☐

Suicidal Behavior:

Suicidal behavior was present during the assessment period? Yes ☐ No ☐

Answer for Actual Attempts Only	Most Recent Attempt Date:	Most Lethal Attempt Date:	Initial/First Attempt Date:
Actual Lethality/Medical Damage:	*Enter Code*	*Enter Code*	*Enter Code*
0. No physical damage or very minor physical damage (e.g., surface scratches).			
1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains).			
2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel).			
3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures).	_____	_____	_____
4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area).			
5. Death			
Potential Lethality: Only Answer if Actual Lethality=0	*Enter Code*	*Enter Code*	*Enter Code*
Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over).			
0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	_____	_____	_____