CLINICAL STUDY PROTOCOL

Title	A Phase 2a, Randomized, Double-Blind, Vehicle-Controlled Study to Assess the Safety, Tolerability, and Systemic Exposure of Cerdulatinib Gel, 0.37% in Adults with Vitiligo
Sponsor	Dermavant Sciences GmbH Viaduktstrasse 8 4051 Basel, Switzerland
Compound Name	Cerdulatinib (DMVT-502)
Protocol Number	DMVT-502-2101
Indication	Vitiligo
Development Phase	2a
IND #	135005
Version/Effective Date:	Original Protocol – Version 1.0 18 June 2019 Amendment 1 (Version 2.0): 31 Oct 2019

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SPONSOR SIGNATURE PAGE

Study Title: A Phase 2a, Randomized, Double-Blind, Vehicle-Controlled Study to Assess the Safety, Tolerability, and Systemic Exposure of Cerdulatinib Gel, 0.37% in Adults with Vitiligo

Protocol Number: DMVT-502-2101

This protocol has been approved by a representative of Dermavant Sciences, Inc. The following signature documents this approval.

[redacted]

Chief Medical Officer

MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/Serious Adverse Event Contact Information

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number
Primary Medical Monitor	[redacted]	[redacted]	[redacted]
Secondary Medical Monitor	[redacted]	[redacted]	[redacted]
Sponsor Contact	[redacted]	[redacted]	[redacted]
SAE/Pregnancy Reporting Contact Information	[redacted]	[redacted]	[redacted]

Study Sponsor

This study is sponsored by Dermavant Sciences, GmbH.

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USA

INVESTIGATOR STATEMENT

Study Title:

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations and comply with the study protocol. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Principal Investigator Name (Printed)	Signature
Date	Site

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Term	Description
%BSA	percent body surface area
AD	atopic dermatitis
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
Anti-HBc	anti-hepatitis B core antigen
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
BID	twice daily
BP	blood pressure
BSA	body surface area
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
CXCL9	chemokine (C-X-C) motif ligand 9
CXCL10	chemokine (C-X-C) motif ligand 10
CV	cardiovascular
Dermavant	Dermavant Sciences GmbH
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
FLIM	Fluorescence lifetime imaging microscopy
FSH	follicle-stimulating hormone
FTIH	first time in human
HCV	hepatitis C virus
HBsAg	hepatitis B surface antigen
Hep	hepatitis

Term	Description
HIV	human immunodeficiency virus
HR	heart rate
ICF	informed consent form
I/E	inclusion/exclusion
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
JAK	Janus kinase
LTS	Local Tolerability Scale
MedDRA	Medical Dictionary for Regulatory Activities
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MPM	Multiphoton microscopy
NB UVB	narrow band ultraviolet light B
NOAEL	no observed adverse effect level
NOEL	no observed effect level
PIH	post-inflammatory hyperpigmentation
PK	pharmacokinetic(s)
PUVA	psoralen plus ultraviolet light A
QTcF	QT interval corrected with Fridericia's formula
RBC	red blood cell(s)
RCM	Reflectance confocal microscopy
[redacted]	[redacted]
[redacted]	[redacted]
SAE	serious adverse event
SD	standard deviation
Syk	spleen tyrosine kinase
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

Term	Description
UC-Irvine	University of California -Irvine
[redacted]	[redacted]
US; USA	United States (of America)
UV	ultraviolet
[redacted]	[redacted]
WBC	white blood cell(s)
WOCBP	women of childbearing potential

SYNOPSIS

Name of Sponsor/Company:		
Dermavant Sciences GmbH		
Name of Investigational Product:		
DMVT-502 (cerdulatinib gel, 0.37%)		
Name of Active Ingredient:		
Cerdulatinib		
Protocol Number: DMVT-502-2101	**Phase**: 2a	**Country:** United States (US)
Title of Study:		
A Phase 2a, Randomized, Double-Blind, Vehicle-Controlled Study to Assess the Safety, Tolerability, and Systemic Exposure of Cerdulatinib Gel, 0.37% in Adults with Vitiligo		
Study Center(s):		
2 centers in the US		
Objectives: **Primary:** • To evaluate the safety and tolerability of topical administration of cerdulatinib gel, 0.37% in adult subjects with vitiligo **Secondary:** • To evaluate DMVT-502 systemic exposure following topical administration of cerdulatinib gel, 0.37% • To assess changes in chemokine motif ligand 9 (CXCL9) and chemokine motif ligand 10 (CXCL10) concentrations in pooled blister fluid before and after topical administration of cerdulatinib gel, 0.37% or vehicle gel **Exploratory:** • [redacted]		
Methodology: This is a Phase 2a, multicenter, randomized, vehicle-controlled, double-blind, safety, tolerability, and target engagement study. The study will consist of three phases: Screening (approximately 30 days), Treatment (42 days), and Follow-up (7-10 days). At Day 1 (Baseline) eligible subjects will be randomized at a 2:1 ratio to receive twice daily topical cerdulatinib gel, 0.37% or vehicle gel and will be instructed how to apply study drug while under the supervision of site personnel in the clinic. Subjects will return to the clinic on Days 15, 29, and 43 for study assessments and will receive a phone call at Day 8 to assess adverse events (AEs) and concomitant medications, to review study drug administration instructions, and to confirm subject's continued participation in this study. Subjects will return to the clinic for a follow-up visit 7-10 days after the Day 43 visit.		

During the treatment period, subjects will apply study drug to active vitiligo lesions twice daily for 42 days with a visit on Day 43 for scheduled assessments. During clinical visits, subjects will be instructed/reminded on how to apply study drug (except during the final treatment/end-of-study visit). Pharmacokinetic (PK) sampling will be collected on Days 1, 15, 29 (pre-dose and 2 hours post-dose) and 43 (single sample). Suction blistering for blister fluid and/or blister roof collection will be conducted 7-10 days prior to Baseline (Day -10 to Day -7) and Day 43.

Number of Subjects:

Approximately 30 subjects ages 18 years and older will be enrolled in this study as follows:

- Approximately 30 total subjects will be randomized at a 2:1 ratio (at each study site) to receive cerdulatinib gel, 0.37% (approximately 20 subjects) or vehicle gel (approximately 10 subjects)
    - A subset of subjects at the University of Massachusetts-Worcester (UMass) site will be enrolled into a sub-study for single cell RNAseq transcriptomics analysis of blister fluid samples
    - A subset of subjects at the University of California-Irvine (UC-Irvine) site will be enrolled into a sub-study for cellular metabolism and gene expression analysis of blister roof samples

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

Each subject must meet all the following criteria to be eligible to participate in the study:

1. Male or non-pregnant, non-lactating female subjects ages 18 years and older with confirmed clinical diagnosis of nonsegmental vitiligo.
2. At least 3-month history of active, new, or spreading vitiligo lesions with the presence of confetti, trichome, or inflammatory vitiligo lesions, or the Koebner phenomenon upon exam.
3. Vitiligo with depigmented areas, containing normal appearing pigmented hair (hair-baring lesions display less than 30% leukotrichia [white hair]), including ≥0.5% body surface area (BSA) involvement (e.g., 1% BSA is approximately equal to the area of 1 of the Investigator's handprints [palm plus 5 digits]).
    - Active vitiligo lesions must encompass ≥0.5% BSA at body sites appropriate for suction blister induction
    - Subjects with >30% BSA involvement must only treat ≤30% BSA with study drug. Areas to be treated should be pre-identified by study staff and subject at the Baseline (Day 1) visit and only the identified areas should be consistently treated for the duration of the study.
4. Presence of normal-appearing, non-depigmented skin at least 5 cm from the nearest depigmented macule.
5. Women of childbearing potential (WOCBP) must use 1 of the following methods of contraception during the study and for 3 months after the last dose of study drug:

    OPTION 1 – Highly effective methods that can be used alone:

    - Copper intrauterine device
    - Levonorgestrel-releasing intrauterine system
    - Progestin implant
    - Tubal ligation
    - Monogamous with a vasectomized male partner

    OPTION 2 – Acceptable first (hormonal) and second (barrier) methods to be used in combination:

    FIRST (*Hormonal Contraception)*

    - Estrogen & progestin oral contraceptives, transdermal patch, or vaginal ring
    - Progestin only oral contraceptives or injection

    SECOND (*Barrier Method)*

- Diaphragm (with spermicide)
- Cervical cap (with spermicide)
- Male condom (with or without spermicide)

OPTION 3 – Acceptable first (barrier) and second (barrier) methods to be used in combination:

FIRST (*Barrier Method)*

- Diaphragm (with spermicide)
- Cervical cap (with spermicide)

SECOND *(Barrier Method)*

- Male condom (with or without spermicide)

Note: Subjects using hormonal contraceptives must have been on a stable dose for at least 4 weeks before Baseline.

These allowed methods of contraception are only effective when used consistently, correctly, and in accordance with the product label. The Investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

Non-childbearing potential is defined as premenarchal; pre-menopausal females with a documented bilateral tubal ligation, bilateral oophorectomy (removal of the ovaries) or hysterectomy; hysteroscopic sterilization; or postmenopausal females defined as a cessation of menses for at least 12 months without an alternative medical cause. In questionable cases a blood sample with simultaneous follicle-stimulating hormone (FSH) > 40 mIU/mL is confirmatory. Documented verbal history from the subject is acceptable.

Subjects who are abstinent are eligible, but they must agree to use one of the birth control methods listed above if they start engaging in sexual activity that could lead to pregnancy during the study.

WOCBP must have a negative serum pregnancy test at Screening and negative urine pregnancy test at Baseline (Day 1).

6. Male subjects must agree to use condoms during sexual intercourse during the study and for 3 months after the last dose of study drug. If a female partner is of childbearing potential, she should use contraception as detailed in Item 5 above.
8. Capable of giving written informed consent, as applicable, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF); written informed consent must be obtained prior to performing any study-related procedures.

Exclusion Criteria:

A subject who meets any of the following criteria will be excluded and considered ineligible for participation in the study:

1. Diagnosis of segmental vitiligo.
2. Presence of leukotrichia within vitiligo lesions encompassing >30% of the lesional area in all hair-baring lesions.
3. Concurrent conditions or history of other diseases:
   a. Current diagnosis of skin disease types other than vitiligo (e.g., psoriasis, atopic dermatitis [AD], pemphigus, etc.) that may interfere with the clinical assessments of the signs and symptoms of vitiligo.
   b. Immunocompromised (e.g., lymphoma, acquired immunodeficiency syndrome) or medical history of positive human immunodeficiency virus (HIV) antibody at Screening;

c. Current evidence of blood dyscrasia defined as: anemia, thrombocytopenia, neutropenia, and/or lymphopenia of National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 or higher;
d. Chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 4 weeks prior to the Baseline visit;
e. Acute active bacterial, fungal, or viral (herpes simplex, herpes zoster, or chicken pox) skin infection within 1 week prior to the Baseline visit with the exception of herpes labialis or genital herpes infections that are adequately controlled by suppressive therapy as long as the HSV infection site does not coincide with a study drug application site;
f. Malignancy, or history of malignancy, with the exception of adequately treated non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ within the last 5 years (surgical excision or electrodessication and curettage);

4. Screening alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 1.5X the upper limit of normal (ULN);
5. Screening total bilirubin > ULN; total bilirubin > ULN and ≤ 1.5X ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%;
6. A QT interval corrected with Fridericia's formula (QTcF) > 470 msec;
7. Clinically significant abnormal thyroid -stimulating hormone or free T4 at Screening;
8. Current or chronic history of liver disease, known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones), presence of hepatitis B surface antigen (HBsAg), or positive hepatitis C virus (HCV) antibody test result, or a positive anti -hepatitis B core antigen (anti-HBc) result. Patients with a history of HCV infection who were medically cured and have an undetectable viral load are eligible to enroll. Subjects with a history of stable non-alcoholic fatty liver disease without evidence of active inflammation (elevated ALT/AST≥1.5x ULN) or cirrhosis are eligible to enroll;
9. Ultraviolet (UV) light therapy (including UVA, psoralen plus UVA [PUVA], or narrow band [NB UVB]) or prolonged exposure to natural or artificial sources of UV radiation (e.g., phototherapy, tanning beds/booths, or therapeutic sunbathing) within 8 weeks prior to the Baseline visit and/or plans to have such exposures during the study which could potentially impact the subject's vitiligo (as determined by the Investigator);
10. Use of any prohibited medication within the indicated period before the Baseline visit;

    NOTE: Prohibited concomitant medications, therapy, etc., during the defined period are as listed in the bullets below. If a subject requires any of these medications throughout the study period, he/she may be excluded from or discontinued from the study, at the discretion of the Investigator and Medical Monitor.

    - 12 weeks for biologic agents that might significantly affect the evaluation of vitiligo (e.g., etanercept, adalimumab, and infliximab);
    - 4 weeks for immunomodulating oral or systemic treatments: corticosteroids, methotrexate, or cyclosporine;
    - 4 weeks for topical treatments that may affect vitiligo including topical corticosteroids classified as low, medium, or high potency (e.g., flucinonide, hydrocortisone, triamcinolone acetonide), tacrolimus/pimecrolimus, Vitamin D analogs (e.g., calcipotriol), or retinoids;

11. A history of or ongoing serious illness or medical, physical, or psychiatric condition(s) that, in the Investigator's opinion, may interfere with the subject's participation in the study and ability to understand and give informed consent;
12. Pregnant females as determined by positive serum (Screening) or urine (Baseline) human chorionic gonadotropin test at Screening or prior to dosing;
13. Lactating females;

14. History of sensitivity to the study drug, or components thereof or a history of drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates the subject's participation in the study;
15. The subject has received an investigational drug within the following time period prior to the first dosing day in the current study: 4 weeks or 5 half-lives (whichever is known to be longer);
16. Subjects who have previously received janus kinase (JAK) inhibitor therapy, systemic or topical, including cerdulatinib, within the following time period prior to the first dosing day in the current study: 4 weeks or 5 half-lives (whichever is known to be longer);
17. Use of any prior and concomitant therapy not listed above that may interfere with the objective of the study as per discretion of the Investigator, including drugs that cause photosensitivity or skin pigmentation (e.g., antibiotics such as tetracyclines, antifungals, thiazide diuretics) with 8 weeks of Screening;
18. Concurrent skin lesions in the treatment area that, in the opinion of the Investigator, would either interfere with study evaluations or affect the safety of the subject;
19. Subjects with advanced disease or abnormal laboratory test values that could affect the safety of the subject or the implementation of this study;
20. Evidence of significant hepatic, renal, respiratory, endocrine, hematologic, neurologic, psychiatric, or cardiovascular (CV) system abnormalities or laboratory abnormality that will affect the health of the subject or interfere with interpretation of the results.

Study Drug, Dosage and Mode of Administration:

Cerdulatinib gel, 0.37% is a clear to slightly yellow gel containing 4 mg/gram cerdulatinib hydrochloride salt, supplied in 60-gram tubes, and is to be self-administered twice daily via topical application of a thin layer to the affected areas.

Reference Therapy, Dosage and Mode of Administration:

Vehicle gel is a clear to slightly yellow gel, supplied in 60-gram tubes, to be self-administered twice daily via topical application of a thin layer to the affected areas.

Duration of Treatment: Study duration is approximately 12 weeks in total (including up to 30 days for Screening, 42 days of treatment, and a 7-10 day follow-up period).

Study Endpoints:

Primary:

- Frequency, duration, and severity of AEs (local and systemic)
- Vital signs
- Laboratory values
- Local tolerability scale (LTS) scores

Secondary:

- Plasma concentration of cerdulatinib (DMVT-502) on Days 1, 15, 29, and Day 43
- CXCL9 concentrations in pooled blister fluid from active treated lesions and untreated nonlesional skin at Baseline and Week 6
- CXCL10 concentration in pooled blister fluid from active treated lesions and untreated nonlesional skin at Baseline and Week 6

Exploratory:

- [redacted]
- [redacted]
- [redacted] 6

- Correlation of change from Baseline to Week 6 in CXCL9 concentrations in pooled blister fluid from active treated lesions with clinical response (change from Baseline to Week 6 in VASI)
- Correlation of change from Baseline to Week 6 in CXCL10 concentrations in pooled blister fluid from active treated lesions with clinical response (change from Baseline to Week 6 in VASI)

Statistical Methods:

Safety Analyses:

- Safety assessments including AEs, clinical laboratory tests, vital signs, and physical examinations will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA).
- Safety and cerdulatinib plasma concentration data will be presented in tabular and/or graphical format and summarized descriptively.

Efficacy Analyses:

- Change in CXCL9 concentration from Baseline to Week 6 in pooled blister fluid will be listed by subject and treatment; and will be summarized by treatment.
- Change in CXCL10 concentration from Baseline to Week 6 in pooled blister fluid will be listed by subject and treatment; and will be summarized by treatment.
- Individual subject efficacy measures at the end of the treatment period will be compared to baseline values using a one sample t-test.
- Analysis of mean change from Baseline to Week 6 in the concentration of CXCL9 in pooled blister fluid from cerdulatinib gel, 0.37% treatment group versus vehicle gel treatment group
- Analysis of change from Baseline to Week 6 in the concentration of CXCL10 in pooled blister fluid from cerdulatinib gel, 0.37% treatment group versus vehicle gel treatment group

Exploratory Analyses:

- [redacted]

SCHEDULE OF ASSESSMENTS

Table 1: Schedule of Assessments

Procedure	Screening		Treatment Period (Study Drug; Twice Daily)					Follow-up +/- 3 days or Early Termination
	V1	V2	V3	Phone Call	V4	V5	V6	V7
		Day -10 (+3 days)	Baseline Day 1	Week 1[a] (+/- 3 days)	Week 2 (+/- 3 days)	Week 4 (+/- 3 days)	Week 6 (+/- 4 days	Week 7 (+/- 4 days)
Target Day	-30	-10	1	8	15	29	43	50
Visit Window	-30 to -8	-10 to -7	n/a	5 to 11	12 to 18	26 to 32	39-45	46-54
Informed Consent	X							
I/E Criteria	X	X	X					
Demography	X							
Brief Physical Exam (including height & weight)	X							X
Fitzpatrick Skin Scale	X							
Medical History (includes year of vitiligo diagnosis, substance use, family history)[b]	X							
HIV, Hep B, and Hep C Screen	X							
Pregnancy Test (WOCBP) [Serum @ screen, Urine @ other visits]	X		X		X	X	X	X
Laboratory Assessments chemistry, hematology (including liver chemistries), urinalysis	X		X		X	X	X	X
Randomization			X					
Dispense/Collect Subject Diary[c]			X		X	X	X	
Training on Study Drug Application			X	X	X	X		
Local Tolerability Scale Assessment[c]			X		X	X	X	X

Procedure	Screening		Treatment Period (Study Drug; Twice Daily)					Follow-up +/- 3 days or Early Termination
	V1	V2	V3	Phone Call	V4	V5	V6	V7
		Day -10 (+3 days)	Baseline Day 1	Week 1[a] (+/- 3 days)	Week 2 (+/- 3 days)	Week 4 (+/- 3 days)	Week 6 (+/- 4 days	Week 7 (+/- 4 days)
Target Day	-30	-10	1	8	15	29	43	50
Visit Window	-30 to -8	-10 to -7	n/a	5 to 11	12 to 18	26 to 32	39-45	46-54
Study Drug Administration in-clinic Under Supervision			X		X	X		
PK Sampling[d]			X		X	X	X	
Vital Signs (pre-dose; HR, BP, temperature)	X		X		X	X	X	X
ECG	X						X	
Study Drug Dispensation & Collection[e]			X		X	X	X	
AE/SAE Review	X	X	X	X	X	X	X	X
Concomitant Medication Review	X	X	X	X	X	X	X	X
% BSA	X	X					X	
Photography[f]		X					X	
Noninvasive Microscopy Imaging[g]		X					X	
Lesional/Nonlesional Blister Induction/Fluid and/or Roof Collection		X					X	
[redacted]	X	X			X	X	X	

Abbreviations: I/E = inclusion/exclusion; Hep = Hepatitis; WOCBP = women of childbearing potential; PK = pharmacokinetic; HR = heart rate; BP = blood pressure; ECG = electrocardiogram;; AE= adverse event; SAE = serious adverse event; % BSA = percent body surface area; [redacted]

[a]Week 1 Visit=Phone Call; [b]Substances = drugs, alcohol, tobacco, and caffeine; [c]Pre-dose assessment at baseline; [d]PK sampling timepoints=pre-dose and 2 hours post-dose at indicated visits except Day 43 (pre-dose only); [e]Day 43=collection only; [f]Photography = pre-suction blister induction; Day -10 and Day 43; [g]Noninvasive Microscopy Imaging=Optional analysis at UC-Irvine site; this is not required of subjects for participation in the study. A separate informed consent and imaging release (permission) will be required.

1. INTRODUCTION

1.1. Background Information and Study Rationale

1.1.1. Background Information

Vitiligo is an autoimmune skin disease resulting from the destruction of melanocytes within the epidermis ultimately leading to progressive depigmentation. This disfiguring disorder is common, reportedly affecting 0.5 to 2% of the world's population with no evident preference for race or sex [Rodrigues, 2017]. Although the exact prevalence of vitiligo in the pediatric population is unknown, approximately 30 to 50% of all vitiligo cases report onset during childhood [Ezzedine, 2016]. In pediatric cases, the median age of onset is between 5 and 10 years of age, with onset in 40% of pediatric cases occurring between 5 and 10 years and 21% between the ages of 10 and 18 years [Marinho, 2013].

Although sometimes regarded as a cosmetic disease, the clinical appearance of white spots is disfiguring, and the psychological impact of vitiligo is profound, greatly affecting a patient's self-esteem and impairing their quality of life. Currently, there are no Food and Drug Administration (FDA) approved or labeled vitiligo therapies and many patients report that general physicians are unaware of treatment options. The existing topical vitiligo treatments, which are used-off label, are nontargeted immunomodulators such as steroids, calcineurin inhibitors, and Vitamin D analogues that deliver modest efficacy. In extensive disease, phototherapy, particularly NB-UVB, has become the therapy of choice as treatment can address both repigmentation and disease stabilization. However, common side effects associated with phototherapy including stinging, burning, blistering, erythema, itch, and phototoxicity; these side effects, coupled with the requirement for frequent clinic visits, often limit patient use. Surgical approaches, including autologous grafting are reserved for stable vitiligo lesions (with no progression for at least 1 year) and therefore are best indicated for the treatment of stable segmental vitiligo. Several grafting techniques have been utilized in vitiligo, including punch and split-thickness skin grafting as well as melanocyte transfer grafting. However, all of these grafting techniques are painful and associated with potential scarring or pigmentation side effects on both the recipient and donor sites; additionally, uncertainty about long-term maintenance remains. Given the limitations of the above approaches, there remains a need for the development of effective targeted therapies with favorable safety profiles to treat vitiligo.

Cerdulatinib (DMVT-502), is a reversible, small molecule adenosine triphosphate competitive inhibitor of JAK family members and the nonreceptor spleen tyrosine kinase (Syk) that is being developed by Dermavant Sciences GmbH (Dermavant) for topical use in the treatment of dermatologic conditions, including inflammatory skin diseases such as AD and the autoimmune skin disease vitiligo. Cerdulatinib is also being developed for systemic administration (via capsules administered orally) by Portola Pharmaceuticals, Inc. for the treatment of B and T cell malignancies, including non-Hodgkin lymphoma and chronic lymphocytic leukemia/small lymphocytic lymphoma.

Cerdulatinib gel, 0.37% is a colorless to yellow gel of medium viscosity intended for topical application to AD and vitiligo lesions. DMVT-502, by blocking both Syk and JAK signaling, is postulated to disrupt vitiligo disease pathogenesis in at least three steps, antigen presenting cell-

mediated disease initiation, T-cell mediated inflammation, as well as IL-15 and JAK3-mediated inhibition of resident memory T cell differentiation and maintenance.

A single clinical study has been conducted in healthy adults and adults with AD using topical DMVT-502 formulations (ointment and gel) to evaluate safety, PK, and pharmacodynamics. This initial human trial with topical DMVT-502 evaluated two different formulations at various concentrations (0.09% and 0.18% DMVT-502 ointment; 0.18% and 0.37% DMVT-502 gel) and was conducted in two parts. Part 1 evaluated DMVT-502 formulations in 32 healthy adult subjects following single dose and repeat dosing (up to 13 days); and Part 2 enrolled 10 adults with AD [i.e., having an IGA score of 2 to 4] with twice daily (BID) dosing for 14 days.

In Part 1, systemic plasma exposures were below the limit of quantification of 250 pg/mL for the gel formulation at both concentrations (0.18% and 0.37% of DMVT-502, respectively) and the ointment formulation at both concentrations (0.09% and 0.18% of DMVT-502, respectively), following BID application on the arms over the last 13 days of dosing. In addition to measuring systemic exposure, the amount of DMVT-502 that penetrated the skin was measured via skin biopsy after the morning application of the last day of dosing (Day 15 of the study). Evaluable skin biopsies were available from 29 of 32 subjects who received at least one application of DMVT-502 ointment or gel. Tissue sample concentrations of DMVT-502 above the level of quantification were found in skin biopsy samples for 1 of 8 subjects in the 0.09% ointment group, 4 of 6 subjects in the 0.18% ointment group, 5 of 7 subjects in the 0.18% gel group, and 7 of 8 subjects in the 0.37% gel group. Results in adult subjects with mild to severe AD showed increased systemic exposure to DMVT-502 following topical administration of 0.37% gel BID as compared to healthy subjects exposed to the same formulation and concentration.

The most frequently reported dermatological AEs, regardless of formulation were application site pruritus (8 of 42 individuals across all treatment groups), eczema (one subject), and wound (single subject). The eczema was observed on the subject's hand where no study drug had been applied. Preliminary results suggest no clinically relevant skin irritation in healthy subjects, and all application site pruritus was mild in severity. Headache was the most frequently reported nondermatological AE (2/42 subjects). Two subjects had clinically significant on-study laboratory values (protein in urine and bacteria/cells in urine) at the follow-up visit. Both subjects were lost to follow-up and therefore no repeat laboratory assessments were performed. These treatment-emergent adverse events (TEAEs) were considered Grade 1 in intensity and deemed possibly related to study treatment (0.09% ointment and 0.37% gel, respectively). There were no clinically significant changes or findings reported in vital signs or electrocardiograms (ECGs) in subjects in Parts 1 or 2.

1.1.2. Study Rationale

This Phase 2a study is being conducted as part of a clinical development program to evaluate the safety, tolerability, and systemic exposure of cerdulatinib gel, 0.37% in adults with vitiligo.

1.2. Rationale for Study Design and Dose

The dose concentration (0.37%) of cerdulatinib gel being evaluated in this protocol is the maximum feasible concentration that can be formulated in a topical gel and which has been evaluated in dermal nonclinical studies in rat and minipig. Cerdulatinib gel was administered to

healthy subjects in a Phase 1 study using both the 0.18% and 0.37% gels, along with a small number of AD subjects who received 0.37% gel. Serial blood sampling was performed in the morning of the final day of treatment for healthy subjects and first and final day for AD subjects to estimate systemic exposure following twice daily administration of cerdulatinib gel. Additionally, a skin biopsy was obtained 12 hours after the morning application of cerdulatinib gel to estimate skin exposure in healthy subjects only. The Phase 1 study results showed all plasma PK samples in healthy subjects were below the level of quantification of 250 pg/mL following either application of 0.18% or 0.37% gel, but both formulations had detectable levels of DMVT-502 in the skin biopsy samples, illustrating there is skin penetration of the drug in healthy subjects. Both strengths were well tolerated with all reported AEs being mild to moderate in severity and all were listed as resolved or resolving by end of treatment. In AD subjects, 4 out of 8 individuals had at least one measurable concentration above 250 pg/mL following the morning application of 0.37% cerdulatinib gel on day 1, and 5 out of 8 individuals had at least one measurable concentration above 250 pg/mL following the morning application on day 14. The highest concentration achieved was 2.1 ng/mL in one subject on day 1. In the 5 subjects with measurable concentrations on day 14, the PK profiles were relatively flat, indicative that steady state had been reached and skin levels were likely saturated. The average concentration on day 14 was less than 1 ng/mL over the 12-hour dosing interval.

In the Phase 2a vitiligo study (DMVT-502-2101) individuals can have up to a 30% BSA involvement. The anticipated systemic exposure following treatment with cerdulatinib gel, 0.37% in vitiligo patients is expected to be substantially lower than the exposure at the no observed adverse effect level (NOAEL) in the 13-week oral dog toxicity study (>200 ng/mL).

1.3. Potential Risks and Benefits

To assess any potential impact on subject eligibility with regard to safety, the Investigator must refer to the current version of the DMVT-502 Investigator's Brochure for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the study drug being used in this study.

Topical application of cerdulatinib gel is proposed to limit systemic exposure, providing a favorable safety profile, while targeting delivery to the skin and the underlying inflammation. Clinical pharmacology data support the use of the highest concentration of topical cerdulatinib gel evaluated (0.37%), which demonstrated penetration into skin and minimal systemic absorption for AD subjects.

While clinical safety data to date are limited, preliminary assessments in 40 adults exposed to topical cerdulatinib gel (32 healthy volunteers and 8 subjects with AD) did not reveal any clinically significant safety findings. The safety of repeated administration of topical cerdulatinib gel has yet to be evaluated in adults beyond 2 weeks, or in vitiligo patients.

Vitiligo subjects could experience improvement in the signs and symptoms of their condition, however, clinical efficacy of topical cerdulatinib gel for the treatment of vitiligo has yet to be established. Further, the short treatment duration (6 weeks) is not likely to demonstrate significant repigmentation. There is a small risk of pain, local inflammation, cramping and rarely infection or bleeding at the site of suction blistering. The suction blisters are performed under clean conditions to minimize the risk of infection. Post-inflammatory hyperpigmentation

(PIH) may occur in the area of skin over the blister site; and this is more commonly observed in subjects with darker skin. Previous studies have shown no risk of scarring with the suction blistering procedure; however, improper wound care following the procedure can lead to the formation of a scar. To avoid scare tissue formation and PIH at the biopsied site, the subjects will be instructed to change their bandages 1-2 times daily and to cover the wounds with petroleum jelly. No specific potential risks of clinical significance have been identified in nonclinical studies or clinical trials to date and no mitigation strategies are required other than standard safety monitoring.

1.3.1. Risk Assessment

1.3.1.1. Dermatological Adverse Events, Including Skin Irritation, or Allergic Reaction:

Cerdulatinib gel or its excipients may induce skin irritation. Allergic or irritant reactions in the exposed areas may present as erythema, edema, papules, or vesicles. In the event of pronounced skin reaction, spreading of the eczematous reaction beyond the original application site(s) and/or more generalized (remote) skin reactions may be observed.

In the first time in human (FTIH) study with healthy volunteers and AD patients, the most frequently reported dermatologic TEAEs were application site pruritus, pruritus, and skin exfoliation. TEAEs experienced during the study were rated Grade 1 (96%) or Grade 2 (5%) in intensity and generally resolved by the end of the study (96%). There were no relevant dose-related trends observed in the incidence of TEAEs and dose level of topical cerdulatinib gel applied.

1.3.1.2. Systemic Adverse Events:

Headache was the most frequently reported nondermatological AE in the FTIH study in healthy volunteers and AD subjects (3 of 8 AD subjects).

In nonclinical repeat-dose toxicity studies using oral administration of DMVT-502, clinical observations of toxicity were limited to gastrointestinal-related findings of occasional and reversible episodes of vomiting and fecal changes in dogs, and minimal enteropathy in mice. Occasional incidences of opportunistic bacterial and parasitic infections were noted in the dog during the 13-week oral toxicity study at the highest dose (5 mg/kg/day, prior to reduction to 2.5 mg/kg/day on Day 36) that were clinically manageable and were secondary to the pharmacology-related immunosuppression by DMVT-502 systemically administered at high doses/exposures.

Consistent findings in the mice, rat, and dog oral toxicity studies at doses ≥ 2.5 mg/kg/day were lower thymic and splenic weight with thymic lymphoid depletion evident histologically. Lymphoid depletion in the lymph nodes was less consistently reported but was reported in dogs. These effects are likely attributed to the JAK1 and JAK3 inhibitory activities or Syk inhibitory activity of DMVT-502. Additionally, bone marrow hypoplasia was noted in mice, rats, and dogs in the oral toxicity studies and is considered to likely be a consequence of the less potent JAK2 inhibitory activity of DMVT-502. In the rat and dog repeat-dose oral toxicity studies altered hematology parameters (reduced WBC, neutrophil, lymphocyte numbers, red cell mass) correlated with the observed bone marrow effects. Observed immunosuppressive and bone

marrow suppression changes never reached adverse severity and were reversible following the respective off-dose/recovery periods in the rat and dog oral toxicity studies.

Evidence of immunosuppression has not been observed in any of the dermal toxicity studies in rats and minipigs conducted to date.

To mitigate potential systemic risks, subjects will be monitored for AEs and any abnormal vital signs, physical examination, and laboratory test results.

1.3.1.3. Reproductive and Developmental Toxicity

In a combined male and female fertility study in rats, no DMVT-502-related effects on estrous cycling in treated females, mating, fertility, or early embryonic survival in either sex were observed. In males, no DMVT-502-related microscopic findings were observed in the testes, epididymis, prostate, seminal vesicles, or mammary glands at any dose. Detailed evaluation of stage-dependent spermatogenesis revealed no DMVT-502-related alterations in the testes as any dose. The no observed effect level (NOEL) for paternal, maternal, and general toxicity of DMVT-502 is 15 mg/kg/day (134- to 249-fold the estimated human area under the plasma concentration versus time curve [AUC] for 0.37% gel).

In oral embryo-fetal developmental studies in rats and rabbits, the toxicity observed (moribundity/mortality and decreased body weights/gain) was only evident at doses that clearly exceeded the maximum tolerated dose and the fetal gross external and skeletal abnormalities only occurred at maternally toxic doses, indicating that DMVT-502 is not a selective developmental toxicant. The maternal and developmental NOEL and thereby, the NOAEL for DMVT-502 was 6 mg/kg/day for rats and 5 mg/kg/day for rabbits. Maximum plasma concentrations and AUC_{0-24} values for DMVT-502 in gestating rabbits at 5 mg/kg/day on gestation day 19 were 2720 ng/mL and 12,100 ng·hr/mL, respectively. On an AUC basis, this represents at least a 100-fold safety margin over the 'worst case scenario' systemic exposure in AD patients with significant BSA involvement and barrier defect.

To mitigate these potential risks, WOCBP must utilize abstinence or a highly effective method of contraception consistently and correctly during the study and for 4 weeks after the end of treatment (Section 4.2). Pregnant women and subjects under 18 years of age will be excluded from the study. If a woman becomes pregnant during the study, she will immediately discontinue study drug. Additionally, AEs will be monitored and clinical laboratory testing will be performed.

1.3.2. Benefit Assessment

Subjects may experience improvements in their vitiligo during the course of the study and may benefit from the additional safety assessments conducted as part of the study (e.g., physical examination, laboratory tests). Subjects in the study will also contribute to the process of developing a novel anti-inflammatory agent for the topical treatment of vitiligo.

1.3.3. Overall Benefit Risk

Taking into account the measures taken to minimize risk to subjects in this study, the potential risks identified in association with cerdulatinib gel are justified by the potential benefits to future subjects with vitiligo.

2. OBJECTIVES AND ENDPOINTS

The objectives and associated endpoints of the study are as follows:

Objectives	Associated Endpoint
Primary	**Primary**
• To evaluate the safety and tolerability of topical administration of cerdulatinib gel, 0.37% in adult subjects with vitiligo	• Frequency, duration, and severity of AEs (local and systemic) • Vital signs • Laboratory values • LTS scores
Secondary	**Secondary**
• To evaluate DMVT-502 systemic exposure in adult subjects with vitiligo following topical administration of cerdulatinib gel, 0.37% • To assess changes in CXCL9 and CXCL10 concentrations in pooled blister fluid before and after topical administration of cerdulatinib gel, 0.37% or vehicle gel	• Plasma concentration of cerdulatinib (DMVT-502) on Days 1, 15, 29 and 43 • CXCL9 concentration in pooled blister fluid from treated lesions and untreated nonlesional skin at Baseline and Week 6 • CXCL10 concentration in pooled blister fluid from treated lesions and untreated nonlesional skin at Baseline and Week 6
Exploratory	**Exploratory**
• [redacted] • [redacted]	• [redacted]

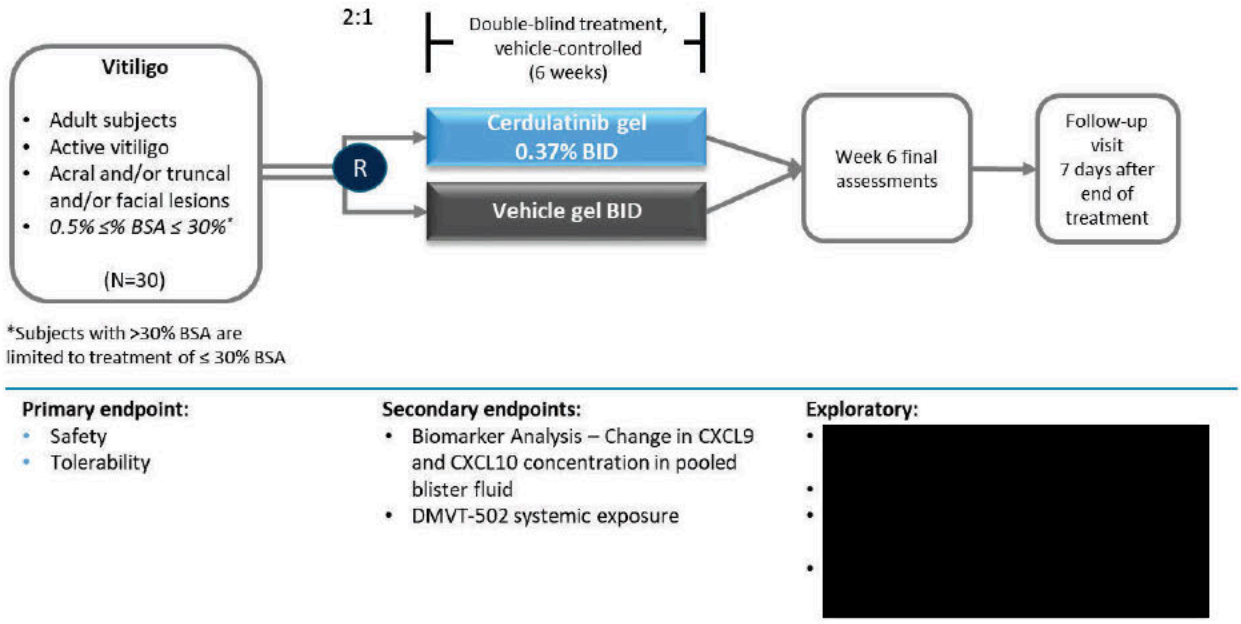
3. STUDY DESIGN

3.1. Overall Design

This is a Phase 2a, randomized, double-blind, vehicle-controlled, multicenter study to evaluate the safety, tolerability, and systemic exposure following topical administration of cerdulatinib gel, 0.37% in adults with vitiligo. The study will consist of three phases: Screening (up to 30 days), Treatment (43 days), and Follow-up (7-10 days).

Eligible subjects will be enrolled during screening. Subjects will be randomized on Day 1 (Baseline). During the treatment period, subjects will receive either topical cerdulatinib gel, 0.37% or vehicle gel (Figure 1).

Figure 1: DMVT-502-2101 Study Design



Subjects will return to the clinic on Days 1, 15, 29, and 43 for study assessments and will receive a phone call on Day 8. Subjects will return to the clinic for a follow-up visit 7-10 days after the Day 43 visit. On clinic visit days, subjects will apply the study drug under the supervision of site personnel, after assessments have been completed.

Study drug will be dispensed to subjects during the clinic visits and will be administered at home between clinic visits as instructed by site personnel. Subjects will apply sufficient study drug to completely cover each lesion with a thin layer of study drug and will record the time of study drug application in a daily diary provided by the study site. Subjects will be instructed to apply study drug twice daily approximately 12 hours apart throughout the entirety of their participation in the study. During the phone call on Day 8, subjects will be reminded to complete their daily diary and bring it to the next clinic visit.

Study drug application instructions will be reviewed at all post-randomization clinic visits. On clinic visit days, subjects will be instructed/reminded how to apply study drug (except during the final treatment/end-of-study visits). During the clinic visits, subjects will apply a daily dose of study drug while on-site under the supervision of site personnel, after other assessments have been completed.

Subjects who withdraw from the study before Day 43 will complete an Early Termination Visit. Study duration for subjects who complete this Phase 2a study is approximately 11 weeks in total. Refer to Section 6 for descriptions of study assessments and procedures and Section 7 and the Schedule of Assessments (Table 1) for timing of assessments and procedures.

3.2. Treatment Groups and Duration

During the Vehicle-Controlled Treatment Phase, subjects will be randomized in a 2:1 manner to one of 2 treatment arms:

- Topical cerdulatinib gel, 0.37% BID for 6 weeks (approximately 20 subjects)
- Topical vehicle gel BID for 6 weeks (approximately 10 subjects)

4. STUDY POPULATION

4.1. Type and Number of Subjects

Approximately 30 adult subjects with vitiligo will be enrolled in the study at 2 sites in the US.

Protocol violations from inclusion and exclusion criteria are prohibited because ineligible study subjects can potentially jeopardize the scientific integrity of the study, regulatory acceptability, and/or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

4.2. Inclusion Criteria

Each subject must meet all of the following criteria to be eligible to participate in the study:

1. Male and female subjects ages 18 years or older with confirmed clinical diagnosis of nonsegmental vitiligo.
2. At least 3-month history of active, new, or spreading vitiligo lesions with the presence of confetti, trichrome, or inflammatory lesions, or the Koebner phenomenon upon examination;
3. Vitiligo with depigmented areas, containing normal appearing pigmented hair (hair-baring lesions display less than 30% leukotrichia), including ≥0.5% BSA involvement and ≤30% BSA involvement;
    - Active vitiligo lesions must encompass ≥0.5% BSA at body sites appropriate for suction blister induction
    - Subjects with >30% BSA involvement must only treat ≤30% BSA with study drug. Areas to be treated should be pre-identified by study staff and subject at the Baseline visit (Day 1) and only these identified areas should be consistently treated for the duration of the study.
4. Presence of normal-appearing, non-depigmented skin at least 5 cm from the nearest depigmented macule;
5. WOCBP must use 1 of the following methods of contraception during the study and for 3 months after the last dose of study drug:

    OPTION 1: Highly effective methods that can be used alone:
    - Copper intrauterine device
    - Levonorgestrel-releasing intrauterine system
    - Progestin implant
    - Tubal ligation
    - Monogamous with a vasectomized male partner

    OPTION 2: Acceptable first (hormonal) and second (barrier) methods to be used in combination:

    FIRST (*Hormonal Contraception)*
    - Estrogen & progestin oral contraceptives, transdermal patch or vaginal ring
    - Progestin only oral contraceptives or injection

SECOND *(Barrier Method)*

- Diaphragm (with spermicide)
- Cervical cap (with spermicide)
- Male condom (with or without spermicide)

OPTION 3: Acceptable first (barrier) and second (barrier) methods to be used in combination:

FIRST *(Barrier Method)*

- Diaphragm (with spermicide)
- Cervical cap (with spermicide)

SECOND ***(****Barrier Method)*

- *Male condom (with or without spermicide)*

Note: Subjects using hormonal contraceptives must have been on a stable dose for at least 4 weeks before Baseline.

These allowed methods of contraception are only effective when used consistently, correctly, and in accordance with the product label. The Investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

Non-childbearing potential is defined as premenarchal; pre-menopausal females with a documented bilateral tubal ligation, bilateral oophorectomy (removal of the ovaries) or hysterectomy; hysteroscopic sterilization; or postmenopausal females defined as a cessation of menses for at least 12 months without an alternative medical cause. In questionable cases a blood sample with simultaneous FSH > 40 mIU/mL is confirmatory. Documented verbal history from the subject is acceptable.

Subjects who are abstinent are eligible, but they must agree to use one of the birth control methods listed above if they start engaging in sexual activity that could lead to pregnancy during the study.

WOCBP must have a negative serum pregnancy test at Screening and negative urine pregnancy test at Baseline (Day 1).

6. Male subjects must agree to use condoms during sexual intercourse during the study and for 3 months after the last dose of study drug. If a female partner is of childbearing potential, she should use contraception detailed in Item 5 above.
8. Capable of giving written informed consent, as applicable, which includes compliance with the requirements and restrictions listed in the ICF; written informed consent must be obtained prior to performing any study related procedures.

4.3. Exclusion Criteria

A subject who meets any of the following criteria will be excluded and considered ineligible for participation in the study:

1. Diagnosis of segmental vitiligo;
2. Presence of leukotrichia within vitiligo lesions encompassing >30% of the lesional area in all hair-baring lesions;

3. Concurrent conditions or history of other diseases:
    a. Current diagnosis of skin disease types other than vitiligo (i.e., psoriasis, AD, pemphigus, etc.) that may interfere with the clinical assessments of the signs and symptoms of vitiligo;
    b. Immunocompromised (e.g., lymphoma, acquired immunodeficiency syndrome) or medical history of positive HIV antibody at Screening visit or a medical history of malignant disease within 5 years prior to the Screening visit;
    c. Current evidence of blood dyscrasia defined as: anemia, thrombocytopenia, neutropenia, and/or lymphopenia of CTCAE Grade 2 or higher;
    d. Chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 4 weeks prior to the Baseline visit with the exception of herpes labialis or genital herpes infections that are adequately controlled by suppressive therapy as long as the HSV infection site does not coincide with a study drug application site;
    e. Acute active bacterial, fungal, or viral (herpes simplex, herpes zoster, or chicken pox) skin infection within 1 week prior to the Baseline visit;
    f. Malignancy, or history of malignancy, with the exception of adequately treated non-metastatic basal cell or squamous cell cancer of the skin or cervical carcinoma in situ, within the last 5 years (surgical excision or electrodessication and curettage;
4. Screening ALT or AST ≥1.5X ULN;
5. Screening total bilirubin > ULN; total bilirubin > ULN and ≤ 1.5X ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%;
6. QTcF interval > 470 msec;
7. Clinically significant abnormal thyroid-stimulating hormone or free T4 at Screening;
8. Current or chronic history of liver disease, known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones), presence of HBsAg, or positive HCV antibody test result, or a positive anti-HBc result. Patients with a history of HCV infection who were medically cured and have undetectable viral load are eligible to enroll. Subjects with a history of stable non-alcoholic fatty liver disease without evidence of active inflammation (elevated ALT/AST≥1.5x ULN) or cirrhosis are eligible to enroll;
9. UV light therapy (including UVA, PUVA, or NB UVB) or prolonged exposure to natural or artificial sources of UV radiation (e.g., phototherapy, tanning beds/booths, or therapeutic sunbathing) within 8 weeks prior to the Baseline visit and/or plans to have such exposures during the study which could potentially impact the subject's vitiligo (as determined by the Investigator);
10. Use of any prohibited medication within the indicated period before the Baseline visit:

    NOTE: Prohibited concomitant medications, therapy, etc., during the defined period areas listed in the bullets below. If a subject requires any of these medications throughout the study period, he/she may be excluded from or discontinued from the study, at the discretion of the Investigator and Medical Monitor.

- 12 weeks for biologic agents that might significantly affect the evaluation of vitiligo (e.g., etanercept, adalimumab, and infliximab);
- 4 weeks for immunomodulating oral or systemic treatments: corticosteroids, methotrexate, or cyclosporine;
- 4 weeks for topical treatments that may affect vitiligo including topical corticosteroids classified as low, medium, or high potency (e.g., flucinonide, hydrocortisone, triamcinolone acetonide), tacrolimus/pimecrolimus, Vitamin D analogs (e.g., calcipotriol) or retinoids;

11. A history of or ongoing serious illness or medical, physical, or psychiatric condition(s) that, in the Investigator's opinion, may interfere with the subject's participation in the study and ability to understand and give informed consent.
12. Pregnant females as determined by positive serum (Screening) or urine (Baseline) human chorionic gonadotropin test at Screening or prior to dosing;
13. Lactating females;
14. History of sensitivity to the study drug, or components thereof, or a history of drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates the subject's participation in the study;
15. The subject has received an investigational drug within the following time period prior to the first dosing day in the current study: 4 weeks or 5 half-lives, whichever is known to be longer;
16. Subjects who have previously received JAK inhibitor therapy, systemic or topical, including cerdulatinib; within the following time period prior to the first dosing day in the current study: 4 weeks or 5 half-lives, whichever is known to be longer;
17. Use of any prior and concomitant therapy not listed above that may interfere with the objective of the study as per discretion of the Investigator, including drugs that cause photosensitivity or skin pigmentation (e.g., antibiotics such as tetracyclines, antifungals, thiazide diuretics) within 8 weeks of Screening;
18. Concurrent skin lesions in the treatment area that, in the opinion of the Investigator, would either interfere with study evaluations or affect the safety of the subject;
19. Subjects with advanced disease or abnormal laboratory test values that could affect the safety of the subject or the implementation of this study;
20. Evidence of significant hepatic, renal, respiratory, endocrine, hematologic, neurologic, psychiatric, or CV system abnormalities or laboratory abnormality that will affect the health of the subject or interfere with interpretation of the results.

4.4. Lifestyle Restrictions

Subjects must avoid UV light, phototherapy, and excessive sun exposure throughout the study. When prolonged exposure cannot be avoided, use of sunscreen products and protective apparel are recommended.

4.5. Screening/Baseline Failures

To determine subject eligibility at Screening and Baseline, a single repeat of tests or procedures may be allowed at the discretion of the Investigator in consultation with the Medical Monitor.

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

4.6. Withdrawal Criteria

A subject may voluntarily discontinue treatment and/or withdraw from participation in this study at any time at his/her own request or may be discontinued from study drug at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.

4.6.1. Reasons for Withdrawal from the Study

Study drug will be discontinued for any of the following reasons:

- Subject has an AE considered to be related to study drug or procedures AND is severe enough to warrant treatment discontinuation, as determined by the Investigator
- Subject requires concurrent prohibited medication during the study. If, in the opinion of the Investigator and the study Medical Monitor, such medication will not interfere with the conduct or interpretation of the study or compromise the safety of the subject, then the subject may continue to receive study drug.
- Pregnancy
- Any Grade 3 or 4 AE considered causally related to study drug

Study drug may be discontinued for any of the following reasons:

- Subject noncompliance
- Investigator noncompliance
- Discontinuation of the study at the request of the Sponsor, regulatory agency, or an Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

If a subject meets a withdrawal criterion during treatment, an Early Termination Visit will be required (Section 7.8).

4.6.2. Withdrawal Procedures

The primary reason for the discontinuation of study drug and/or withdrawal from study must be recorded in the source document and on the electronic case report form (eCRF). If a subject is prematurely discontinued from study drug, the Investigator must make every effort to perform an Early Termination Visit (Section 7.8) and document the primary reason for withdrawal.

Should a subject fail to attend a required study visit, the site should attempt to contact the subject and reschedule the missed visit as soon as possible. The site should also counsel the subject on

the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study based on previous noncompliance. In cases where the subject does not return for the rescheduled visit or cannot be reached to reschedule the missed visit, the site should make every effort to regain contact with the subject so that they can appropriately be withdrawn from the study with a primary reason of "Lost to Follow-up."

4.7. Lost to Follow-Up

A subject is considered lost to follow-up if he/she repeatedly fails to return to the study site for scheduled visits and is unable to be contacted by the study site. The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

5. STUDY TREATMENT

5.1. Study Drug

5.1.1. Description, Packaging, and Labeling

The study treatments administered in this study are presented in Table 2.

Table 2: Study Drug

Study Drug	Cerdulatinib (DMVT-502)	Vehicle
Formulation Description:	polyethylene glycol-based formulation	polyethylene glycol-based formulation
Physical Description:	Clear, slightly yellow to yellow gel	Clear, slightly yellow to yellow gel
Unit dose strength / How Supplied	0.37% (4 mg/gram HCl salt) / 60-gram tube	Vehicle gel / 60-gram tube
Route of Administration/Duration	Topical / 6 weeks	Topical / 6 weeks
Dosing Instructions:	Twice daily topical application of a thin layer to affected areas (Section 5.1.5)	Twice daily topical application of a thin layer to affected areas (Section 5.1.5)
Manufacturer	[redacted]	[redacted]

5.1.2. Storage

All study drug must be stored in a secure, environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the Investigator and authorized site staff.

5.1.3. Handling and Disposal

Under normal conditions of handling and administration, study drug is not expected to pose significant safety risks to site staff. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or the Sponsor study contact.

A Material Safety Data Sheet/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the Investigator, where this is required by local laws, or is available upon request from the Sponsor.

Arrangements will be made for used and unused drug supplies to be returned to the Sponsor or Sponsor designee, or for destruction on site following acceptable, documented procedures. Further guidance and information for final disposition of unused study drug will be provided.

5.1.4. Preparation

No special preparation of study drug is required.

5.1.5. Administration of Study Drug

Study drug will be dispensed to subjects at the clinical site in appropriately labeled tubes.

Subjects will take the tubes home and self-administer study drug twice daily; on clinic visit days a dose of study drug will be applied under supervision at the site to affected areas.

Subjects will be instructed to apply study drug as follows:

- If a subject has >30% BSA involvement, the study staff and subject should pre-identify areas to be treated that are limited to ≤ 30% BSA at the Baseline visit (Day 1). Only these identified areas should be consistently treated for the duration of the study.
- Twice daily application to affected areas at approximately the same time each day; except on study visit days where dosing times may be altered to allow dosing under site supervision.
- Study drug should be applied to clean, dry skin.
- Wash hands after application, unless treating lesions on the hands.
- Study drug should be applied to all lesions, including newly appearing lesions and lesional areas that have improved during the study (not to exceed 30% BSA).
- If there is residual gel visible on the disease-affected lesional skin, then the subject should be instructed to continue to lightly rub the gel into the skin until it is no longer visible.
- Subject should record the time of study drug application in the daily diary.
- Subjects should avoid swimming, bathing, showering, or strenuous activities for at least 2 hours after application of study drug.
- Subjects should apply camouflage makeup or sunscreen a minimum of 1 hour following application of study drug.
- On clinic visit days, study drug should be applied in the clinic under the supervision of site personnel and after assessments have been completed.
- Subjects will be instructed/reminded on how to apply study drug at each clinic visit and phone call (except during the final treatment visit).

5.2. Randomization/Treatment Assignment

Subjects will be assigned to treatments in accordance with the randomization schedule, prior to the start of the study, using validated software. At Day 1, subjects will be randomized according to the scheme in Table 3 using a site-based randomization.

Table 3: Randomization Scheme for the Treatment Phase

Regimen	Number of Subjects
cerdulatinib gel, 0.37% applied twice daily for 6 weeks	20
vehicle gel applied twice daily for 6 weeks	10

5.3. Blinding

The Treatment Phase will be double-blinded and the following instructions will apply:

- The Investigator or treatment physician will have access to unblind a subject's treatment assignment only in the case of an emergency OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the Investigator.
- The Investigator should make every effort to first contact the medical monitor or appropriate study personnel to discuss options before unblinding the subject's treatment assignment.
- If the Sponsor personnel are not contacted before the unblinding, the Investigator must notify the Sponsor as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study.
- The date and reason for the unblinding must be fully documented in the eCRF.
- If the subject's treatment code is unblinded by the Investigator or treating physician, then the subject will be withdrawn. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the eCRF.
- The Sponsor or their designee may unblind the treatment assignment for any subject with a SAE. If the SAE requires an expedited regulatory report be sent to one or more regulatory agencies, then a copy of the report, identifying the subject's treatment assignment, may be sent to Investigators in accordance with local regulations.

5.4. Compliance with Study Drug Administration

At Baseline, study staff will provide the subject with detailed instructions concerning protocol requirements and use of study drug. Study staff will identify areas to be treated in subjects with >30% BSA involvement. Study staff will instruct subjects with >30% BSA involvement to treat only these pre-identified areas with study drug for the duration of the study. Additionally, subjects will be asked to complete a daily diary with the time of each application of study drug. At each post-Baseline study visit, study staff will review use of study drug, as applicable, with the subject.

When subjects are dosed at the site, they will apply the study drug under supervision of the study staff. The date and time of each dose administered in the clinic will be recorded in the source documents. The study drug and study subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person dispensing the study drug.

At the time of dispensing study drug to each subject, site personnel will weigh the combined weight of tubes to be dispensed and will record the combined weight of all tubes dispensed at each visit in the drug accountability log. Subjects will be instructed to bring all used and unused tubes of study drug with them to each study visit. Site personnel will weigh returned tubes (used and unused) and record the combined tube weight in the drug accountability log. If a tube has been lost, discarded, or forgotten by the subject, site personnel will make a notation of this on the drug accountability log. The site personnel will remind the subject to keep all tubes of study drug dispensed and to bring all used and unused tubes to each clinic visit. These data will be used to estimate subject compliance with use of study drug. Tubes of study drug dispensed at the most recent prior visit which remain unopened (the foil cap on the tube remains fully intact/undisturbed) may be re-dispensed to study subjects at the current visit. Opened, partially used tubes or tubes with foil overlay removed are not to be re-dispensed to study subjects. If there is any question as to re-dispensation, sites should issue new tubes of study drug to the subject(s).

5.5. Treatment after the End of the Study

Subjects will not receive any additional treatment with the study drug from the Sponsor after completion of the study because the indication being studied is not life-threatening or seriously debilitating and other treatment options are available.

The Investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition.

5.6. Prior and Concomitant Therapy

Any medication (including over the counter or prescription medication, vitamins and/or herbal supplements) administered to the subject up to 30 days before the Screening visit, at the time of enrollment, and during the study must be recorded in the eCRF along with the reason for use. The information to be recorded must also include name of the medication (generic name, as a general rule), dose, frequency, administration routes, and dates of the first and last dose, as applicable.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

5.6.1. Permitted Medications and Nondrug Therapies

Concomitant medications for medical treatment of other conditions are allowed under the condition that the dosage and administration of these treatments are not planned to change during the course of the study and that the medication is not a prohibited medication as described in the Exclusion Criteria (Section 4.3).

Oral vitamins, minerals, and dietary supplements are permissible during the course of the study as long as the list of dietary supplements has been discussed with the Investigator.

Inhaled and nasal corticosteroids may be used during study as long as the dosage and administration of these treatments are consistent and are not anticipated to change during the course of the study.

In the event of skin infection, topical antibacterial agents can be applied to the infected area; however, study drug must not be applied to the area until the skin infection is healed.

Subjects must avoid excessive sun exposure throughout the study. When prolonged exposure cannot be avoided, use of mineral-based sunscreen products (such as zinc oxide or titanium dioxide-based) with sun protection factor of at least 30 and protective apparel are recommended. Sunscreen should be applied a minimum of 1 hour following study drug application.

Nonmedicated emollients may be used on skin; emollients should not be applied to skin on the morning of the clinic visits involving suction blistering (Day -10 and Day 43). The same emollient should be used throughout the subject's participation in the study.

Note: Any emollient used during the study must be recorded as a concomitant medication.

Subjects may apply camouflage makeup during the course of the study provided that application occurs 1 hour following study drug application.

5.6.2. Prohibited Medications and Nondrug Therapies

Medications and nondrug therapies that are prohibited throughout the study duration are as follows:

- **Biologic agents:** rituximab, ustekinumab, secukinumab, golimumab, ixekizumab, infliximab, adalimumab, alefacept, etanercept (list is not exclusive, contact Medical Monitor for questions)
- **Systemic treatments**: cyclosporin, interferon, methotrexate, apremilast, other systemic immunosuppressive or immunomodulating agents, Vitamin D3 and analogs, retinoids (e.g., acitretin, isotretinoin), or corticosteroids
- **UV light**: UV light therapy (including UVA, PUVA, NB UVB) or prolonged exposure to natural or artificial sources of UV radiation (e.g., phototherapy, tanning beds/booths, or therapeutic sunbathing); when prolonged exposure cannot be avoided, use of sunscreen products and protective apparel are recommended.
- **Topical treatments**: corticosteroids (with the exception of stable regimens of inhaled or nasal corticosteroids), immunomodulators, tacrolimus/pimecrolimus, Vitamin D derivatives (e.g., calcipotriene, calcipotriol), retinoids (e.g., tazarotene), or coal tar
- **Drugs known to alter photosensitivity or skin pigmentation**: antibiotics (such as tetracyclines), antifungals, or thiazide diuretics
- **Immunizations:** live, attenuated vaccines (inactivated or subunit vaccines are acceptable when required)
- **Other:** Any investigational drugs or investigational procedures

6. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and assessments are summarized in the Schedule of Assessments and in Section 7. Adherence to the study design requirements, including those specified in the Schedule of Assessments (Table 1) are essential and required for study conduct. Protocol waivers or exemptions are not allowed, except for immediate safety concerns.

6.1. Medical History, Demography, and Baseline Characteristics

6.1.1. Medical History

Medical history will be collected to ensure subjects are eligible for participation in the study (per inclusion [Section 4.2] and exclusion [Section 4.3] criteria).

Data collected will include year of vitiligo diagnosis, Fitzpatrick skin type, CV medical history and risk factors (including height, weight, blood pressure [BP], smoking history, medical conditions, and family history of premature CV and liver disease).

Information on Fitzpatrick skin type can be found in Appendix 1 .

6.1.2. Demographics

Demographic information collected will include age, sex, race, and ethnicity.

6.1.3. Baseline Characteristics

Single 12-lead ECGs will be obtained at the timepoints indicated in the Schedule of Assessments Table (Table 1) using an ECG machine that automatically calculates the heart rate (HR) and measures PR, QRS, QT, and QTcF intervals. Subjects should be in a supine or semi-recumbent position for at least 5 minutes before ECG is measured. The ECG should occur prior to safety and efficacy assessments.

6.2. Vitiligo Disease Assessments

6.2.1. Body Surface Area Affected

The assessment of the percent body surface area (%BSA) affected is an estimate of the percentage of total involved skin with vitiligo. For the purpose of clinical estimation, the total palmar surface of the investigator's palm (including fingers) may be assumed to be approximately equivalent to 1% BSA. The %BSA affected by vitiligo will be evaluated (from 0 to 100%). Details on calculation of approximate %BSA involvement in each subject (total and individual areas) are provided in Appendix 2. %BSA is a static assessment made without reference to previous scores.

Note: At screening the ≥1% BSA inclusion criteria must include a minimum of 1% BSA of active vitiligo lesions located in an area permissible for suction blister induction (i.e. exclusion of the face, hands, and feet).

6.2.2. [redacted]

[redacted]

6.2.3. Photography

A qualified investigational staff member will take photographs of a representative area of the subject's disease area at the timepoints specified in the Schedule of Assessments (Table 1; see also Section 7). Photographs of the selected skin area will be taken in a standardized manner (i.e., same camera, angle, background, and distance).

6.2.4. Optional Noninvasive Microscopy Imaging

Multiphoton microscopy (MPM) and reflectance confocal microscopy (RCM) in vivo imaging may be performed in a subgroup of subjects at the UC-Irvine study site. A separate informed consent and image release (permission) will be required.

MPM and RCM imaging will be utilized to image lesional and adjacent nonlesional skin at the time points specified in the Schedule of Assessments (Table 1; see also Section 7). Procedures for the noninvasive microscopy imaging will be contained in the UC-Irvine Study Reference Manual.

6.2.5. Suction Blister Induction and Blister Fluid and/or Roof Collection

Suction blister induction will be performed on Day -10 (prior to Baseline) and Day 43 on both lesional and nonlesional skin. Small vacuum pumps and controlled heat will be applied to a defined area to generate suction and the creation of small fluid filled blisters. The blisters will be no greater than 1 cm in diameter and no deeper than the epidermis (<1 mm deep). The relevant sites will be selected by the Principal Investigator and will include blistering areas induced

specifically over confetti, trichome, or inflammatory lesions. Lesional suction blisters will be positioned on the lesional edge and will incorporate lesional and perilesional skin to ensure capture of immune infiltrates. Nonlesional suction blisters sites will be positioned at least 5 cm from the nearest depigmented macule. Up to 10 blisters will be induced simultaneously. A negative pressure instrument consisting of a vacuum suction apparatus with plastic circular templates and heated chambers will be attached to the skin and gentle suction will be applied from a vacuum pump. This process will separate the epidermis from the dermis resulting in a skin blister after approximately 45 minutes. Using multiple vacuum chambers and standard plates with multiple openings, multiple blisters can be induced simultaneously within 45 to 60 minutes. The blister fluid accumulates cells and soluble molecules from a large area in the skin, can be analyzed using state-of-the-art technologies to identify immunological changes in lesional skin that result from treatment with study drug as compared to placebo treatment. After the formation of blisters, the blister fluid (epidermal fluid collecting under the stratum basale) will be extracted using a syringe. The blister roof will then be removed using sterile forceps and scissors. [redacted] Following the blister procedure, the site may be covered with petrolatum and a band-aid and allowed to heal prior to the Baseline (Day 1) visit and study drug application to the site. This approach is a less invasive method of assessing cells and performing other immunologic assays (CXCL9 and CXCL10) directly from lesional and nonlesional skin.

6.3. Safety Assessments

6.3.1. Adverse Events

All AEs will be collected from the time the subject signs the ICF until the final visit/contact with the subject. Additional safety information, including the definition of an AE and the methods for recording, evaluating, and assessing causality of AEs and the procedures for completing and transmitting SAE reports are provided in Section 8.

6.3.2. Brief Physical Exam

A brief physical examination will include, at a minimum, assessments of the CV, respiratory, gastrointestinal and neurological systems, and skin. Investigators should pay special attention to clinical signs related to previous serious illness.

6.3.3. Vital Signs

Vital signs will be measured before blood collection for clinical laboratory assessments and PK analysis (where applicable) and will include measurement of systolic and diastolic BP, HR, and body temperature. Subjects should be in a supine or semi-recumbent position for at least 5 minutes before vital signs measurement.

6.3.4. Clinical Safety Laboratory Assessments

All protocol-required laboratory assessments must be conducted in accordance with the protocol Schedule of Assessments (Table 1). Laboratory requisition forms must be completed, and samples must be clearly labeled with the subject number, protocol number, site/center number, and visit date. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

A list of clinical laboratory tests and parameters is provided in Table 4.

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or Baseline. If such values do not return to normal within a period judged reasonable by the Investigator, then the etiology should be identified, when possible, and the Sponsor notified.

Table 4: Laboratory Tests

Diagnostic Screening Tests		
• HBsAg • HCV antibody • Anti-HBc • TSH	• Pregnancy Tests: (serum at Screening and urine at other visits; WOCBP only) • FSH (as needed in women of non-childbearing only) • At the Investigator's discretion, subjects may be screened for alcohol and illicit drug use.	
Serum Chemistry		
• BUN • Creatinine • Glucose (fasting not required) • Sodium • Potassium • Chloride	• Total carbon dioxide • Calcium • AST • ALT • Alkaline phosphatase	• Uric acid • Total bilirubin (+fractionated if required) • Total protein • Albumin
Hematology		
• Platelet count • RBC count • WBC count (absolute) • Reticulocyte count (absolute or percentage) • Hemoglobin • Hematocrit	• RBC Indices: MCV MCH MCHC	• WBC Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Routine Urinalysis		
• Specific gravity • Microscopic examination (if blood or protein is abnormal)	• Dipstick: pH Glucose Protein Blood Ketones	

Abbreviations: ALT = alanine aminotransferase; Anti-HB c= anti-hepatitis B core antigen; AST = aspartate aminotransferase; BUN = blood urea nitrogen; FSH = follicle-stimulating hormone; HCV = hepatitis C virus; HBsAg = hepatitis B surface antigen; HIV = human immunodeficiency virus; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell(s); WBC = white blood cell(s); WOCBP = women of childbearing potential.

6.3.5. Local Tolerability Scale

At each specified study visit, the Investigator (or qualified evaluator) will assess the presence and overall degree of irritation at the application sites, according to the LTS (an example of the LTS is provided in Table 5). The score will ideally represent an 'average' across all application sites. To the fullest extent possible, the same Investigator (or designated evaluator) will perform all tolerability assessments for an individual participant throughout the study.

Table 5: Grading Scale for Local Tolerability

Score	Severity	Description
0	No irritation	No evidence of local irritation/intolerance
1	Mild	Minimal erythema and/or edema, slight glazed appearance
2	Moderate	Definite erythema and/or edema with peeling and/or cracking but does not require treatment modification
3	Severe (report as an AE)	Erythema, edema glazing with fissures, few vesicles or papules
4	Very Severe (report as an AE)	Strong reaction spreading beyond the treated area, bullous reaction, erosions

Abbreviations: AE=adverse event

6.4. Treatment of Study Drug Overdose

For this study, accidental or intentional oral ingestion of study drug will be considered an overdose. Ingestion of a 60-gram tube of cerdulatinib gel, 0.37% would result in an oral dose of 0.222 gram of DMVT-502.

The Sponsor does not recommend specific treatment for an overdose; however, in the event of an overdose, the Investigator (or treating physician) should do the following:

- Contact Medical Monitor to discuss the event;
- Closely monitor the subject for AEs/SAEs and laboratory abnormalities;
- Provide general symptomatic treatment as necessary;
- Document the quantity of the excess dose as well as the duration of the overdosing in the eCRF;
- If the Medical Monitor requests a plasma sample for PK analysis, then a blood sample for PK should be obtained within 2 days from the date of the last dose of study drug.

Decisions regarding dose interruptions or modifications following an overdose will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

6.5. Pharmacokinetics

Blood samples for PK analysis of DMVT-502 will be collected at time points indicated in the Schedule of Assessments (Table 1) and Section 7. The actual date and time of each blood sample collection will be recorded as well as the date and time of the last dose of study drug prior to sample collection. The area utilized for blood draws must be thoroughly cleaned prior to blood collection (using the approved cleaning protocol; see PK reference manual) to reduce the risk of contaminating blood samples with surface study drug. Collection, processing, storage, and shipping procedures will be provided.

Concentrations of DMVT-502 will be determined in plasma samples using a validated bioanalytical method. Raw data will be archived at the bioanalytical site.

7. TIMING OF ASSESSMENTS AND PROCEDURES

This section lists the assessments and procedures to be performed at scheduled time points during the study as outlined in the Schedule of Assessments (Table 1). Information on study assessments and procedures is provided in Section 6.

- Any change in timing or any addition of a time point(s) for any planned study assessment must be documented in a "Note to File," which is approved by the relevant Sponsor study team member and then archived in the study Sponsor and site study files; this will NOT constitute a protocol amendment.
- The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

NOTE: Assessments and procedures should be performed pre-dose on clinic visit days.

7.1. Visit 1; Screening Period (Up to 30 Days Prior to Day 1)

After the subject has signed the ICF, potential study subjects will undergo Screening procedures and assessments to confirm eligibility to participate in the study. Screening assessments will include the following:

- Serum pregnancy test (WOCBP only)
- ECG recording
- Medical history recording
- Demography recording
- Brief physical exam (including height and weight)
- Vital signs measurements
- Fitzpatrick Skin Scale Assessment
- %BSA affected calculation [redacted]
- [redacted]
- Blood sample collection for clinical laboratory tests (serum chemistry, hematology, diagnostic tests)
- Urinalysis
- AE recording (from the time the ICF is signed)
- Concomitant medication recording (from the time ICF is signed)

To determine subject eligibility at Screening, a single repeat of tests or procedures may be allowed at the discretion of the Investigator in consultation with the Medical Monitor.

7.2. Visit 2; Day -10

On Day -10, subjects will be reassessed to confirm continued eligibility to participate in the study. All subjects who continue to meet study eligibility criteria will receive suction blister induction. The following additional procedures and assessments will be performed at Visit 2:

- AE recording
- Concomitant medication recording
- %BSA affected calculation (performed before VASI)
- VASI
- Photography
- Noninvasive MPM and RCM microscopy imaging of lesional and nonlesional skin (optional; at UC-Irvine site only)
- Suction blister induction and blister fluid and/or roof collection (lesional and nonlesional skin)

7.3. Visit 3, Day 1 (Baseline)

On Day 1, subjects will be reassessed to confirm continued eligibility to participate in the study. All subjects who continue to meet study eligibility will be randomized to treatment.

The following additional procedures and assessments will be performed at Visit 3:

- Vital signs measurements
- Urine pregnancy test (WOCBP only)
- Blood and urine sample collection for clinical laboratory tests
- LTS scoring (pre-dose)
- Blood sample collection for PK analysis (pre-dose and 2 hours post-dose)
- AE recording
- Concomitant medication recording
- Paper diary dispensed (subjects will be instructed in how and when to complete diary)
- Dispense study drug
- Instruction on how to administer study drug
- Study drug administration under supervision

7.4. Day 8 (Phone Call)

The following procedures and assessments will be performed by phone call on Day 8:

- AE recording
- Concomitant medication recording
- Instruction on how to administer study drug

7.5. Visit 4; Day 15

The following procedures and assessments will be performed at Visit 4:

- Vital signs measurements

- AE recording
- Concomitant medication recording
- Urine pregnancy test (WOCBP only)
- Blood and urine sample collection for clinical laboratory tests
- Blood sample collection for PK analysis (pre-dose and 2 hours post-dose)
- LTS scoring
- [redacted]
- Collect and dispense study drug
- Collect and dispense subject diary
- Instruction on how to administer study drug
- Study drug administration under supervision

7.6. Visit 5; Day 29

The following procedures and assessments will be performed at Visit 5:

- Vital signs measurements
- AE recording
- Concomitant medication recording
- Urine pregnancy test (WOCBP only)
- Blood and urine sample collection for clinical laboratory tests
- Blood sample collection for PK analysis (pre-dose and 2 hours post-dose)
- LTS scoring
- [redacted]
- Collect and dispense study drug
- Collect and dispense subject diary
- Instruction on how to administer study drug
- Study drug administration under supervision

7.7. Visit 6; Day 43

The following procedures and assessments will be performed at Visit 6:

- Vital signs measurements
- ECG recording
- AE recording
- Concomitant medication recording
- Urine pregnancy test (WOCBP only)
- Blood and urine sample collection for clinical laboratory tests
- Blood sample collection for PK analysis (single sample)

- LTS scoring
- %BSA affected calculation ([redacted])
- [redacted]
- Photography
- Noninvasive MPM and RCM microscopy imaging of lesional and nonlesional skin (optional; at UC-Irvine site only)
- Suction blister induction and blister fluid and/or roof collection (lesional and nonlesional skin)
- Collect subject diary
- Collect study drug

7.8. Visit 7; Follow-up (4-7 Days After Day 43)/Early Termination

Follow-up/Early Termination assessments are as follows:

- Vital signs measurements
- Brief physical examination
- AE recording
- Concomitant medication recording
- Urine pregnancy test (WOCBP only)
- Blood and urine sample collection for clinical laboratory tests
- LTS scoring

8. SAFETY MONITORING AND REPORTING

8.1. Adverse Events, Treatment-Emergent Adverse Events, Serious Adverse Events, and Adverse Events of Special Interest

The Investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE, TEAE, SAE, or adverse event of special interest (AESI). At each visit/contact, subjects should be questioned in a general way so as not to introduce bias in detecting AEs, TEAEs, and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE and TEAE occurrence.

Investigators are not obligated to actively seek AEs, TEAEs, or SAEs in former study subjects. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study drug or study participation, the Investigator should promptly notify the Sponsor.

8.1.1. Definition of Adverse Events

An AE is any untoward medical occurrence in a subject temporally associated with the use of a study drug, whether considered causally related or not related to the study drug.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study drug.

Events meeting the definition of an AE **include**:

- Any abnormal laboratory test results (e.g., hematology, clinical chemistry) or other safety assessments (e.g., vital signs measurements), including those that worsen from Baseline, and felt to be clinically significant in the medical and scientific judgment of the Investigator;
- Exacerbation of a chronic or intermittent pre-existing condition (e.g., AD) including either an increase in frequency and/or intensity of the condition;

For skin-related AEs, it should be noted whether or not the event is in the area of active application of study drug, and/or if spreading beyond the application site.

- New conditions detected or diagnosed after study drug administration even though it may have been present prior to the start of the study;
- Signs, symptoms, or the clinical sequelae of a suspected interaction;
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication (overdose per se will not be reported as an AE/SAE);
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
- Evaluation of local tolerability at the site of topical application (e.g., burning/stinging, pruritus, and erythema).

Events that **do not** meet the definition of an AE include:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition;
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition;
- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital);
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

8.1.2. Definition of Treatment-Emergent Adverse Event

A TEAE is an AE that occurs following the first application of study drug.

8.1.3. Definition of Serious Adverse Event

If an event is not an AE per Section 8.1.1 or a TEAE per Section 8.1.2, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc.).

An SAE is any untoward medical occurrence that, at any dose:

- Results in death;
- Is life-threatening 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.
- Requires hospitalization or prolongation of existing hospitalization;
  - In general, signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.
- Results in disability/incapacity: a substantial disruption of a person's ability to conduct normal life functions;

This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma

(e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

- Results in a congenital anomaly/birth defect;
- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

8.1.4. Adverse Events of Special Interest

AEs that meet the following criteria will be considered AESIs:

- Subjects with AE of Grade 2 or greater severity in the System-Organ Classes of Blood and Lymphatic System Disorders (CTCAE v5.0, page 3) as well as Cardiac Disorders (CTCAE v5.0, page 5) and discontinue study drug
- Subjects who have scores on the LTS that result in an AE

For each AESI, a narrative may be written and included in the Clinical Study Report.

8.2. Classification of Adverse Events

8.2.1. Assigning Severity Rating for Adverse Events

8.2.1.1. Criteria for Determining Adverse Event Severity

The Investigator will make an assessment of the severity of each AE and SAE according to the CTCAE, v. 5.0, 2017. For terms not specified with the CTCAE, the criteria in Table 6 should be used to determine the grade severity.

Table 6: Criteria for Determining the Grade/Severity of Adverse Event Terms Not Specified by the National Cancer Institute Common Terminology Criteria for Adverse Events

Grade	Criteria
1	Mild; asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated
2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living[a]
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living[b]
4	Life-threatening consequences; urgent intervention indicated
5	Death related to AE

Abbreviation: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events
[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b] Self-care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

AE severity should be recorded in the appropriate section of the eCRF and in the subject's source documents.

8.2.1.2. Toxicity Management Criteria

8.2.1.2.1. Grade 1 or Grade 2 Adverse Event

Subjects who develop a Grade 1 or Grade 2 AE may continue study drug at the discretion of the Investigator. Subjects who choose to withdraw from study due to a Grade 1 or 2 AE should have early termination assessments completed as outlined in Section 7.8.

8.2.1.2.2. Grade 3 Adverse Event

Subjects who develop a Grade 3 AE should be managed as follows:

- If the Investigator has compelling evidence that the Grade 3 AE has not been caused by study drug, then dosing may continue after discussion with the Medical Monitor.
- Subjects who develop a Grade 3 AE that the Investigator considers related to study drug should have the study drug discontinued. Subjects experiencing Grade 3 AEs requiring permanent discontinuation of study drug should be followed weekly until resolution or stability of the AE and encouraged to have early termination assessments completed as outlined in Section 7.8.

8.2.1.2.3. Grade 4 Adverse Event

Subjects who develop a Grade 4 AE should have study drug permanently discontinued.

Subjects experiencing Grade 4 AEs requiring permanent discontinuation of study drug should be followed weekly until resolution or stability of the AE and encouraged to have early termination assessments completed as outlined in Section 7.8.

8.2.1.2.4. Other Management Criteria

The Medical Monitor should be notified if any of the following occur:

- Severe signs or symptoms, or significant changes in any of the safety assessments, that put the safety of the subject at risk (e.g., laboratory tests or vital signs, etc.) as judged by the Investigator.

8.2.2. Assigning Causal Relationship to Study Drug

The Investigator is to make the causality assessment. Causality assessment is not to be delegated; however, if delegation is unavoidable due to Investigator inaccessibility, this must be recorded as a protocol deviation. The reasonable possibility of the relationship of an AE to study

drug is to be assessed with careful medical consideration at the time of evaluation of an AE. The following definitions are to be used for the relationship of the AE to study drug:

- **Related**: A clinical event, including laboratory test abnormality, with a temporal relationship to study drug administration that makes a causal relationship plausible, unlikely attributed to concurrent disease or other drugs or chemicals, and that follows a clinically reasonable response on re-administration (rechallenge) or withdrawal (dechallenge), although information on drug withdrawal may be lacking or unclear.
- **Not related**: A clinical event, including laboratory test abnormality, with a temporal relationship to study drug administration that makes a causal relationship improbable and/or in which other drugs, chemicals, or underlying disease provide a plausible explanation.

Any AEs /SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to study drug will be recorded from the time a subject consented to participate in the study up to and including any follow-up contact.

All AEs, whether related to study drug or not, must be fully and completely documented on the AE page of the eCRF and in the subject's clinical record. In the event a subject is withdrawn from the study because of an AE, the primary reason for withdrawal (i.e., due to an AE) must be recorded on the eCRF as such.

8.3. Time Period and Frequency for Event Assessment and Follow-Up

8.3.1. Adverse Event and Serious Adverse Event Reporting

All AEs will be collected from the time of signed ICF until the final visit.

Any AEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) will be recorded from the time a subject consented to participate in the study up to and including any follow-up contact.

All SAEs will be recorded in the eCRF and reported to the Sponsor within 24 hours via email or phone (see Section 8.4).

8.3.2. Follow-Up of Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs and nonserious AEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.

The Investigator will assess the outcome of each AE using the following criteria:

- **Recovered/Resolved:** The event has improved or subject recuperated.
- **Recovered/Resolved with sequelae**: The subject has recuperated but retained pathological conditions resulting from the prior disease or injury.
- **Recovering/Resolving**: The event is improving.
- **Not recovered/Not resolved:** The event has not improved or subject recuperated.

- **Unknown**: The outcome of the event is not known, not observed, not recorded, or refused.
- **Fatal:** Termination of life as an outcome of the AE.

8.4. Reporting Procedures

8.4.1. Serious Adverse Event Reporting

When an Investigator determines that an AE meets the protocol definition of a SAE during the study, he/she must notify the Sponsor using an SAE Report Form **within 24 hours of the study site personnel's knowledge of the event**, regardless of the Investigator assessment of the relationship of the event to study drug. Relevant information will be entered on the AE page and on all other applicable pages of the eCRF; these pages will be submitted with the SAE Report Form.

Follow-up information received on SAEs should be emailed or faxed to the Sponsor within one business day of receipt. This information should be included on a follow-up SAE form and placed with the original SAE information.

All SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.

The completed SAE Report form should be submitted via email or fax to the SAE Reporting Contact which can be found on the Medical Monitor/Sponsor Information Page of this protocol.

Do not delay reporting a suspected SAE in order to obtain additional information. Any additional information, if collected, can be reported as a follow-up to the initial report.

8.4.2. Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of SAEs (even for non-interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will file it with the Investigator's Brochure and will notify the IRB/IEC, if appropriate, according to local requirements.

8.5. Pregnancy Management and Reporting

Any female subject who becomes pregnant during the study will be withdrawn. Details will be collected for all pregnancies in female subjects and female partners of male subjects that begin

after the start of dosing and through the Follow-up visit. Pregnancy is not automatically considered an AE.

If a pregnancy is reported, then the Investigator should complete a pregnancy data collection form and submit via email or fax to the Pregnancy Reporting Contact for which contact information can be found on the Medical Monitor/Sponsor Information Page of this protocol, within 2 weeks of learning of the pregnancy. The subject will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

Any SAE occurring in association with a pregnancy brought to the Investigator's attention after the subject has completed the study and considered by the Investigator as possibly related to the study drug must be promptly reported to the Sponsor or the Sponsor's representative.

The Investigator must attempt to collect pregnancy information on any female partners of male study subjects who become pregnant while the subject is enrolled in the study. Pregnancy information must be reported to the Sponsor or the Sponsor's representative as described above. The partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to Sponsor or the Sponsor's representative. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported on the pregnancy report form.

8.6. Safety Oversight

No independent Data Monitoring Committee will be used for this study; however, the Sponsor (including the Medical Monitor) will monitor safety on a periodic basis throughout the study.

9. DATA MANAGEMENT

For this study, subject data will be entered into the Sponsor defined eCRFs, transmitted electronically to the Sponsor or designee and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable Sponsor standards and data cleaning procedures will be used to ensure the integrity of the data, e.g., errors will be corrected, and inconsistencies queried in the data.

AEs and relevant medical history will be coded using the most current version of the MedDRA. Concomitant medications will be coded with the most current version of World Health Organization Drug Global Dictionary.

The Investigator will retain original source documents and the Sponsor will receive eCRF-required data as electronic datasets. Subject initials will not be collected or transmitted to the Sponsor.

10. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

This study will evaluate the safety, tolerability, and systemic exposure following treatment with cerdulatinib gel, 0.37% or vehicle gel in adults with vitiligo.

10.1. General Considerations

All study data will be summarized using descriptive statistics. Categorical variables will be reported using frequency and percentage (e.g., gender, race). Continuous variables will be reported using number of subjects, mean, standard deviation (SD), median, minimum, and maximum. All data will be listed by subject.

10.2. Determination of Sample Size

This study will be conducted to evaluate the safety and tolerability of cerdulatinib gel, 0.37% in adult subjects with vitiligo. There is no formal statistical hypothesis testing planned for the primary endpoints and the sample size is mainly based on feasibility and logistical considerations. A sample size of 30 randomized subjects is planned without replacement for early discontinuation.

10.3. Analysis Sets

10.3.1. Safety Analysis Set

All randomized subjects who receive at least 1 application of study drug will be included in the safety analysis set. Subjects will be analyzed as treated.

10.3.2. Efficacy Evaluable Analysis Set

The Efficacy Evaluable Analysis Set will consist of all subjects randomized to treatment who have used at least one application of study drug and who have both pre-treatment/baseline primary efficacy assessments and Week 6 efficacy assessments. This will be the primary population used for efficacy analyses.

10.3.3. PK Analysis Set

All subjects who have at least 1 application of study drug and have at least 1 evaluable PK assay result, even if the result is below the limit of quantification, will be included in the PK analysis set.

10.3.4. [redacted]

[redacted]

10.3.5. [redacted]

[redacted]

10.4. Planned Analyses

All measurements over the course of the study will be presented. Details of planned analyses will be described in the statistical analysis plan which will be finalized prior to database lock.

10.4.1. Disposition and Demographics

Demographic and Baseline characteristics as well as medical history will be summarized using the safety analysis set, including frequency and percentages for categorical variables and mean, SD, median, minimum, and maximum for continuous variables.

10.4.2. Safety Analyses

The safety analysis set will be used in the analysis of safety and tolerability data. Data will be listed by subject and summarized. No formal statistical comparisons will be made for safety data.

The number and proportion of subjects with TEAEs will be summarized by treatment, system organ class, and preferred term for all TEAEs, all TEAEs considered by the Investigator to be related to study drug, all SAEs, and all TEAEs leading to study drug discontinuation. All AE summaries will include information for TEAEs that occurred after administration of the first dose of study drug until completion of the final study visit. Data listings will be provided for subjects who discontinued the study due to an AE and for subjects with an SAE.

Selected laboratory and biomarker data will be analyzed using descriptive summary statistics and will be presented by study visit/time point, including the number of non-missing observations, mean and SD, median, upper and lower quartiles, minimum and maximum for values and changes from Baseline. Categorical safety data will be analyzed using frequency tables and, if applicable, shift tables.

Vital signs will be listed by subject and summarized by visit.

Scores from the LTS will be listed by subject and summarized by visit.

10.4.3. Pharmacokinetic Analysis

The PK analysis set will be used in the analysis of PK data. DMVT-502 plasma concentrations will be listed by subject and treatment; and will be summarized by treatment. The number and percent of subjects with a measurable concentration at each time point and any time during the study will be provided.

10.4.4. Efficacy Analyses

All efficacy analyses will be performed based on the Efficacy Evaluable analysis set.

%BSA Assessments

The percent change from baseline in the %BSA will be summarized by treatment group and visit. The mean and 95% confidence interval (CI) for percentage change from Baseline will be presented.

[redacted]

CXCL9 and CXCL10 Assessments

Chemokine quantitation is collected for both the lesional and nonlesional skin. The CXCL9 and CXCL10 results will be summarized for each type. The change from pre-treatment/baseline to Week 6 will be calculated for both the lesional and nonlesional skin.

[redacted]

11. RESPONSIBILITIES

11.1. Investigator Responsibilities

11.1.1. Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" (as amended in Edinburgh, Tokyo, Venice, Hong Kong, and South Africa), International Conference on Harmonization (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study subject. For studies conducted under a US Investigational New Drug Application, the Investigator will ensure that the basic principles of "Good Clinical Practice," as outlined in 21 Code of Federal Regulations (CFR) 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50, 1998, and 21 CFR, part 56, 1998, are adhered to. These standards are consistent with the requirements of the European Community Directive 2001/20/EC.

Since this is a "covered" clinical trial, the Investigator will ensure that 21 CFR, Part 54, 1998, is adhered to; a "covered" clinical trial is any "study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or US FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that Investigators and all sub-Investigators must provide documentation of their financial interest or arrangements with the Sponsor, or proprietary interests in the drug being studied. This documentation must be provided before participation of the Investigator and any sub-Investigator. The Investigator and sub-Investigator agree to notify the Sponsor of any change of reportable interests during the study and for one year following completion of the study. Study completion is defined as the date that the last subject has completed the protocol-defined activities.

11.1.2. Institutional Review Board/Independent Ethics Committee Approval

This protocol and any accompanying material to be provided to the subject (such as advertisements, subject information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the Investigator to an IRB or IEC. Approval from the IRB or IEC must be obtained before starting the study and should be documented in a letter to the Investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval.

Any modifications made to the protocol after receipt of IRB or IEC approval must also be submitted to the IRB or IEC for approval before implementation.

11.1.3. Informed Consent/Assent

The Investigator is responsible for obtaining written informed consent/assent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The Investigator must utilize an IRB- or IEC-approved ICF for documenting written informed

consent. Each informed consent/assent will be appropriately signed and dated by the subject or the subject's legally authorized representative and the person obtaining consent.

11.1.4. Confidentiality

The Investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only subject number, date of birth, and an identification code (i.e., not names) should be recorded on any form or biological sample submitted to the Sponsor, IRB or IEC, or laboratory. The Investigator must keep a Screening log showing codes, names, and addresses for all subjects screened and for all subjects enrolled in the trial.

The Investigator agrees that all information received from the Sponsor, including but not limited to the Investigator's Brochure, this protocol, eCRFs, the investigational new drug, and any other study information, remain the sole and exclusive property of the Sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the Sponsor. The Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

11.1.5. Study Files and Retention of Records

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories: 1) Investigator's study file, and 2) subject clinical source documents.

The Investigator's study file will contain the protocol/amendments, eCRF and query forms, IRB or IEC and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

The required source data should include at least the following information for each subject:

- Subject identification (name, date of birth, gender);
- Documentation that subject meets eligibility criteria, i.e., history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria);
- Participation in trial (including trial number);
- Trial discussed and date of informed consent;
- Dates of all visits;
- Documentation that protocol-specific procedures were performed;
- Results of efficacy parameters, as required by the protocol;
- Start and end dates (including dose regimen) of study drug (preferably drug dispensing and return should be documented as well);
- Record of all AEs and other safety parameters (start and end date, and preferably including causality and intensity);

- Concomitant medication (including start and end dates, dose if relevant; dose changes should be motivated);
- Date of trial completion and reason for early discontinuation, if applicable.

All clinical study documents must be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region (i.e., US, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. Investigators may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with the Sponsor. The Investigator must notify the Sponsor before destroying any clinical study records.

Should the Investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified in advance.

If the Investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the Investigator and the Sponsor to store these in sealed containers outside of the site so that they can be returned sealed to the Investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies should be made for storage outside of the site.

Biological samples at the conclusion of this study may be retained in storage by the Sponsor for a period up to 10 years for purposes of this study.

11.1.6. Electronic Case Report Forms

For each subject enrolled, an eCRF must be completed and signed by the Investigator or sub-Investigator (as appropriate). This also applies to records for those subjects who fail to complete the study. If a subject withdraws from the study, the reason must be noted on the eCRF. If a subject is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

11.1.7. Drug Accountability

The Investigator or designee (i.e., pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study drug (quantity and condition), subject dispensing records, and returned or destroyed study drug. Dispensing records will document quantities received from the Sponsor and quantities dispensed to subjects, including lot number, date dispensed, subject identifier number, and the initials of the person dispensing the study drug.

At study initiation, the monitor will evaluate the site's procedure for study drug disposal/destruction in order to ensure that it complies with the Sponsor requirements. At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the site cannot meet the Sponsor's requirements for disposal, arrangements will be made between the site and the Sponsor or its representative for destruction or return of unused study drug supplies.

All study drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

11.1.8. Inspections

The Investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Sponsor or its representatives, to IRBs or IECs, or to regulatory authority or health authority inspectors.

11.1.9. Protocol Compliance

The Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

11.2. Sponsor Responsibilities

11.2.1. Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study subjects, may be made only by the Sponsor. All protocol modifications must be submitted to the IRB or IEC and regulatory authorities in accordance with local requirements. Approval must be obtained before changes can be implemented.

11.2.2. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency(ies). The Sponsor will ensure that the report meets the standards set out in the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3). Note that an abbreviated report may be prepared in certain cases.

After conclusion of the study and without prior written approval from Dermavant, Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media only after the following conditions have been met:

- the results of the study in their entirety have been publicly disclosed by or with the consent of Dermavant in an abstract, manuscript, or presentation form; OR
- the study has been completed at all study sites for at least 5 years.

No such communication, presentation, or publication will include Dermavant confidential information (see Section 11.1.4).

The Investigator will submit any proposed publication or presentation along with the respective scientific journal or presentation forum at least 30 days before submission of the publication or presentation. The Investigator will comply with Dermavant request to delete references to its confidential information (other than the study results) in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection if deemed necessary.

11.2.3. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins. Results will be posted as required.

11.3. Joint Investigator/Sponsor Responsibilities

11.3.1. Access to Information for Monitoring

In accordance with ICH Good Clinical Practice guidelines, the study monitor must have direct access to the Investigator's source documentation in order to verify the data recorded in the eCRFs for consistency.

The monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any subject records needed to verify the entries on the eCRFs. The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

11.3.2. Access to Information for Auditing or Inspections

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, Dermavant may conduct a quality assurance audit.

Authorized representatives of Dermavant, a regulatory authority, an IEC or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a Dermavant audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the ICH, and any applicable regulatory requirements. The Investigator should contact Dermavant immediately if contacted by a regulatory agency about an inspection.

11.3.3. Study Discontinuation

The Sponsor reserves the right to terminate the study at any time. Should this be necessary, the Sponsor will arrange discontinuation procedures and notify the appropriate regulatory authority(ies), IRBs, and IECs. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the subjects' interests.

12. REFERENCES

Cerdulatinib Investigator's Brochure, Version 3, June 2019.

Ezzedine K, Silverberg N. A practical approach to the diagnosis and treatment of vitiligo in children. PEDIATRICS. 2016; 138(1):e20154126.

Hamzavi I, Jain H, McLean D, Shapiro J, Zeng H, Lui H. Parametric modeling of narrowband UV-B phototherapy for vitiligo using a quantitative tool. Arch Dermatol. 2004; 140:677-683.

Marinho FS, Cirino PV, Fernandes NC. Clinical epidemiological profile of vitiligo in children and adolescents. An Bras Dermatol. 2013; 88(6):1026-8.

Rodrigues M, Ezzedine K, Hamzavi I, Pandya A, Harris JE. New discoveries in the pathogenesis and classification of vitiligo. JAAD. 2017; 77:1-13.

APPENDICES

APPENDIX 1. FITZPATRICK SKIN TYPE SCALE

Skin Type	Sunburn Tendency	Suntan Tendency
Type I	**Always burns easily**	**Never Tan**
Type II	**Always burns easily**	**Tans slightly**
Type III	**Burns moderately**	**Tans gradually**
Type IV	**Burns minimally**	**Tans moderately**
Type V	**Rarely burns**	**Tans profusely**
Type VI	**Never burns**	**Tans profusely**

APPENDIX 2. CALCULATION OF TOTAL PERCENT BODY SURFACE AREA AFFECTED

The total %BSA affected will be calculated using the following regional body areas:

- Head and neck
- Trunk, includes internal axillae and groin
- Upper extremities, includes arms, external axillae, and hands
- Lower extremities, includes legs, buttocks, and feet

Note: At screening the ≥0.5% BSA inclusion criteria must include a minimum of 0.5% BSA of active vitiligo lesions located in an area permissible for suction blister induction. Subjects with >30% BSA involvement must only treat ≤30% BSA with study drug. Areas to be treated should be pre-identified by study staff and subject at Baseline (Day 1) visit and only the identified areas should be treated consistently for the duration of the study.

Complete the %BSA assessment before the [redacted]

Calculation of Total %BSA Affected:

Measurement of involved BSA is estimated by the handprint method: the total palmar surface of the investigator's palm and digits is approximately1% of their total BSA.

Estimate the involved regional area by determining the number of "full" handprints plus the number of handprints covered if several smaller lesions are "pushed together." Each region can have up to 100% involvement.

- Head and neck = 10% of overall BSA (10 handprints);
  1 hand-sized patch ~ 10% of head and neck area
- Upper extremities = 20% of overall BSA (20 handprints);
  1 hand-sized patch ~ 5% of the upper extremities
- Trunk (including axillae and groin) = 30% of overall BSA (30 handprints);
  1 hand-sized patch ~ 3.33% of the trunk
- Lower extremities (including buttocks) = 40% of overall BSA (40 handprints);
  1 hand-sized patch ~ 2.5% of the lower extremities

Estimates of the % involvement in each body region will be multiplied by the fraction of total body area to obtain the total %BSA involved by region and overall.

Body Region	% Involvement for Each Region (0-100%)	Multiplier	Regional %BSA Involvement
Head and neck		x 0.1	=
Arms / upper extremities		x 0.2	=
Trunk		x 0.3	=
Legs / lower extremities		x 0.4	=
TOTAL Involved %BSA – sum of the 4 regional values (0-100%)			=

Note: Shaded cells are either fixed values or will be calculated in the eCRF. Multiplier is a fixed number representing fraction of total body area.

APPENDIX 3. [redacted]

[redacted]

[redacted]

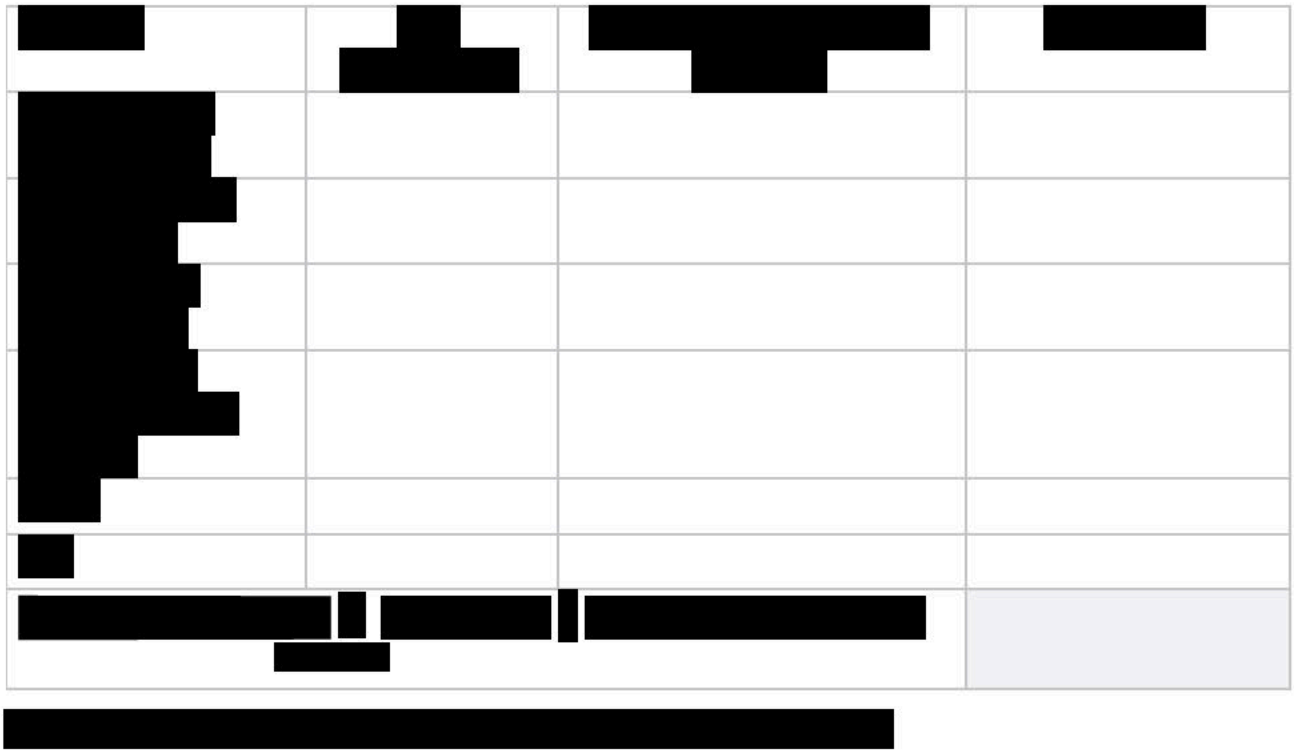
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



APPENDIX 4. PROTOCOL AMENDMENT SUMMARY OF CHANGES

The protocol has been updated with the following changes. Minor grammatical corrections and edits were made throughout the document. Edits to the protocol are shown in **bold.** The protocol synopsis and Schedules of Assessments were updated to reflect the changes below.

Section 2. Objectives and Endpoints

[redacted]

Exploratory Objective:

- [redacted]

Exploratory Endpoint:

- [redacted]

Section 3.1 Overall design

Figure 1: The study diagram has been updated to reflect the changes to the inclusion criteria.

Section 4.2 Inclusion Criteria #1

Expanded inclusion criteria to include all subjects 18 years and older. Male and female subjects ages 18 **years and older** with confirmed clinical diagnosis of nonsegmental vitiligo.

Section 4.2 Inclusion Criteria #3

Reduced % body surface involvement to a minimum of 0.5% and clarified that hands, feet, and face may be included in % BSA involvement provided that these sites are suitable for suction blister induction.

Vitiligo with depigmented areas, containing normal appearing pigmented hair (hair-baring lesions display less than 30% leukotrichia [white hair]), including ≥**0.5%** body surface area (BSA) involvement (e.g., 1% BSA is approximately equal to the area of 1 of the Investigator's handprints [palm plus 5 digits]).

a. Active vitiligo lesions must encompass ≥**0.5**% BSA at body sites appropriate for suction blister induction.

b. Subjects with >30% BSA involvement must only treat ≤30% BSA with study drug. Areas to be treated should be pre-identified by study staff and subject at the Baseline visit (Day 1) and only the identified areas should be consistently treated for the duration of study.

Section 4.2 Inclusion Criteria #1

Removed inclusion criteria requiring venous access for blood draws on an area that is devoid of vitiligo. A cleaning procedure has been included in Section 6.5 Pharmacokinetics to be

performed prior to all blood draws. Numbering of the inclusion criteria remains to maintain consistency with CRF.

Section 4.2 Exclusion Criteria #3

Added clarifying wording regarding adequately controlled herpes skin infections.

3. Concurrent conditions or history of other diseases:

   e. Acute active bacterial, fungal, or viral (herpes simplex, herpes zoster, or chicken pox) skin infection within 1 week prior to the Baseline visit **with the exception of herpes labialis or genital herpes infections that are adequately controlled by suppressive therapy as long as the HSV infection site does not coincide with a study drug application site;**

Section 4.3 Exclusion Criteria #8

Added clarifying wording regarding liver disease.

Subjects with a history of stable non-alcoholic fatty liver disease without evidence of active inflammation (elevated ALT/AST≥1.5x ULN) or cirrhosis are eligible to enroll;

Section 5.1.5 Administration of Study Drug

Added wording for pre-identification of areas to be treated if a subject has >30% BSA involvement.

If a subject has >30% BSA involvement, the study staff and subject should pre-identify areas to be treated that are limited to ≤ 30% BSA at the Baseline visit (Day 1). Only these same identified areas should be treated consistently for the duration of the study.

Section 5.4 Compliance with Study Drug Administration

Added wording for pre-identification of areas to be treated if a subject has >30% BSA involvement.

Study staff will identify areas to be treated in subjects with >30% BSA involvement. Study staff will instruct subjects with >30% BSA involvement to treat only these pre-identified areas with study drug for the duration of the study.

Section 6.2.4 Optional Noninvasive Microscopy Imaging

Added to optional analysis to Schedule of Assessments (Table 1) and included Section 6.2.4 detailing this analysis: **Multiphoton microscopy (MPM) and reflectance confocal microscopy (RCM) in vivo imaging may be performed in a subgroup of subjects at the UC-Irvine study site. Separate informed consent and image release (permission) will be required.**

MPM and RCM imaging will be utilized to image lesional and adjacent nonlesional skin at the time points specified in the Schedule of Assessments (Table 1; see also Section 7). Procedures for the noninvasive microscopy imaging will be contained in the UC-Irvine Study Reference Manual.

[redacted]

[redacted]

Section 6.3.4 Clinical Safety Laboratory Assessments

Added **TSH** to diagnostic screening labs presented in Table 4.

Section 6.5 Pharmacokinetics

Added clarifying wording to include the procedure for cleaning the blood draw area prior to blood collection.

The area utilized for blood draws must be thoroughly cleaned prior to blood collection (using the approved cleaning protocol; see PK reference manual) to reduce the risk of contaminating blood samples with surface study drug.

Section 7.2, Visit 2; Day -10

Added clarification wording: "suction blister induction and blister fluid **and/or roof** collection (lesional and nonlesional skin)"

Addition of optional efficacy assessments. **Noninvasive Imaging (MPM and RCM) of lesional and nonlesional skin** added at Visit 2.

Section 7.7, Visit 6; Day 43

Addition of optional efficacy assessments. **Noninvasive Imaging (MPM and RCM) of lesional and nonlesional skin** added at Day 43 visit.

Added clarification wording: "suction blister induction and blister fluid **and/or roof** collection (lesional and nonlesional skin)"

Secction 10.2 Determination of Sample Size

Added clarification wording regarding sample size.

This study will be conducted to evaluate the safety and tolerability of cerdulatinib gel, 0.37% in adult subjects with vitiligo. There is no formal statistical hypothesis **testing** planned for the primary endpoints and the sample size is mainly based on feasibility and logistical considerations. **A sample size of 30 randomized subjects is planned without replacement for early discontinuation.**

Section 10.3.5. [redacted]

[redacted]

Section 10.4.4 Efficacy Analyses

[redacted]

Appendix 2. Calculation of Total Body Service Area Affected

Updated the note to reflect the change in BSA inclusion criteria at screening:

Note: At screening the ≥**0.5%** BSA inclusion criteria must include a minimum of **0.5%** BSA of active vitiligo lesions located in an area permissible for suction blister induction. Subjects with >30% BSA involvement must only treat ≤30% BSA with study drug. Areas to be treated should be pre-identified by study staff and subject at Baseline (Day 1) visit and only the identified areas should be treated consistently for the duration of the study.