Protocol ARQ-252-213

A Phase 2a, Proof of Concept, 24-Week, Parallel Group, Double Blind, Vehicle-Controlled Study of the Safety and Efficacy of ARQ-252 Cream 0.3% in Subjects with Non-Segmental Facial Vitiligo

Sponsor:	Arcutis Biotherapeutics, Inc. [redacted]
Sponsor Representative:	[redacted]
IND Number:	140409
Protocol Version:	Amendment 1 (US)
Date:	14 April 2021

GCP Statement

This study is to be performed in full compliance with the protocol, International Conference on Harmonisation Good Clinical Practices (ICH GCP), and applicable regulatory requirements. All required study documentation will be archived as required by regulatory authorities.

Confidentiality Statement

SITE INVESTIGATOR SIGNATURE PAGE

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SPONSOR: Arcutis Biotherapeutics, Inc.
[redacted]

ISSUE DATE: 14 April 2021

I have read this protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein, in accordance with the current International Conference on Harmonisation Good Clinical Practices (ICH GCPs) and applicable local and regional regulations.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Arcutis Biotherapeutics, Inc.. I will discuss the material with them to ensure that they are fully informed about ARQ-252 Cream 0.3% and the study.

I agree that I or my designee will completely inform all subjects in this study concerning the pertinent details and purpose of the study prior to their agreement to participate in the study in accordance with cGCPs and regulatory authority requirements. I will be responsible for maintaining each subject's consent form in the study file and providing each subject with a signed copy of the consent form.

I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Investigational Site Name: _____

Print Investigator Name: _____

Investigator Signature: _____ Date: _____

SUMMARY OF CHANGES

The following sections have been changed in Amendment 1 (US) of the ARQ-252-213 protocol:

Section	Summary of Changes
1.3 Schedule of Visits and Assessments	Added BSA (Full Body) and T-VASI to Screening Visit Added subject weight assessment at the Screening Visit. Removed Compliance Calculation from Baseline Visit Clarified Footnote q to indicate a subject will be issued a new USB stick at each visit during the treatment period to obtain data from the Phototherapy Unit.
4.5.1 Inclusion Criteria	Updated inclusion criterion for age and Fitzpatrick Skin Type
4.5.2 Exclusion Criteria	Added exclusion criteria for subjects ages 18-21 years with first degree family members (parents, children, and/or siblings) who have a history of melanoma.
4.10.2 Treatment Administration	Added statement that subjects will be instructed to treat any new lesions that appear in the treatment areas during the treatment period. Added requirement for subjects 18-21 years of age with pigmented lesions in the treatment field to cover pigmented lesions to prevent NB-UVB exposure.
5.1 Safety Assessments	Added safety assessments to include monitoring of the reactivation of herpes simplex virus or varicella zoster virus and changes in the nails following the initiation of phototherapy treatment.
Figure 1: Contraception Requirements for Female Subjects	Added Bilateral tubal occlusion as a Highly Effective Method of contraception.
5.7.1 Adverse Event Definition	Added definition of an AE to include worsening of a pre-existing medical condition.
5.7.4. Safety Review with Subject	Updated safety review to classify outcome based on current standards (defined in eCRF completion guideline).
5.7.5 Adverse Event Reporting	Updated the classification of the event outcome based on current standard (define in eCRF completion guideline).

Section	Summary of Changes
5.9 Treatment Stopping Rules	Updated to include stopping rule by the Investigator rating of the dermal response.
5.9 Treatment Stopping Rules	Clarified discontinuation for treatment-emergent severe (Grade 3) laboratory abnormality.
6.0 Statistical Methods	Removed Interim Analysis
Appendix 1: Vitiligo NB-UVB Treatment Protocol	[redacted]
Editorial changes made throughout to improve accuracy or readability	

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ACR20	American College of Rheumatology 20
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BID	Twice Daily (bis in die)
BSA	Body Surface Area
C_{max}	Maximum Concentration
Cm	Centimeter
CNS	Central Nervous System
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CXCL	C-X-C Motif Chemokine Ligand
DMARD	Disease Modifying Anti-Rheumatic Drug
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
FsIGA	Facial Static Investigator or Global Assessment
F-BSA	Facial Body Surface Area
FDA	Food and Drug Administration
F-VASI	Facial Vitiligo Area Scoring Index
F/N-VASI	Face/Neck Vitiligo Area Scoring Index
F/N-BSA	Face and Neck Body Surface Area
FOCBP	Female of Child-bearing Potential
GCP	Good Clinical Practices
HDL	High-density Lipoprotein
HECSI	Hand Eczema Severity Index
HGB	Hemoglobin
Hr	Hour
IB	Investigational Brochure
ICF	Informed Consent Form

Abbreviation	Definition
ICH	International Conference on Harmonisation
ID	Identification
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent to Treat
JAK	Janus Kinase
Kg	Kilogram
LDL	Low-density Lipoprotein
µg	Microgram
MAD	Multiple Ascending Dose
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
Min	Minute
mJ	Millijoule
MKTP	Melanocyte-keratinocyte transplantation procedure
mL	Milliliter
MTX	Methotrexate
NB-UVB	Narrowband Ultraviolet B
NCI	National Cancer Institute
NIH	National Institutes of Health
Ng	Nanogram
NOAEL	No Observed Adverse Effect Level
P-450	Cytochrome P450
PaGIC-V	Patient Global Impression of Change-Vitiligo
PDE-4	Phosphodiesterase 4
PI	Principal Investigator
PK	Pharmacokinetics
PUVA	Psoralen Ultraviolet A
QD	Once Daily ("quaque die")

Abbreviation	Definition
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SUSAR	Suspected Unexpected Serious Adverse Reaction
T4	Thyroxine
TCPS	Tri-Council Policy Statement
TEAE	Treatment Emergent Adverse Event
T_{max}	Time to Reach Maximum Concentration
TSH	Thyroid Stimulating Hormone
US	United States
VASI	Vitiligo Area Scoring Index
VitiQoL	Vitiligo-Specific Quality of Life Instrument
VNS	Vitiligo Noticeability Scale
WBC	White Blood Cell

1. PROTOCOL SUMMARY

1.1. Synopsis

Name of Sponsor/Company: Arcutis Biotherapeutics, Inc.		
Protocol Number: ARQ-252-213	**Phase:** 2a	**Country:** US and Canada
Title of Study: A Phase 2a, Proof of Concept, 24-Week, Parallel Group, Double Blind, Vehicle-Controlled Study of the Safety and Efficacy of ARQ-252 Cream 0.3% in Subjects with Non-Segmental Facial Vitiligo		
Clinical Indication: Vitiligo		
Number of Sites: Approximately 50		
Number of Subjects (planned): Approximately 500		
Objectives: **Primary:** The purpose of this study is to assess the safety and efficacy of ARQ-252 cream 0.3% BID vs vehicle cream BID, with and without NB-UVB phototherapy treatment in individuals with non-segmental facial vitiligo. **Secondary:** To assess other efficacy measures of ARQ-252 cream 0.3% BID with and without NB-UVB phototherapy treatment in subjects with non-segmental vitiligo on the face, in addition to vitiligo on the neck, hands, forearms, and elbows.		
Study Population: Subjects will be male and female adults (≥18 y/o) with non-segmental facial vitiligo. Subjects can have vitiligo in other areas of the body, however the areas to be treated in the study will only include the face, neck, hands, forearms, and elbows. At least 30% of subjects will have active vitiligo as defined as new or expanding vitiligo lesions with or without the presence of confetti, trichrome, or inflammatory vitiligo lesion patterns or other clinical signs of active vitiligo in the past 3 months. At least 65% of subjects will have treatable non-facial vitiligo on the hands, forearms, and elbows. Subjects will have Facial Body Surface Area (BSA) ≥ 0.25% and F-VASI ≥ 0.25. The maximum BSA (total body inclusive of the face, whether or not in areas to be treated in this study) is 15%. At least 50% of subjects will have Fitzpatrick skin type IV-VI.		

Name of Investigational Product: ARQ-252 cream will be supplied as ARQ-252 cream 0.3%. Matching vehicle cream will contain only excipients of ARQ-252 cream.

The study will also include the following devices:

- [redacted] NB-UVB Home Phototherapy Unit – Active Units
- [redacted] NB-UVB Home Phototherapy Unit – Sham Units

Name of Active Ingredient: The active ingredient in ARQ-252 cream is SHR0302, a selective JAK1 inhibitor.

Duration of Treatment: The total duration for subjects on study includes up to 5 weeks in screening, 24 weeks of treatment with ARQ-252 cream 0.3% or matching vehicle cream plus phototherapy/sham phototherapy and 1 week post-treatment follow-up for a total of 30 weeks.

Endpoints:

Primary:

The primary efficacy endpoint is:

- Proportion of subjects achieving F-VASI75 (≥ 75% improvement from baseline in Facial Vitiligo Area Scoring Index (F-VASI) score) at Week 24.

Secondary:

The secondary endpoints will include:

- Proportion of subjects achieving F-VASI75 (≥ 75% improvement from baseline in F-VASI score) at visits prior to Week 24.
- Percent change from baseline in F-VASI score at all visits.
- Percent change from baseline in facial body surface area (F-BSA) at all visits.
- Proportion of subjects achieving F-VASI50 (≥ 50% improvement from baseline in F-VASI score) at all visits.
- Proportion of subjects achieving F-VASI90 (≥ 90% improvement from baseline in F-VASI score) at all visits.
- Proportion of subjects in each category of VNS at specified visits.
- Change from Baseline in the VNS at specified visits.
- Change from Baseline in the VitiQoL at specified visits.
- Patient Global Impression of Change-Vitiligo (PaGIC-V), proportion of patients in each PaGIC-V category at specified visits.
- Proportion of subjects who report PaGIC-V of very much improved or much improved during the treatment period.

- Time to achieve F-VASI50.
- Time to achieve F-VASI75.
- Time to achieve FsIGA of clear or almost clear (0 or 1).
- FsIGA of clear or almost clear (0 or 1).
- FsIGA of clear or almost clear (0 or 1) plus 2-grade improvement from baseline.
- Time to achieve a PaGIC-V of very much improved or much improved.

Exploratory:

The exploratory endpoints will include:

- Percent change from baseline in combined face and neck body surface area (F/N-BSA) at all visits.
- Percent change from baseline in surface area BSA (hands/forearms/elbows) at all visits.
- Percent change from baseline in BSA affected across all treatable sites (face, neck, hands, forearms, elbows) at all visits.
- Proportion of subjects achieving F/N-VASI50 (≥ 50% improvement from baseline in F/N-VASI score) at all visits.
- Proportion of subjects achieving F/N-VASI75 (≥ 75% improvement from baseline in F/N-VASI score) at all visits.
- Proportion of subjects achieving F/N-VASI90 (≥ 90% improvement from baseline in F/N-VASI score) at all visits.
- Percent change from baseline in FOREARM-VASI (forearms/elbows) score at all visits.
- Percent change from baseline in HAND-VASI (hands only) score at all visits.
- Serum levels of ARQ-252.
- The proportions of subjects who maintain 80% treatment compliance with both application of ARQ-252 cream 0.3% or vehicle cream and phototherapy or sham phototherapy up through 24 weeks.

Study Design:

ARQ-252-213 is a Phase 2a, Proof of Concept, 24-week, parallel group, double blind, vehicle-controlled study of the safety and efficacy of ARQ-252 cream 0.3% in subjects with non-segmental facial vitiligo. Subjects with facial vitiligo will apply either ARQ-252 0.3% cream BID or vehicle cream BID for 24 weeks to all affected areas of vitiligo on the face, neck, hands, forearms, and elbows (extending 3 cm from the border of the affected area), but not vitiligo elsewhere.

Subjects will be randomized to a blinded treatment group including the [redacted] Home Phototherapy Unit (NB-UVB) active unit or a sham unit to expose the entire face and areas affected on the neck, hands, forearms, and elbows for up to 3 times per week per a standardized phototherapy protocol.

Methodology:

The randomization scheme will be 3:3:3:1 to the following 4 treatment groups:

- Approximately 150 subjects will receive ARQ-252 cream 0.3% BID with phototherapy.
- Approximately 150 subjects will receive ARQ-252 cream 0.3% BID with sham phototherapy.
- Approximately 150 subjects will receive matching vehicle cream BID with phototherapy
- Approximately 50 subjects will receive matching vehicle cream BID with sham phototherapy

The primary comparisons will be performed at the 5% significance level and will include:

- ARQ-252 cream 0.3% in combination with phototherapy vs. vehicle cream in combination with phototherapy
- ARQ-252 cream 0.3% in combination with phototherapy vs. ARQ-252 cream 0.3% in combination with sham phototherapy

Sample Size Justification:

The primary statistical comparisons will be to compare

- ARQ-252 cream 0.3% in combination with phototherapy vs. vehicle cream in combination with phototherapy
- ARQ-252 cream 0.3% in combination with phototherapy vs. ARQ-252 cream 0.3% in combination with sham phototherapy at the 5% significance level.

A sample size of 500 subjects will provide approximately 84% power to detect an ARQ-252 cream 0.3% in combination with phototherapy response rate of at least 50% vs. a vehicle cream in combination with phototherapy response rate of 30%, and approximately 84% power

to detect an ARQ-252 cream 0.3% in combination with phototherapy rate of at least 50% vs. an ARQ-252 cream 0.3% in combination with sham phototherapy rate of 30% using a stratified Cochran-Mantel-Haenszel test conducted at the 0.025 alpha level for each comparison.

A drop-out rate of 15% (at 24 weeks) is assumed.

Upon successful testing for the comparisons above, a hierarchical testing scheme will be used to test the following secondary comparisons:

- ARQ-252 cream 0.3% in combination with phototherapy vs. vehicle cream BID in combination with the sham phototherapy
- ARQ-252 cream 0.3% in combination with sham phototherapy vs. vehicle cream BID in combination with the sham phototherapy
- Vehicle cream BID in combination with phototherapy vs. vehicle cream BID in combination with the sham phototherapy

Assuming a vehicle cream BID in combination with the sham phototherapy rate of no more than 5%, these comparisons are expected to have at least 74% power. These comparisons will be made at either the 0.025 or 0.05 level, depending on the outcome of the primary statistical comparisons.

Main Criteria for Inclusion:

1. Subject is legally competent to sign and give informed consent.
2. Males and females ages 18-21 years with Fitzpatrick Skin Type IV-VI or age 22 years and older with Fitzpatrick Skin Type I-VI.
3. Clinical diagnosis of non-segmental vitiligo involving face.
4. A Facial Vitiligo Area Severity Index [F-VASI] score of ≥ 0.25 at baseline.
5. Vitiligo of the face involving at least ≥ 0.25% body surface area (BSA) involvement (ie, one quarter of one handprint). Subjects may have non-facial vitiligo elsewhere which will not be included in the minimum BSA. The maximum BSA (total body inclusive of the face, whether or not in areas to be treated in this study) permitted is 15%.
6. Subjects with vitiligo on the hands, forearms, or elbows agree to treat these areas in addition to the face, with investigational product and phototherapy.
7. Subject agrees to discontinue all agents used to treat vitiligo from screening through the final safety follow-up visit. Over-the-counter preparations deemed acceptable by the Investigator and camouflage makeups are permitted.
8. Female subject of childbearing potential (FOCBP) must have a negative serum pregnancy test at Screening and negative urine pregnancy test at Baseline (Visit 2). For FOCBP involved in any sexual intercourse that could lead to pregnancy: the subject must agree to use a highly effective contraceptive method for at least 4 weeks

prior to Day 1. Additionally, from Day 1 until at least 4 weeks after the last investigational product administration, these subjects must agree to use at least 1 highly effective contraceptive method in addition to 1 barrier method. Figure 1

9. Female subject of non-childbearing potential must either be post-menopausal with spontaneous amenorrhea for at least 12 months prior to baseline (post-menopausal status will be confirmed with FSH testing) or have undergone surgical sterilization (permanent sterilization methods include hysterectomy, bilateral oophorectomy, or bilateral salpingectomy). Figure 1
10. Males, if engaging in sexual intercourse with a female who is pregnant or a female of child-bearing potential, must agree to use a condom every time during the study and every time subsequently until 4 weeks beyond the last dose of investigational product.
11. Males must agree not to donate sperm from the first dose of investigational product until 4 weeks after the last dose of investigational product.
12. Subject is in good health as judged by the Investigator, based on medical history, physical examination, 12-lead electrocardiogram (ECG), serum chemistry labs, hematology values, and urinalysis.

Main Criteria for Exclusion:

1. Males and females ages 18-21 years with first degree family members (parents, children, and/or siblings) who have a history of melanoma.
2. Subjects with any serious medical condition or clinically significant laboratory, ECG, vital signs, or physical examination abnormality that would prevent study participation or place the subject at significant risk, as judged by the Investigator.
3. Subjects who have ever used skin bleaching treatments for treatment of vitiligo or other pigmented areas, eg, depigmenting agents such as monobenzyl ether of hydroquinone, including Benoquin® (Monobenzone)
4. Use of any other prior and concomitant therapy that is a contraindication to phototherapy or may otherwise interfere with the objective of the study as per discretion of the Investigator, such as drugs that cause photosensitivity or skin pigmentation (eg, antibiotics such as tetracyclines, antifungals) within 8 weeks of Baseline (Visit 2).
5. More than 33% leukotrichia in facial lesions (assessed via dermatoscope).
6. Other forms of vitiligo (eg, segmental vitiligo); or other skin depigmentation disorder that would confound study assessments (eg, piebaldism, pityriasis alba, leprosy, post-inflammatory hypopigmentation, progressive macular hypomelanosis, nevus anemicus, chemical leukoderma, and tinea versicolor).
7. Use of oral or systemic immunomodulating medications (eg, corticosteroids, azathioprine, methotrexate, cyclosporine) within 8 weeks of Baseline (Visit 2). (See Excluded Medications and Treatments, Table 2).

8. Use of prescription or over-the-counter topical treatments that may affect vitiligo (eg, corticosteroids, tacrolimus/pimecrolimus, retinoids, vitamin D derivates, psoralens) within 4 weeks prior to Baseline (Visit 2) (See Excluded Medications and Treatments, Table 2).
9. Use of any biological or experimental therapy for vitiligo within 24 weeks of Baseline (Visit 2) (or 5 half-lives, whichever is longer).
10. Use of phototherapy (including laser and tanning beds) within 8 weeks prior to Baseline (Visit 2).
11. Previous oral or topical JAK inhibitor therapy within 24 weeks prior to Baseline (Visit 2), and/or prior non-response to oral or topical JAK inhibitor therapy for vitiligo
12. History of melanocyte-keratinocyte transplantation procedure (MKTP) or other surgical treatment for vitiligo.
13. Contraindication to phototherapy, such as photosensitivity disorder (eg, lupus, polymorphic light eruption, solar urticaria, dermatomyositis) or use of photosensitizing or phototoxic medications.
14. Subjects with clinically significant abnormal thyroid-stimulating hormone or free T4 at screening, or otherwise uncontrolled thyroid function at screening as determined by the investigator (Note: If the subject has a history of thyroid disease and is on treatment, the subject must be on a stable thyroid regimen for at least 3 months prior to baseline)
15. History of chronic alcohol or drug abuse within 6 months prior to baseline.
16. Subjects with a cytopenia at screening, defined as follows: Leukocytes < 3 × 10^9/L (2.5 × 10^9/L for subjects who are African-American), Neutrophils < lower limit of normal (<1.5x10^9/L), Lymphocytes < 0.8 × 10^9/L, Hemoglobin < 10 g/dL, Platelets < 100 × 10^9/L.
17. Subjects with current or a history of non-skin cancer within 5 years with the exception carcinoma in situ of the cervix.
18. Subjects with greater than 3 adequately treated nonmetastatic basal cell carcinomas (BCC) or squamous cell carcinomas (SCC) within 12 months prior to Baseline (Visit 2), or a previous history of multiple BCC or SCC on any area of the body, which may pose additional risks from participation in the study, in the opinion of the Investigator.
19. Subjects with previous history of melanoma anywhere on the body, or basal cell carcinoma (BCC), squamous cell carcinoma (SCC), or actinic keratosis (AK) on the face, neck, hands, forearms, or elbows.
20. Subjects that have received live vaccine therapy less than 4 weeks prior Baseline (Visit 2), or anticipate receiving a live or live-attenuated vaccination during the course of the study, have received immunosuppressive drugs less than 4 weeks prior Baseline, or have known infection with mycobacterium tuberculosis, hepatitis B or C, or HIV, or have a diagnosis of an immunodeficiency disorder.

21. Subject had a major surgery within 4 weeks prior to Baseline or has a major surgery planned during the study.
22. Subjects with severe renal insufficiency (as evidenced by estimated glomerular filtration rate <40 mL/min) or with severely impaired liver function (Child-Pugh Class C), ALT or AST ≥ 2 × ULN, total bilirubin > 1.5 x ULN, or total bilirubin > ULN and ≤ 1.5 x ULN AND direct bilirubin is > 35% of total bilirubin, ALP ≥ 2x ULN.
23. [redacted]
24. Pregnant or lactating women or women planning to become pregnant during the study and / or within 28 days following the last dose of investigational product.
25. Subjects who cannot discontinue the use of strong systemic Cytochrome P-450 CYP3A4 inducers e.g., efavirenz, nevirapine, glucocorticoids, barbiturates (including phenobarbital), phenytoin, rifampin and carbamazepine for 2 weeks prior to Baseline and during the study period.
26. Subjects who cannot discontinue the use of strong systemic Cytochrome P-450 CYP3A4 inhibitors e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, fluconazole, nefazodone, saquinavir, suboxone and telithromycin for 2 weeks prior to Baseline and during the study period.
27. Any dermatologic condition that in the Investigator's assessment would preclude the subject from participating in the study.
28. Subjects who, in the opinion of the Investigator, are unable or unlikely to comply with the administration schedule and study evaluations.
29. Subjects who are family members of the clinical study site, clinical study staff, or sponsor, or family members that live in the same house of enrolled subjects.

Investigational Product, Dosage and Mode of Administration:

ARQ-252 cream 0.3% or matching vehicle cream is to be applied BID to all affected areas of vitiligo on the face, neck, hands, forearms, and elbows (extending 3 cm from the border all around) including any new lesions in those areas that may appear during the course of the 24-week treatment period of the study. Subjects will also receive either an active or sham [redacted] NB-UVB Home Phototherapy Unit to be used on the entire face and on the affected areas of the neck, hands, forearms and elbows for up to 3 times per week per a standardized phototherapy protocol.

Key Assessments:

Safety will be monitored through application site assessments, safety labs, AEs, ECGs, physical examinations, and vital signs.

Efficacy will be evaluated utilizing:

- F-BSA
- F/N-BSA
- BSA (hands, forearms, elbows)
- BSA (total body)
- F-VASI
- F/N-VASI
- FOREARM-VASI (forearms, elbows)
- HAND-VASI
- T-VASI
- Vitiligo Noticeability Scale (VNS)
- Vitiligo Quality of Life (VitiQoL)
- Patient Global Impression of Change-Vitiligo (PaGIC-V)
- Facial Static Investigator Global Assessment (FsIGA)

Criteria for Evaluation:

Pharmacokinetics:

All subjects who are randomized and receive at least one application of investigational product and have at least one PK sample draw will be included in the pharmacokinetic population.

Safety:

All subjects who are randomized and receive at least one confirmed dose of IP will be included in the safety population.

Adverse events (AEs) will be summarized by preferred term, system organ class, and treatment group for all treatment-emergent AEs, serious AEs, related AEs, AEs leading to withdrawal from investigational product

Safety laboratory parameters and vital signs will be summarized at each visit using descriptive statistics or frequencies and percentages, as appropriate. Changes from baseline in laboratory values and vital signs will also be summarized by visit. In addition, changes from baseline in weight and laboratory values will be summarized using shift tables.

Statistical Methods:

Subjects will be stratified by study site, age ≤30 or >30 years, and Fitzpatrick Skin Type (I-III vs. IV-VI).

Descriptive statistics will be presented for endpoint and safety data collected in the clinical trial. This includes the number and percentage of subjects for binary endpoints/categorical data, and mean, SD, median, minimum, and maximum for continuous data.

The primary endpoint of Proportion of subjects achieving F-VASI75 (≥ 75% improvement from baseline in Facial Vitiligo Area Scoring Index (F-VASI) score) at Week 24 will be analyzed using a Cochran-Mantel-Haenszel test stratified by the stratification factors study site, age ≤30 or >30 years, and Fitzpatrick Skin Type (I-III vs. IV-VI).

The analysis will be performed on the Intention-to-Treat (ITT) population and missing data will be imputed using multiple imputation.

Continuous secondary endpoints will be analyzed using Analysis of Covariance with treatment and stratification factor as independent variables. Binary secondary endpoints will be analyzed similarly to the primary endpoint.

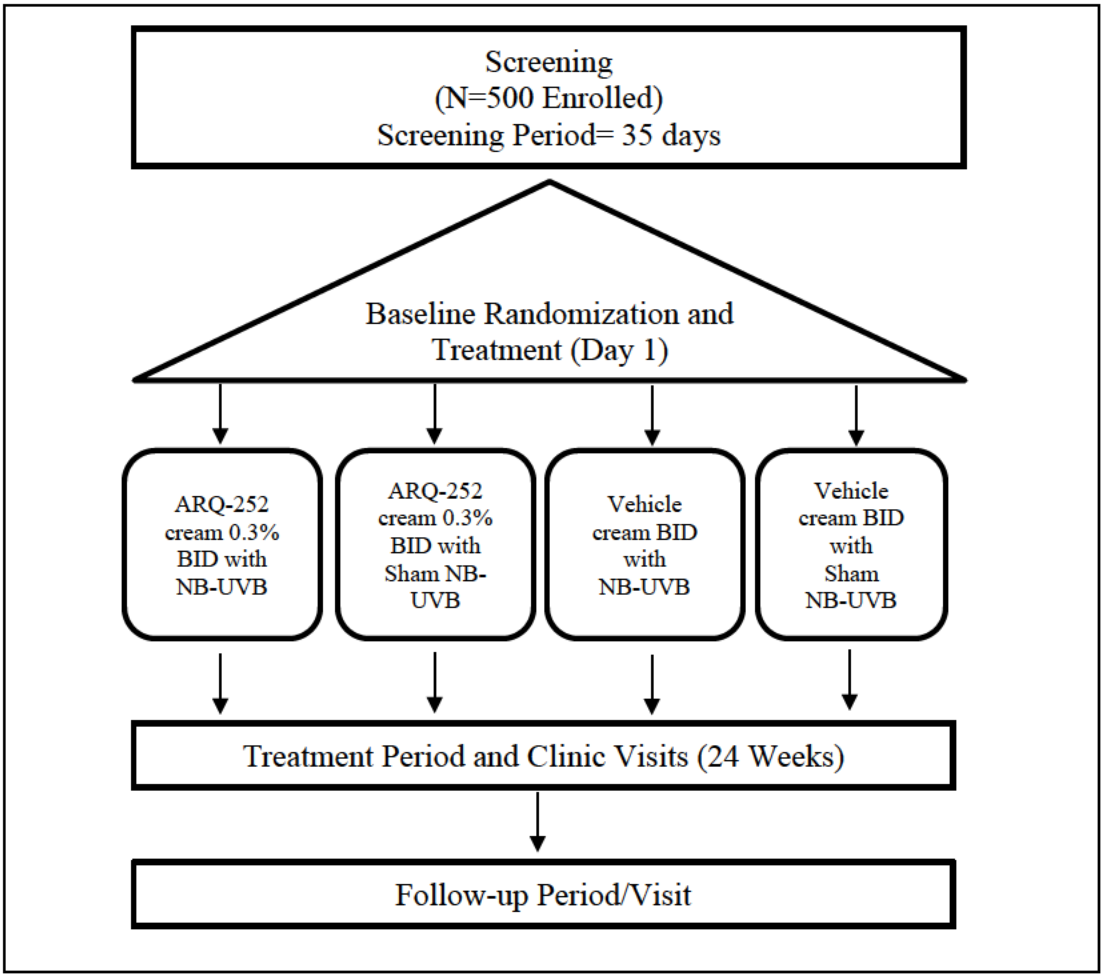
Pharmacokinetics Assessment:

PK will be evaluated through trough/pre-dose sampling at Baseline, Week 4, Week 12, and Week 24.

Pharmacokinetic Parameters:

Plasma pre-dose values will be compared between treatment conditions. Values will be normalized based on dose applied.

1.2. Study Schema



A Phase 2a, Proof of Concept, 24-Week, Parallel Group, Double Blind, Vehicle-Controlled Study of the Safety and Efficacy of ARQ-252 Cream 0.3% in Subjects with Facial Vitiligo

Randomization scheme will be 3:3:3:1 to the following:

- Approximately 150 subjects will receive ARQ-252 cream 0.3% BID with phototherapy
- Approximately 150 subjects will receive ARQ-252 cream 0.3% BID with sham phototherapy
- Approximately 150 subjects will receive matching vehicle cream BID with photothearpy
- Approximately 50 subjects will receive matching vehicle cream BID with sham phototherapy

1.3. Schedule of Visits and Assessments

Study Procedure	Screen	Baseline Day 1	Wk 4 Day 29	Wk 8 Day 57	Wk 12 Day 85	Wk 16 Day 113	Wk 20 Day 141	Wk 24 Day 169	Wk 25 Day 176
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Visit Window	**-35 days**		**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 5 days**	**+/- 7 days**	**+/- 7 days**
Informed consent	X								
Demographics	X								
Fitzpatrick skin type assessment	X								
Medical and surgical history	X								
Physical examination[a]	X	X			X				X
Vital signs, height, weight[b]	X	X	X	X	X	X	X	X	X
I/E criteria	X	X							
Randomization		X							
Hematology, Serum Chemistries, UA, TSH/T4	X	X	X		X			X	
Lipid (Fasting)[c]		X						X	
Resting 12-lead ECG	X		X		X			X	
BSA[d] (Full Body), T-VASI[e]	X	X			X			X	
F-BSA[d], F/N-BSA[d], BSA (Hands, Forearms, Elbows)[d], F-VASI[e], F/N-VASI[e], FOREARM-VASI[e], HAND-VASI[e], FsIGA[f]	X	X	X	X	X	X	X	X	X
VNS[g], PaGIC-V[h]			X	X	X	X	X	X	
VitiQoL[i]		X	X	X	X	X	X	X	
Local Tolerability Assessments[j]		X	X	X	X	X	X	X	
Digital Photography[k]		X	X	X	X	X	X	X	
Urine pregnancy test[l]		X	X	X	X	X	X	X	X
Serum pregnancy test[m]	X								
Follicle-Stimulating Hormone (FSH)[n]	X								

Study Procedure	Screen	Baseline Day 1	Wk 4 Day 29	Wk 8 Day 57	Wk 12 Day 85	Wk 16 Day 113	Wk 20 Day 141	Wk 24 Day 169	Wk 25 Day 176
PK Sampling[o]		X	X		X			X	
NB-UVB Phototherapy in clinic[p]		X							
Return of USB stick to site for phototherapy data uploading[q]			X	X	X	X	X	X	
Dispense IP kit[r]		X	X	X	X	X	X		
IP application in clinic[s]		X	X	X	X	X	X		
Dispense/review diary		X	X	X	X	X	X		
Weigh IP tubes[t]		X	X	X	X	X	X	X	
Compliance calculation[u]			X	X	X	X	X	X	
Adverse event assessment[v]	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X

[a] Limited physical examination: skin, lungs, and heart only

[b] Height will be measured at Baseline only. Weight will be collected at screening, baseline and Week 24.

[c] Fasting required for a minimum of 8 hours prior to blood draw

[d] BSA will utilize the subject's handprint method where 1 handprint will approximate 1% of the body surface area involved. F-BSA will include the % BSA of non-segmental vitiligo on the face only. F/N-BSA will include the % of BSA of vitiligo on the face and neck area only. Full Body BSA will include the % of BSA of vitiligo on all areas of the body. This assessment will be performed by an independent rater per Section 5.2.1.

[e] Vitiligo Area Scoring Index (VASI) per Section 5.2.3: F-VASI will utilize measuring only the face. “Face” is defined as including the area on the forehead to the original hairline, on the check to the jawline vertically to the jawline and laterally from the corner of the mouth to the tragus. The area “face” will not include surface areas of lips, scalp, ears, or neck but will include the eyelids and nose. F/N-VASI will utilize VASI measuring the face and neck as defined by the Face as defined above in addition to the neck area. FOREARM-VASI will include scoring of the forearms and elbows. HAND-VASI will include scoring of the hands only. T-VASI will include the following sites: (1) head/neck, (2) hands, (3) upper extremities (excluding hands), (4) trunk, (5) lower extremities (excluding feet), and (6) feet. All VASI assessments will be performed by an independent rater per Section 5.2.1.

[f] The Facial Static Investigator Global Assessment (FsIGA) is a global score of vitiligo severity for the face only. The outcome measure incorporates location, distribution, size, depigmentation within lesions and presence or absence of signs of activity. Examination of skin should be performed with both normal lighting and Woods lamp. This assessment will be performed by an independent rater per Section 5.2.1.

g Vitiligo Noticeability Scale (VNS) is a 5-point scale which compares vitiligo from before treatment to how noticeable is the vitiligo at the time of the assessment. The VNS will be completed by subjects with respect to vitiligo on the facial target patch. The target patch on the face is selected by the subject as being the patch that they would most like to see in an improvement in. The photos taken on the facial target patch at the Baseline visit prior to treatment and at the subsequent visits will be used as reference to assess the change.

[h] The Patient Global Impression of Change-Vitiligo (PaGIC-V) is a 7-point scale on which the subject will rate improvement compared to baseline and will be evaluated for the face only.

[i] The Vitiligo Quality of Life (VitiQoL) is a 16-item questionnaire with a 7-point numerical scale from (0 - Not at all) to (6 - All of the time). The VitiQOL is completed by the subject.

Footnotes from table above:

[j] Tolerability assessments should be recorded prior to study drug application for Investigator assessment and 10-15 minutes post-drug application for subject ('0-3' burning/stinging assessment). Investigators will specify if any application site reaction is due, in whole or in part, to the effects of phototherapy treatment. Only the Investigator assessment will take place on Week 24.

[k] Digital Photography will be conducted at all sites for all subjects. Required study photos will be taken of the treatment areas during the Baseline Visit. In addition, a photo of the facial target patch will be taken as reference for the VNS assessment. Fixed, multi-angle photos will be taken at select sites for additional evaluation.

[l] A urine pregnancy test will be administered to all females of child-bearing potential. A negative result is required for continued participation in the study, and results must be available prior to dispensing of study drug at each visit.

[m] Serum pregnancy testing will be performed at Screening; a negative result is required for participation in the study.

[n] FSH will be performed (if indicated) at Screening to confirm post-menopausal status.

[o] PK samples will be collected from all subjects at Baseline, Week 4, Week 12, and Week 24. The samples will be drawn prior to application of the investigation product in the clinic. Subjects should apply investigational product 11-12 hours before the PK collection time.

[p] NB-UVB Phototherapy treatment will occur in the clinic at the Baseline Visit prior to the initial IP application. The treatment will be per the NB-UVB Treatment Protocol (Appendix 1) and be tailored per the subject's Fitzpatrick Score. The subject will be provided with the phototherapy unit in addition to a USB stick which will be inserted into the unit to obtain phototherapy data during the course of the treatment period.

[q] Subjects should be instructed return the USB stick from the phototherapy unit to site for the uploading of the phototherapy data. Once the data has been uploaded by the site staff, a new USB stick should be provided to the subject to insert into the NB-UVB phototherapy unit.

[r] IP kits will be dispensed based on % BSA affected. See IP Handling Manual for details.

[s] Subjects to apply assigned IP in clinic at these visits. The time of application will be documented.

[t] Each IP tube will be weighed prior to dispensing at the Baseline visit and at each follow-up clinic visit according to the Schedule of Visits and Assessments. When IP is applied in the clinic, the IP tube will be weighed before and after IP application. See IP Handling Manual for details.

[u] Compliance calculation is described in the IP Handling Manual.

[v] Adverse Events (AEs) and clinically significant abnormal laboratory test value(s) will be evaluated by the PI and treated and/or followed up for up to 30 days after end of treatment or until the symptoms or value(s) return to normal, or acceptable levels, as judged by the PI.

2. BACKGROUND AND RATIONALE

2.1. Introduction

Vitiligo is a common autoimmune disease affecting 0.5% to 2% of the world's population. Although generally more prominent in patients with darker skin types, vitiligo affects all races and both sexes. Vitiligo often presents as acquired, small, asymmetrical lesions that tend to increase in size over time and become more numerous, coalescing into larger areas. Although vitiligo can occur on any area of the body, the face is commonly affected. Vitiligo is associated with a significant burden of disease, greatly affecting a patient's quality of life similar to that seen in psoriasis and atopic dermatitis (Linthorst 2009). Vitiligo can be particularly bothersome and disfiguring when it affects the face and neck (as well as other exposed areas such as hands and forearms) as these areas are visible and may be difficult to camouflage (Elbuluk 2017). Numerous studies have demonstrated that quality of life and mental health are more negatively impacted in patients with vitiligo on the face and other visible areas (Elbuluk 2017, Amer 2016, Eleftheriadou 2012). The negative impact of face/head/neck involvement on quality of life has been reported to be independent of the extent of disease (Bhandarkar 2012). The impact of vitiligo may extend to negative treatment by others, with impact on professional prospects and relationships. With respect to treatment, survey data from patients and providers has identified repigmentation specifically of the face and hands as particularly important (Eleftheriadou 2012).

Vitiligo is characterized by a T helper type 1 (Th1)-mediated immune response with increased expression of interferon (IFN)-γ and chemokines C-X-C Motif Chemokine Ligand (CXCL) 9 and CXCL10 which impair the normal function of melanocytes and produce areas of depigmentation on the skin (Rashighi 2014). Importantly, after IFN-γ binds to its cell surface receptor (IFNGR), signaling is through Janus Kinases (JAKs) especially JAK1 and JAK2. JAK1 is also an important mediator of signaling in the IL-15 pathway which has recently also been strongly implicated in vitiligo (Frisoli 2020). As such, JAK inhibition may represent an effective strategy for the treatment of vitiligo by decreasing INF-γ signaling and downstream chemokine expression (Craiglow 2015, Harris 2016). Topical JAK inhibitors may be particularly well suited for treating vitiligo given the anticipated lower systemic exposures, improved safety profile, and more direct cutaneous delivery offered with topical rather than oral administration of JAK inhibitors. Clinical efficacy of JAK inhibition in autoimmune disease is well established, with tofacitinib, upadacitinib, and baricitinib approved as oral treatments for rheumatoid arthritis (RA), psoriatic arthritis, and/or ulcerative colitis. Over the past few years, there have been multiple reports of oral JAK inhibitors prescribed off-label for vitiligo, with clinical benefit (Relke 2019). Recently, topical JAK inhibition has also been demonstrated to be a potentially efficacious strategy in the treatment of vitiligo, with the most advanced data coming from a 52-week analysis of an ongoing phase 2 study of topical ruxolitinib cream monotherapy, a JAK1/2 inhibitor (Harris 2019, Rosmarin 2020). Importantly, based on the phase 2 results with topical ruxolitinib (Harris 2019) as well as other reports (Rothstein 2017, Rosmarin 2020), topical JAK inhibition has demonstrated considerably greater efficacy for vitiligo on the face compared to vitiligo elsewhere on the body. This has been hypothesized to be due to a high density of follicular units on the face relative to other parts of the body. Pigmented hair follicles are thought to be important reservoirs of melanocytes for repigmentation due to immune

privilege of the follicle and melanocyte stem cells residing in the bulge region of follicles (Frisoli 2020). Additionally, numerous experts and anecdotal reports have suggested that the specific combination of JAK inhibition with ultraviolet light therapy represents the most promising approach for repigmentation of vitiligo (Urso 2017, Liu 2017, Joshipura 2018, Peterson 2020). The rationale for this combined approach is that a 2-step strategy is needed, including JAK inhibition to suppress the local inflammation that contributes to disease, and ultraviolet light therapy to stimulate melanocytes to repigment lesions. Indeed, the combination of topical JAK ruxolitinib with narrow band ultraviolet B (NB-UVB) has been suggested to be especially beneficial specifically for facial vitiligo (Joshipura 2018). Based on clinical observations to date, the combination of JAK inhibition with NB-UVB phototherapy is believed to facilitate more complete and rapid repigmentation relative to JAK inhibition alone (Frisoli 2020).

2.2. Nonclinical Studies

In vitro pharmacology data supports that SHR0302 is a strong JAK1 inhibitor, with inhibitory effects also in a subset of Janus kinases, including JAK2, JAK3 and Tyk2. Additionally, SHR0302 has demonstrated activity comparable to tofacitinib in various *in vivo* models of inflammatory conditions, including the imiquimod-induced murine model of psoriasis, the oxazolone-induced murine model of atopic dermatitis, the rat and murine models of collagen-induced arthritis, the adjuvant induced arthritis rat model, and the murine dextran sulfate sodium-induced colitis model.

The nonclinical safety profile of orally administered SHR0302 has been well characterized through the conduct of safety pharmacology, acute and repeat dose toxicity in rats and monkeys, genetic toxicology (bacterial reverse mutation, in vitro micronucleus, in vivo micronucleus in rats), and reproductive/developmental toxicology (fertility, embryofetal development) studies.

In safety pharmacology studies, SHR0302 did not cause significant changes in cardiovascular, CNS or respiratory functions. After oral administration, SHR0302 was well absorbed and distributed into many tissues.

2.3. Toxicity Summary

JAK inhibitors have emerged as a potential important new therapeutic class in the treatment of eczema as well as other skin conditions. SHR0302 was demonstrated to be a potent inhibitor of JAK1, with inhibitory effects also in a subset of Janus kinases, including JAK2, JAK3 and Tyk2. Results from a cell-based assay demonstrate the preference of SHR0302 for JAK1 over JAK2, which suggests that SHR0302 is likely to provide sparing of JAK2 inhibition under physiologic circumstances. In safety pharmacology studies, SHR0302 did not cause significant changes in cardiovascular, CNS or respiratory functions. After oral administration, SHR0302 was well absorbed and distributed into many tissues.

Local tolerance studies demonstrated SHR0302 is not a skin sensitizer or eye irritant, and it does not have phototoxic potential.

Overall, the results suggest that SHR0302 is safe and well tolerated in both mice an minipigs. Taken together, the results of the nonclinical toxicology studies demonstrated an acceptable topical safety profile and support the progression of SHR0302 into clinical studies in patients with non-segmental vitiligo.

2.4. Clinical Studies

2.4.1. Oral Administration

2.4.1.1. Oral Administration: Phase 1

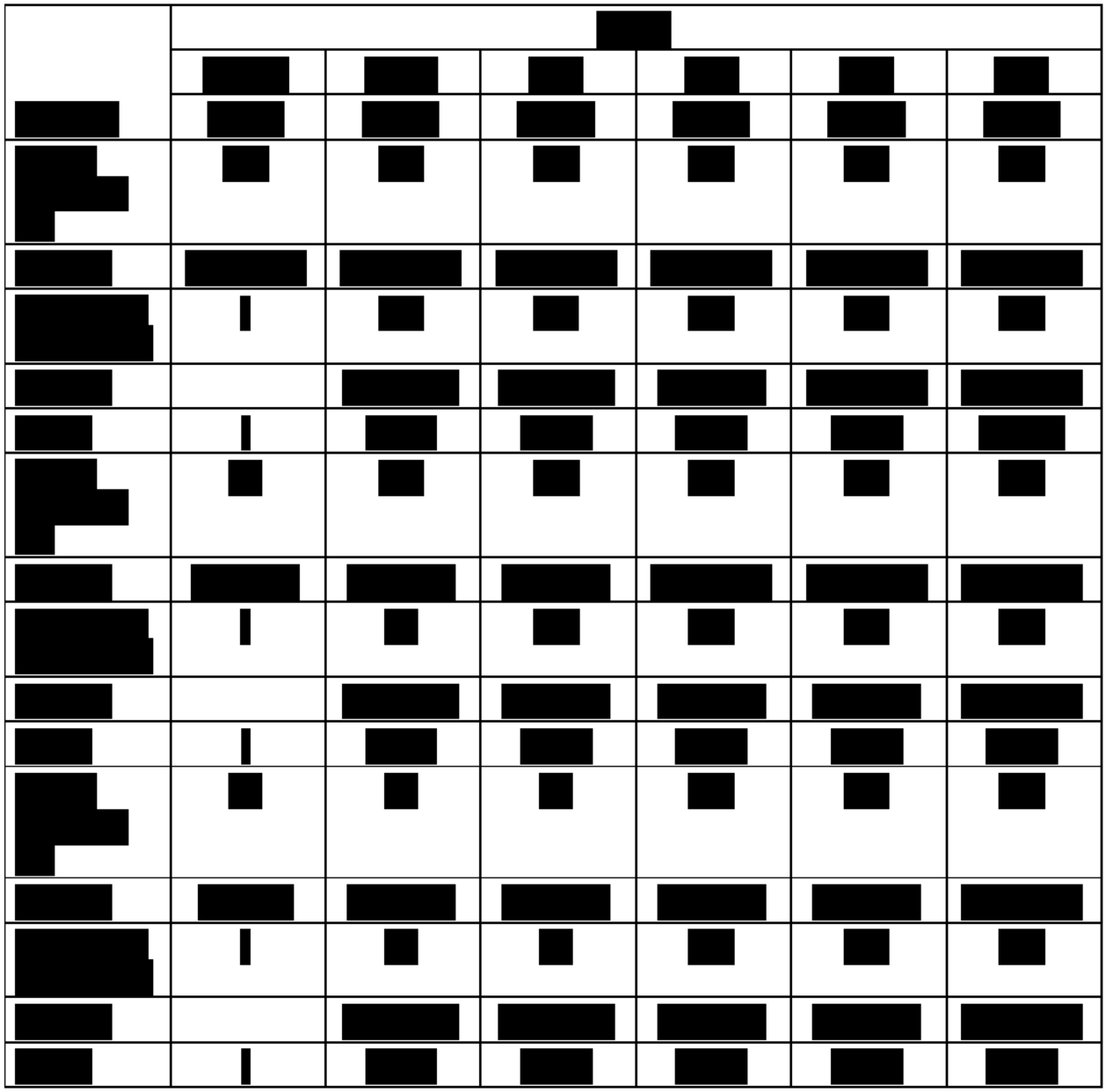
[redacted]

[redacted]

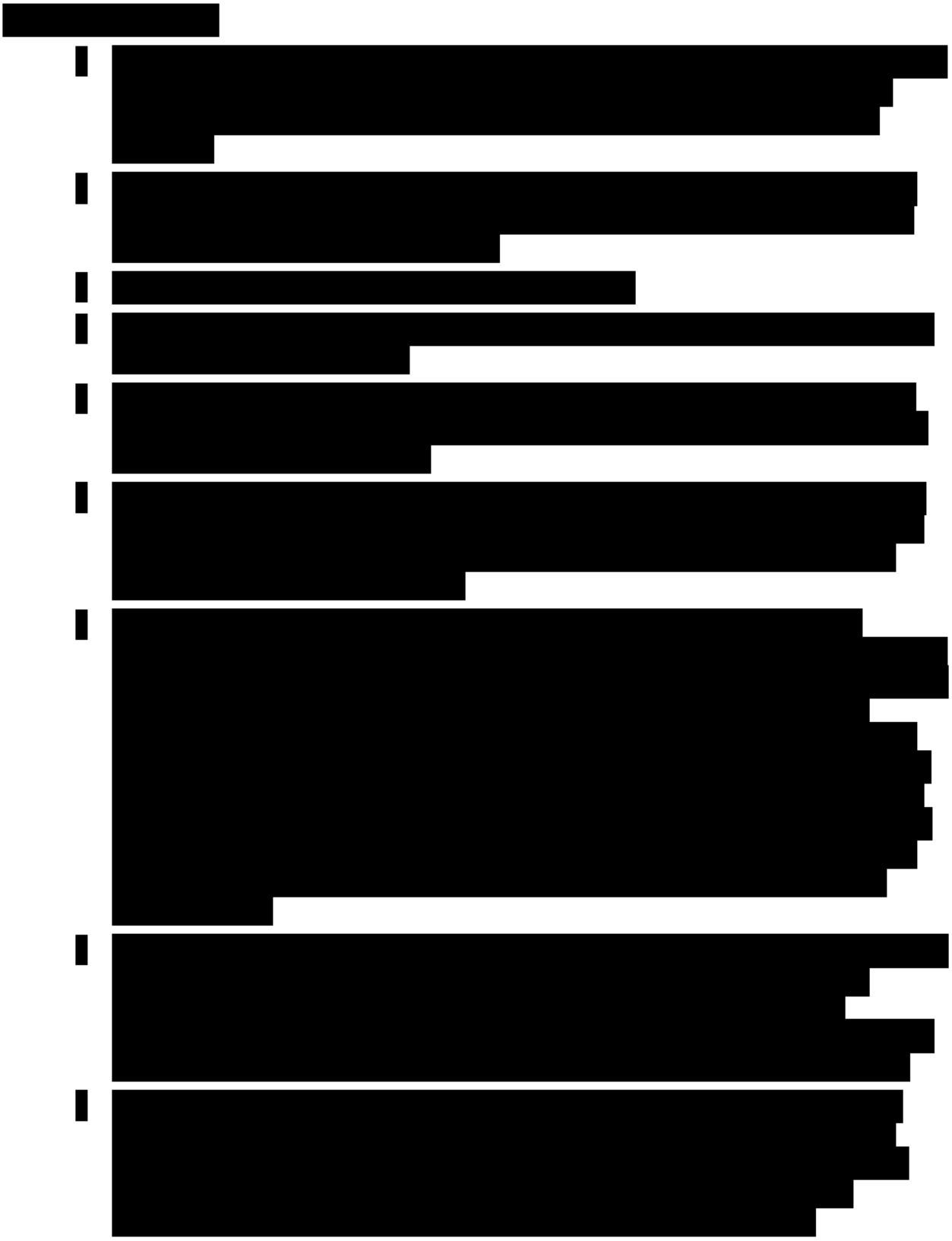
Overall, SHR0302 was well-tolerated with no SAEs reported.

[redacted]

[redacted]



[redacted]



[redacted]

2.4.2. Topical Administration

[redacted]

2.4.2.1. Topical Administration: Phase 1

[redacted]

[redacted]

2.4.2.2. Ongoing Studies

[redacted]

2.5. Rationale for Development

There are currently no FDA-approved topical treatments for repigmentation of vitiligo, leaving numerous off-label topical treatments which have limited supporting safety and efficacy data, especially with long-term use (which is required for the treatment of this chronic disease). Current treatments for vitiligo include topical corticosteroids, topical calcineurin inhibitors, oral steroids and other immunosuppressants. Phototherapies including PUVA, NB-UVB, and targeted phototherapies (e.g., excimer laser) may play an important role in repigmenting vitiligo and it is well established that their efficacy can be considerably increased when used in combination with topical treatments (Lee 2019, Taieb 2013). Nevertheless, there is an unmet need for novel compounds, therapeutic strategies, and combination therapies for vitiligo in order to better treat this common disease which significantly affects patient quality of life. Better treatments are particularly needed for vitiligo of the face (and other exposed sites) given its profound impact on patients.

2.5.1. [redacted]

[redacted]

The safety monitoring practices employed in this protocol (i.e., physical examinations, application site reaction assessments, hematology, serum chemistry, TSH, T4, lipids, urinalysis, ECG, and AE questioning) are considered adequate to protect the subjects' safety and should detect expected AEs.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objective

The purpose of this study is to assess the safety and efficacy of ARQ-252 cream 0.3% BID vs vehicle cream BID, with and without NB-UVB phototherapy treatment in individuals with non-segmental facial vitiligo.

3.1.2. Secondary Objective

Secondary objectives of the study are:

- To assess other efficacy measures of ARQ-252 cream 0.3% BID with and without NB-UVB phototherapy treatment in subjects with non-segmental vitiligo on the face, in addition to vitiligo on the neck, hands, forearms, and elbows.

3.2. Study Endpoints

3.2.1. Primary Endpoints

The primary efficacy endpoint is:

- Proportion of subjects achieving F-VASI75 (≥ 75% improvement from baseline in Facial Vitiligo Area Scoring Index (F-VASI) score) at Week 24.

3.2.2. Secondary Endpoints

The secondary efficacy endpoints will include:

- Proportion of subjects achieving F-VASI75 (≥ 75% improvement from baseline in F-VASI score) at visits prior to Week 24.
- Percent change from baseline in F-VASI score at all visits.
- Percent change from baseline in facial body surface area (F-BSA) at all visits.
- Proportion of subjects achieving F-VASI50 (≥ 50% improvement from baseline in F-VASI score) at all visits.
- Proportion of subjects achieving F-VASI90 (≥ 90% improvement from baseline in F-VASI score) at all visits.
- Proportion of subjects in each category of VNS at specified visits.
- Change from Baseline in the VNS at specified visits.
- Change from Baseline in the VitiQoL at specified visits.
- Patient Global Impression of Change-Vitiligo (PaGIC-V), proportion of patients in each PaGIC-V category at specified visits.
- Proportion of subjects who report PaGIC-V of very much improved or much improved during the treatment period.
- Time to achieve F-VASI50.
- Time to achieve F-VASI75.
- Time to achieve FsIGA of clear or almost clear (0 or 1).
- FsIGA of clear or almost clear (0 or 1).
- FsIGA of clear or almost clear (0 or 1) plus 2-grade improvement from baseline.
- Time to achieve a PaGIC-V of very much improved or much improved.

3.2.3. Exploratory Endpoints

The exploratory endpoints will include:

- Percent change from baseline in combined face and neck body surface area (F/N-BSA) at all visits.
- Percent change from baseline in surface area BSA (hands/forearms/elbows) at all visits.
- Percent change from baseline in BSA affected across all treatable sites (face, neck, hands, forearms, elbows) at all visits.
- Proportion of subjects achieving F/N-VASI50 (≥ 50% improvement from baseline in F/N-VASI score) at all visits.
- Proportion of subjects achieving F/N-VASI75 (≥ 75% improvement from baseline in F/N-VASI score) at all visits.
- Proportion of subjects achieving F/N-VASI90 (≥ 90% improvement from baseline in F/N-VASI score) at all visits.
- Percent change from baseline in FOREARM-VASI (forearms/elbows) score at all visits.
- Percent change from baseline in HAND-VASI (hands only) score at all visits.
- Serum levels of ARQ-252.
- The proportions of subjects who maintain 80% treatment compliance with both application of ARQ-252 cream 0.3% or vehicle cream and phototherapy or sham phototherapy up through 24 weeks.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

ARQ-252 cream 0.3% or matching vehicle cream is to be applied BID to all affected areas of vitiligo on the face, neck, forearms, elbows, and hands (extending 3 cm from the border of the affected area) including any new lesions that may appear during the course of the 24-week treatment period of the study. Subjects will also receive either an active or indistinguishable sham [redacted] 1 NB-UVB Home Phototherapy Unit to be used on aforementioned areas for up to 3 times per week per the NB-UVB Phototherapy Treatment Protocol (Appendix 1).

4.2. Study Population

Subjects will be male and female adults (>18 y/o) with facial non-segmental vitiligo. At least 30% of subjects will have active vitiligo defined as new or expanding vitiligo lesions with or without the presence of confetti, trichrome, or inflammatory vitiligo lesion patterns or other clinical signs of active vitiligo in the past 3 months. At least 65% of subjects will have treatable non-facial vitiligo on the hands, forearms, and elbows. Entry requirements include Facial Body

Surface Area (F-BSA) ≥ 0.25% and F-VASI ≥ 0.25. The maximum BSA (total body inclusive of the face, whether or not in areas to be treated in this study) is 15%. At least 50% of subjects will have Fitzpatrick skin type IV-VI.

4.3. Number of Subjects

Approximately 500 subjects are planned to be randomized across approximately 50 sites in United States and Canada.

4.4. Blinding

The study is double-blinded, therefore neither the subjects nor the Investigator, Independent Rater, or clinical site personnel will be aware of which investigational product (ARQ-252 0.3% cream or vehicle cream) or NB-UVB phototherapy unit (Active or Sham) the subject receives.

4.4.1. Breaking Treatment Codes

In the event of a medical emergency where breaking the blind is required to provide medical care to the subject, the Investigator may obtain treatment assignment directly from the Interactive Response Technology (IRT) system for that subject. Refer to the current version of the IRT plan for details on unblinding. Treatment assignment should, however, remain blinded unless the assignment knowledge is necessary to determine subject emergency medical care. The rationale for unblinding must be clearly explained in source documentation and on the CRF, along with the date on which the treatment assignment was obtained. The Investigator is requested to contact the Sponsor promptly in the event of any treatment unblinding.

Blinding of study treatment is critical to the integrity of this clinical trial and therefore, if a subject's treatment assignment is disclosed to the Investigator, the subject will have the study treatment discontinued. All subjects will be followed until study completion unless consent to do so is specifically withdrawn by the subject.

4.5. Selection of Study Population

4.5.1. Inclusion Criteria

Subjects must fulfill all of the following inclusion criteria to be eligible for participation in the study:

Main Criteria for Inclusion:

1. Subject is legally competent to sign and give informed consent.
2. Males and females ages 18-21 years with Fitzpatrick Skin Type IV-VI or age 22 years and older with Fitzpatrick Skin Type I-VI.
3. Clinical diagnosis of non-segmental vitiligo involving face.
4. A Facial Vitiligo Area Severity Index [F-VASI] score of ≥ 0.25 at baseline.

5. Vitiligo of the face involving at least ≥ 0.25% body surface area (BSA) involvement (ie, one quarter of one handprint). Subjects may have non-facial vitiligo elsewhere which will not be included in the minimum BSA. The maximum BSA (total body inclusive of the face, whether or not in areas to be treated in this study) permitted is 15%.
6. Subjects with vitiligo on the hands, forearms, or elbows agree to treat these areas in addition to the face, with investigational product and phototherapy.
7. Subject agrees to discontinue all agents used to treat vitiligo from screening through the final safety follow-up visit. Over-the-counter preparations deemed acceptable by the Investigator and camouflage makeups are permitted.
8. Female subject of childbearing potential (FOCBP) must have a negative serum pregnancy test at Screening and negative urine pregnancy test at Baseline (Visit 2). For FOCBP involved in any sexual intercourse that could lead to pregnancy: the subject must agree to use a highly effective contraceptive method for at least 4 weeks prior to Day 1. Additionally, from Day 1 until at least 4 weeks after the last investigational product administration, these subjects must agree to use at least 1 highly effective contraceptive method in addition to 1 barrier method. Figure 1
9. Female subject of non-childbearing potential must either be post-menopausal with spontaneous amenorrhea for at least 12 months prior to baseline (post-menopausal status will be confirmed with FSH testing) or have undergone surgical sterilization (permanent sterilization methods include hysterectomy, bilateral oophorectomy, or bilateral salpingectomy). Figure 1
10. Males, if engaging in sexual intercourse with a female who is pregnant or a female of child-bearing potential, must agree to use a condom every time during the study and every time subsequently until 4 weeks beyond the last dose of investigational product.
11. Males must agree not to donate sperm from the first dose of investigational product until 4 weeks after the last dose of investigational product.
12. Subject is in good health as judged by the Investigator, based on medical history, physical examination, 12-lead electrocardiogram (ECG), serum chemistry labs, hematology values, and urinalysis.

4.5.2. Exclusion Criteria

Subjects who meet any of the following exclusion criteria will be excluded from participation in this study:

1. Males and females ages 18-21 years with first degree family members (parents, children, and/or siblings) who have a history of melanoma.
2. Subjects with any serious medical condition or clinically significant laboratory, ECG, vital signs, or physical examination abnormality that would prevent study participation or place the subject at significant risk, as judged by the Investigator.

3. Subjects who have ever used skin bleaching treatments for treatment of vitiligo or other pigmented areas, eg, depigmenting agents such as monobenzyl ether of hydroquinone, including Benoquin® (Monobenzone).
4. Use of any other prior and concomitant therapy that is a contraindication to phototherapy or may otherwise interfere with the objective of the study as per discretion of the Investigator, such as drugs that cause photosensitivity or skin pigmentation (eg, antibiotics such as tetracyclines, antifungals) within 8 weeks of Baseline (Visit 2).
5. More than 33% leukotrichia in facial lesions (assessed via dermatoscope).
6. Other forms of vitiligo (eg, segmental vitiligo); or other skin depigmentation disorder that would confound study assessments (eg, piebaldism, pityriasis alba, leprosy, post-inflammatory hypopigmentation, progressive macular hypomelanosis, nevus anemicus, chemical leukoderma, and tinea versicolor).
7. Use of oral or systemic immunomodulating medications (eg, corticosteroids, azathioprine, methotrexate, cyclosporine) within 8 weeks of Baseline (Visit 2). (See Excluded Medications and Treatments, Table 2).
8. Use of prescription or over-the-counter topical treatments that may affect vitiligo (eg, corticosteroids, tacrolimus/pimecrolimus, retinoids, vitamin D derivates, psoralens) within 4 weeks prior to Baseline (Visit 2) (See Excluded Medications and Treatments, Table 2).
9. Use of any biological or experimental therapy for vitiligo within 24 weeks of Baseline (Visit 2) (or 5 half-lives, whichever is longer).
10. Use of phototherapy (including laser and tanning beds) within 8 weeks prior to Baseline (Visit 2).
11. Previous oral or topical JAK inhibitor therapy within 24 weeks prior to Baseline (Visit 2), and/or prior non-response to oral or topical JAK inhibitor therapy for vitiligo.
12. History of melanocyte-keratinocyte transplantation procedure (MKTP) or other surgical treatment for vitiligo.
13. Contraindication to phototherapy, such as photosensitivity disorder (eg, lupus, polymorphic light eruption, solar urticaria, dermatomyositis) or use of photosensitizing or phototoxic medications.
14. Subjects with clinically significant abnormal thyroid-stimulating hormone or free T4 at screening, or otherwise uncontrolled thyroid function at screening as determined by the investigator (Note: If the subject has a history of thyroid disease and is on treatment, the subject must be on a stable thyroid regimen for at least 3 months prior to baseline).
15. History of chronic alcohol or drug abuse within 6 months prior to baseline.
16. Subjects with a cytopenia at screening, defined as follows: Leukocytes < 3 × 10^9/L (2.5 × 10^9/L for subjects who are African-American), Neutrophils < lower limit of normal (<1.5x10^9/L), Lymphocytes < 0.8 × 10^9/L, Hemoglobin < 10 g/dL, Platelets < 100 × 10^9/L.

17. Subjects with current or a history of non-skin cancer within 5 years with the exception carcinoma in situ of the cervix.
18. Subjects with greater than 3 adequately treated nonmetastatic basal cell carcinomas (BCC) or squamous cell carcinomas (SCC) within 12 months prior to Baseline (Visit 2), or a previous history of multiple BCC or SCC on any area of the body, which may pose additional risks from participation in the study, in the opinion of the Investigator.
19. Subjects with previous history of melanoma anywhere on the body, or basal cell carcinoma (BCC), squamous cell carcinoma (SCC), or actinic keratosis (AK) on the face, neck, hands, forearms, or elbows.
20. Subjects that have received live vaccine therapy less than 4 weeks prior Baseline (Visit 2), or anticipate receiving a live or live-attenuated vaccination during the course of the study, have received immunosuppressive drugs less than 4 weeks prior Baseline, or have known infection with mycobacterium tuberculosis, hepatitis B or C, or HIV, or have a diagnosis of an immunodeficiency disorder.
21. Subject had a major surgery within 4 weeks prior to Baseline or has a major surgery planned during the study.
22. Subjects with severe renal insufficiency (as evidenced by estimated glomerular filtration rate <40 mL/min) or with severely impaired liver function (Child-Pugh Class C), ALT or AST $\geq 2 \times$ ULN, total bilirubin > 1.5 x ULN, or total bilirubin > ULN and $\leq$ 1.5 x ULN AND direct bilirubin is > 35% of total bilirubin, ALP $\geq$ 2x ULN.
23. [redacted]
24. Pregnant or lactating women or women planning to become pregnant during the study and / or within 28 days following the last dose of investigational product.
25. Subjects who cannot discontinue the use of strong systemic Cytochrome P-450 CYP3A4 inducers e.g., efavirenz, nevirapine, glucocorticoids, barbiturates (including phenobarbital), phenytoin, rifampin and carbamazepine for 2 weeks prior to Baseline and during the study period.
26. Subjects who cannot discontinue the use of strong systemic Cytochrome P-450 CYP3A4 inhibitors e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, fluconazole, nefazodone, saquinavir, suboxone and telithromycin for 2 weeks prior to Baseline and during the study period.
27. Any dermatologic condition that in the Investigator's assessment would preclude the subject from participating in the study.
28. Subjects who, in the opinion of the Investigator, are unable or unlikely to comply with the administration schedule and study evaluations.

29. Subjects who are family members of the clinical study site, clinical study staff, or sponsor, or family members that live in the same house of enrolled subjects.

4.6. Removal of Subjects from Investigational Product

A subject may discontinue investigational product for any of the following reasons:

- Occurrence of any medical condition or circumstance that, in the opinion of the Investigator, does not allow the subject to adhere to the requirements for investigational product as per the protocol.
- Occurrence of an Adverse Events as described in Section 5.9. The Investigator must follow the subject until the AE resolves or satisfactorily stabilizes.
- Pregnancy: Treatment must be discontinued immediately in the event of a subject's pregnancy.
- Subject's decision to withdraw from investigational product.
- Requirement for use of prohibited concomitant medication after consultation with the Sponsor and Medical Monitor.
- Subject's repeated failure to comply with protocol requirements or study related procedures.

4.7. Removal of Subjects from the Study

A subject may be removed from study participation for any of the following reasons:

- Subject death.
- Subject's decision to withdraw from study.
- Subject is lost to follow-up. A subject will be considered lost to follow-up after three phone and three email attempts and documentation of a certified letter sent to the subject's address.
- Termination of the study by the Sponsor, FDA, or other regulatory authorities.

4.8. Replacement of Subjects that Withdraw or are Discontinued from the Study

Subjects who withdraw or are discontinued from the study will not be replaced.

4.9. Prohibitions and Concomitant Therapy

Prohibited medications and products are detailed in the Excluded Medications and Treatments (Table 2).

Generally, the addition of new medications, including nonprescription medications, during the course of the study is discouraged. However, the short-term use of a medication may be authorized by the Investigator. The Investigator must make the decision to authorize the use of

any such a medication only after consideration of the clinical situation, the potential for masking symptoms of a more significant underlying event, and whether the use of the medication will compromise the outcome or validity of the clinical investigation.

If medication is required, the name, strength, frequency, duration of use, and reason for use will be recorded in source documents and entered into the CRFs. Medications which have been used chronically by subjects, in particular statins and anti-hypertensives, are allowed for use during the study, except as prohibited in (Table 2).

Table 2: Excluded Medications and Treatments

Excluded Medications and Treatment	Washout Period Prior to Baseline
Melanocyte-keratinocyte transplantation procedure (MKTP) or other surgical treatment for vitiligo	Lifetime history is prohibited
Skin bleaching treatments for past treatment of vitiligo or other pigmented areas, eg, depigmenting agents such as monobenzyl ether of hydroquinone, including Benoquin® (Monobenzone)	Lifetime history is prohibited
Topical treatments that may affect vitiligo (eg, corticosteroids, tacrolimus/ pimecrolimus, retinoids, vitamin D derivatives/preparations, psoralens), whether prescription or over-the-counter	4 weeks
Immunomodulating oral or systemic medications (eg, corticosteroids, azathioprine, methotrexate, cyclosporine)	8 weeks
Oral or topical JAK inhibitors	24 weeks (prior lack of response is exclusionary)
Biological or experimental therapy for vitiligo within 12 weeks of screening	24 weeks or 5 half-lives (whichever is longer)
Cell-depleting biologics such as rituximab	6 months
Strong Cytochrome P-450 3A4 inhibitors and strong Cytochrome P-450 3A4 inducers	2 weeks
UVB or PUVA phototherapy (home or office-based), Excimer Laser, and tanning booths	8 weeks
All investigational drugs	24 weeks (biologics); 8 weeks (oral); 4 weeks (topical) - or 5 half-lives (whichever is longer)
Live vaccine therapy	4 weeks

Notes:

- Ear drop, eye drop and nasal corticosteroid preparations are allowed.
- Non-medicated emollients should not be applied to treatment sites 2 hours before or after study drug application.
- All topical products should be avoided (with the exception of mineral oil) for 30 minutes before phototherapy because of the possibility of deactivation or interference with transmission of NB-UVB radiation. Mineral oil should only be used in unique circumstances of significant dryness and scaling in the treatment area and under the direction of the Investigator.
- Subjects should avoid application of products with SPF on the day of phototherapy, prior to treatment. Subjects can apply sunscreen following the phototherapy treatment.
- All subjects regardless of Fitzpatrick skin type, should apply a broad-spectrum sunscreen with a SPF $\geq$ 30, with reapplication as needed when exposed to sunlight, and avoid sunlight to decrease the risk of additional UVB exposure and phototoxic effect.
- Subjects must notify the Investigator if they are prescribed or intend to take any new medications, supplements, etc as they could be photosensitizing.

4.10. Treatment

4.10.1. IP Supplies, Packaging, and Labeling

ARQ-252 cream 0.3% or vehicle formulation will be packaged in 12-gram tubes. These tubes will be packaged in kits, containing 2 tubes each of investigational product for dispensation to randomized subjects. The number of kits dispensed to a subject will be based on % BSA at baseline. The kits and tubes will be labeled with a unique number, in a blinded manner.

Either an active or sham [redacted] NB-UVB Home Phototherapy unit will be provided to the subject for home use based on randomization arm.

Records will be made of the receipt and dispensation of investigational product and phototherapy unit. At the conclusion of the study, any unused investigational product will be returned to the Sponsor or designee, or destroyed, as per Sponsor instructions. Phototherapy units will be returned to the designee as per Sponsor instructions.

Refer to the most current version of the IP Handling Plan for details on accountability, storage, and management of IP and the NB-UVB Home Phototherapy Unit.

4.10.2. Treatment Administration

Initial treatment with the IP and phototherapy will occur on Day 1 (Baseline) visit. The treatment of IP will occur **after** the treatment with the phototherapy in the clinic.

At the Day 1 (Baseline) visit, the study staff will instruct the subject how to apply IP using the first tube that is assigned to the subject at randomization. Study site staff will inform the subject that one pea size amount of IP should be used to cover approximately 2% BSA (approximately 2 hand prints), and instruct the subject to extrude the appropriate amount of investigational product based on the vitiligo BSA in each treatment area (face, neck, hands, forearms, and elbows). Subjects will be instructed to treat (with IP and phototherapy), any new lesions that appear in the treatment areas during the treatment period.

Study staff will provide oversight while the subject extrudes and applies the initial dose, including how the IP is applied as a thin film and rubbed in thoroughly but gently, until the cream has absorbed in the vitiligo areas on the face, neck, hands, forearms, and elbows and include 3 cm around the border of the application area. The study staff will confirm that the subject's application technique is correct.

All dispensed IP tubes must be returned by subjects at each study visit, to be weighed at the clinic. Re-training on the application of the IP will be conducted at subsequent visits as needed (i.e., if the returned tube weighs substantially different than the expected weight).

At the Day 1 (Baseline) visit, the initial treatment with the phototherapy unit will occur **prior** to IP application. The study staff will set up the phototherapy unit and review the instructions for use with each subject. Subjects should avoid application of products with SPF on the day of phototherapy, prior to treatment. Subjects can apply sunscreen following the phototherapy treatment. Washing the face and treatment areas is encouraged prior to phototherapy treatment.

Subjects will be instructed to refrain from use of any topical products on the treated area with the exception of mineral oil for 30 minutes before phototherapy because of the possibility of deactivation or interference with transmission of NB-UVB. Mineral oil should only be used in unique circumstances of significant dryness and scaling in the treatment area and under the direction of the Investigator. Use of topical products for any reason will be recorded in the subjects' diary and CRF.

Subjects 18-21 years of age with pigmented lesions (eg, nevi) in the treatment field will be instructed to cover pigmented lesions (not areas of vitiligo repigmentation) to prevent NB-UVB exposure.

Each subject will be instructed to complete the initial phototherapy treatment in accordance to the Vitiligo NB-UVB Treatment Protocol (Appendix 1) in the clinic. The phototherapy treatment plan will be in alignment with the Fitzpatrick Skin Type.

4.10.3. Treatment Compliance

IP Compliance:

Each IP tube will be weighed prior to dispensing at the Baseline visit and subsequently at each follow-up clinic visit according to the Schedule of Visits and Assessments (Section 1.3). When IP is applied at the clinic, the tube will be weighed before and after application. If the subject's actual use is substantially different than the expected use (see IP Handling Plan), the subject will be retrained on the investigational product extrusion and application technique.

Subjects will complete a daily diary recording the date and time of each dose applied, any missed doses, and any relevant comments e.g., to record potential AEs or issues with the study medication/investigational product. Site personnel will review the diaries and use the information to question the subject regarding compliance and AEs to record in source documents and CRFs.

If a subject misses a dose of IP, they should be instructed to return to the protocol-specified investigational product administration schedule (i.e., if subject forgets a dose they should wait until the next planned application and apply as usual). The subject should document the missed dose in the subject diary card.

A subject will be considered compliant with the IP dosing regimen if the subject applies at least 80% of the expected doses during the treatment period and does not miss more than 3 consecutive doses. If the diary shows less than 80% of expected use, the subject is using too little investigational product and retraining must be conducted and documented.

Compliance will be assessed by review of the dosing diary. Weight of investigational product applied will be measured for reporting purposes.

Phototherapy Compliance:

If a subject misses a phototherapy treatment, the subject should be instructed to document the missed treatment in the subject diary. The subject should follow the guidance in the NB-UVB Vitiligo Treatment Protocol (Appendix 1) to determine the phototherapy dose of the next treatment.

A subject will be considered compliant with the phototherapy treatment dosing regimen if the subject completes 80% of the required treatments over the total of the 24 week treatment period.

Compliance will be assessed by review of the subject diary and will be documented in source and in CRF.

5. STUDY PROCEDURES

5.1. Safety Assessments

The Schedule of Visits and Assessments (Section 1.3) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the PI and/or the Sponsor for reasons related to subject safety.

This study assesses the safety, efficacy, and PK of ARQ-252 cream 0.3% and vehicle cream in combination with active or sham phototherapy. Safety will be determined by evaluating physical examinations, 12-lead ECGs, vital signs/weight, clinical laboratory parameters, local tolerability assessments, and AEs as outlined in the Schedule of Visits and Assessments (Section 1.3). Subjects will be monitored for the reactivation of herpes simplex virus or varicella zoster virus following the initiation of phototherapy treatment. In addition, subjects who will treat vitiligo on the hands will be monitored for changes in the nails following the initiation of phototherapy treatment. Changes noted from these assessments will be recorded in the CRF.

If deemed necessary, additional safety assessments will be performed at the discretion of the Investigator.

5.1.1. Screening

Before a subject's participation in the clinical study, the Investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the study design, anticipated benefits, and the potential risks.

The following procedures/assessments will be performed at the Screening Visit (within 4 weeks after signing the informed consent):

- Review of medical and surgical history, including any history of allergies
- Review of childbearing potential (subject or partner of male subject) and contraceptive use (Section 5.1.2)
- Collection of demographic data including sex, age, race, ethnicity
- Limited physical examination of skin, lungs, and heart
- Vital signs including weight, temperature, heart rate, and blood pressure
- ECG
- Medical history of vitiligo will include the following information, which will be recorded in the CRF:
  - Location (ie, face, neck, hands, forearms)
  - Distribution/Characteristics: Presence of confetti, trichrome, or inflammatory vitiligo lesion patterns or other clinical signs of active vitiligo
- Assessment of Fitzpatrick skin type

- BSA Assessments (F-BSA, F/N-BSA, BSA (hands, forearms, elbows), BSA (total body)
- Vitiligo assessments (F-VASI, F/N-VASI, FOREARM-VASI, HAND-VASI, T-VASI, and FsIGA)
- Laboratory tests: hematology, chemistry, urinalysis, TSH, T4, serum pregnancy test (for female subjects of childbearing potential), FSH (if indicated to confirm post-menopausal status)
- Collection of concomitant medications and adverse events

All screened subjects will receive a screening number and will be entered into the Interactive Response Technology (IRT) system at the time of consent.

Subjects may be re-screened one time, the original assigned Subject ID screening number will be used for re-screening.

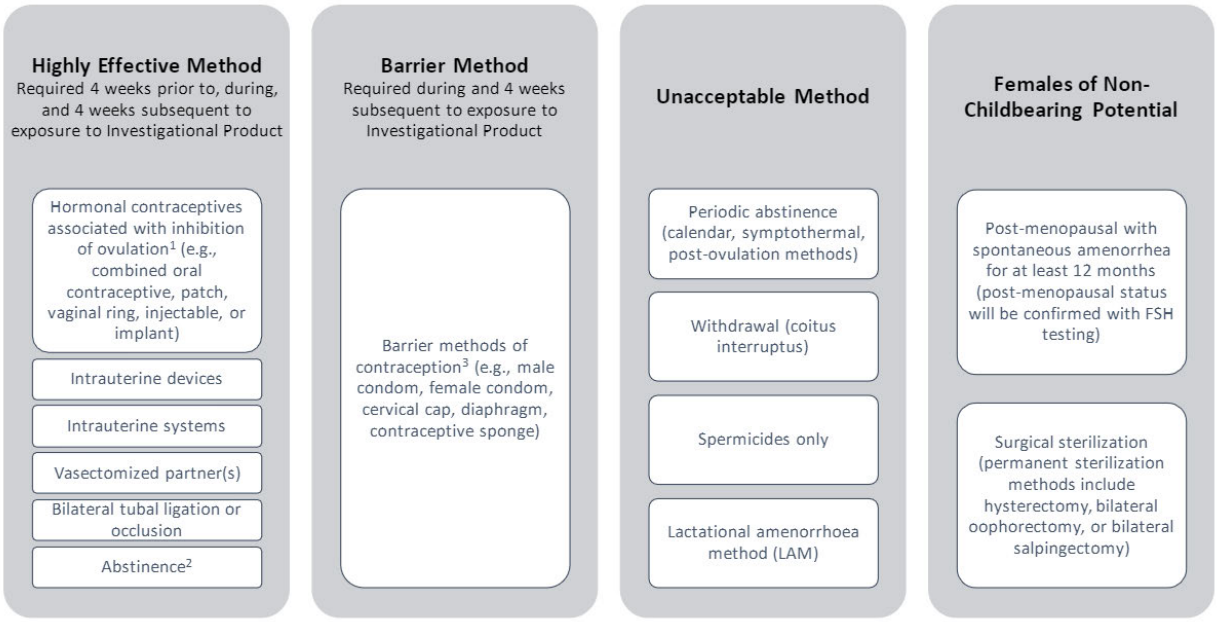
5.1.2. Contraception Requirements

Previous nonclinical research showed that the active ingredient in ARQ-252 can harm fetal development. Subjects engaging sexual intercourse that could lead to pregnancy must adhere to the following pregnancy testing and/or contraception requirements.

Female Subjects:

Female subjects of childbearing potential (FOCBP) must have a negative serum pregnancy test at Screening and negative urine pregnancy test at Baseline (Visit 2). For FOCBP involved in any sexual intercourse that could lead to pregnancy: the subject must agree to use a highly effective contraceptive method for at least 4 weeks prior to Day 1. Additionally, from Day 1 until at least 4 weeks after the last investigational product administration, these subjects must agree to use at least 1 highly effective contraceptive method in addition to 1 barrier method of contraception. The acceptable methods of contraception are listed below in the Figure 1.

Figure 1: Contraception Requirements for Female Subjects



[1]Subjects using hormonal contraceptives must have been on a stable dose for at least 4 weeks before Day 1.
[2]The above list of contraceptive methods does not apply to subjects who are abstinent for at least 4 weeks before Day 1 and will continue to be abstinent from penile-vaginal intercourse throughout the study. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant.
[3]Female condom and male condom should not be used together.

Male Subjects:

Males, if engaging in sexual intercourse with a female who is pregnant or a female of childbearing potential, must agree to use a condom every time during the study and every time subsequently until 4 weeks after the last investigational product administration.

5.1.3. Physical Examination

Physical examinations will be performed according to the Schedule of Visits and Assessments (Section 1.3). The physical exam will be limited to skin, lungs and heart only.

5.1.4. Vital Signs, Height and Weight

Vital signs will be performed according to the Schedule of Visits and Assessments (Section 1.3). Blood pressure, heart rate, and temperature will be collected in seated position after approximately 5 mins. Subjects will be instructed to void prior to weight being taken and to remove any objects of significant weight (i.e., jackets, outerwear, shoes, cell phones, wallet, key chains, etc.).

Height will be measured at Baseline (Day 1) only.

5.1.5. Fitzpatrick Skin Type Assessment

At screening, Fitzpatrick skin phototype will be rated:

I: Always burns easily; never tans (sensitive)

II: Always burns easily; tans minimally (sensitive)

III: Burns moderately; tans gradually (light brown) (normal)

IV: Burns minimally; always tans well (moderate brown) (normal)

V: Rarely burns; tans profusely (dark brown) (insensitive)

VI: Never burns; deeply pigmented (insensitive)

5.1.6. 12-lead ECGs

12-lead ECGs will be performed according to the Schedule of Visits and Assessments (Section 1.3).

ECGs will be obtained on subjects after approximately 5 minutes in the supine position. All ECG tracings and readouts will be reviewed by the Investigator and central reader at the ECG laboratory.

5.1.7. Laboratory Tests

Hematology	**Serum Chemistry**
• Hemoglobin • Hematocrit • Total and differential leukocyte count • Red blood cell count with indices and morphology • Platelet count • Reticulocyte count[1]	• Blood Urea Nitrogen • Bilirubin (total and direct) • Alkaline phosphatase • Aspartate aminotransferase • Alanine aminotransferase • Albumin • Sodium • Potassium • Chloride • Glucose • Creatinine • Creatine kinase
Urinalysis	**Additional Tests**
• pH • Specific gravity • Protein[2] • Glucose • Ketones • Bilirubin • Blood[2] • Nitrite[2] • Urobilinogen • Leukocyte esterase[2]	• Thyroid Stimulating Hormone T4 (TSH/T4) • Urine pregnancy test[3] (for females of childbearing potential only) • Serum pregnancy test (hCG)[4] • Follicle-stimulating Hormone (FSH) [5] • Pharmacokinetic (PK) assessments • Fasting Lipids (cholesterol, triglycerides, HDL, and LDL) [6]

From table above:

[1] If red blood cell count, hemoglobin or hematocrit values are below the lower limit of normal, reticulocyte count will be performed
[2] If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.
[3] At Baseline, Week 4, 8, 12, 16, 20, and 24 for FOCBP only.
[4] At screening only for FOCBP.
[5] If indicated to confirm post-menopausal status
[6] Fasting required for a minimum of 8 hours prior to blood draw

5.1.8. Local Tolerability Assessment

The Investigator Local Tolerability Assessments will be performed according to the Schedule of Visits and Assessments (Section 1.3). Application site reactions are graded using the scale detailed in the following section (Berger 1982).

The Investigator Local Tolerability Assessment will be conducted by the Investigator **prior to investigational product application** in the clinic.

Investigators will specify if any application site reaction is due, in whole or in part, to the effects of phototherapy treatment.

Dermal Response

0. no evidence of irritation
1. minimal erythema, barely perceptible
2. definite erythema, readily visible; minimal edema or minimal papular response
3. erythema and papules
4. definite edema
5. erythema, edema, and papules
6. vesicular eruption
7. strong reaction spreading beyond application site

Other Effects

A. = slight glazed appearance
B. = marked glazing
C. = glazing with peeling and cracking
D. = glazing with fissures
E. = film of dried serous exudates
F. = small petechial erosions and/or scabs
G. = no other effects

The Subject Local Tolerability Assessments will be performed according to the Schedule of Visits and Assessments (Section 1.3).

The Subject Local Tolerability Assessment will be administered by the site **10 to 15 minutes after investigational product application** in the clinic.

The subject will assess burning/stinging (0-3 score):

Local Tolerability Assessment

Grade	Sensation Following Investigational Product Application
0 (none)	No sensation
1 (mild)	Slight warm, tingling sensation; not really bothersome
2 (moderate)	Definite warm, tingling sensation that is somewhat bothersome
3 (severe)	Hot, tingling/stinging sensation that has caused definite discomfort

5.1.9. Adverse Events

Serious adverse events (SAEs) will be collected from the time the Informed Consent Form (ICF) is signed through 30 days after the last day of the application of the investigational product or the end of study (whichever is later).

Adverse events (AEs) will be collected following the first application of investigational product through the end of the study.

Please see Section 5.7 for further details regarding the collection and reporting of adverse events.

5.2. Efficacy Evaluations

5.2.1. Independent Rater Requirement

To reduce possible functional unblinding and bias, independent raters will conduct efficacy assessments while separate trained members of the research team will conduct safety assessments and other activities of study oversight.

An independent rater is a trained research team member that is not aware of a subject's response to treatment as it pertains to safety including AEs such as local treatment site reactions.

The independent rater assigned for a subject:

- may conduct screening activities.
- have not participated in any activities prohibited for that role (e.g., safety assessments) following initial IP/phototherapy treatment for that subject.
- is not absolutely required to be the same person for each assessment, although it is strongly preferred that the same rater be used consistently wherever possible.

At the end of the study, the independent rater will be asked to complete an attestation to determine if they remain blinded as to the subject's treatment group.

5.2.2. Body Surface Area

BSA assessments will be performed according to the Schedule of Visits and Assessments (Section 1.3).

The BSA affected with vitiligo will be assessed as a percentage of the total BSA, and will be determined to the nearest 0.01% using, as guides, the palm plus 5 digits, with fingers tucked together and thumb tucked to the side (handprint), as 1% BSA and the thumb as 0.1% BSA.

- Facial BSA (F-BSA) will be evaluated for the purpose of inclusion in the study. The area "Face" is defined as including the area on the forehead to the original hairline, on the cheek to the jawline vertically to the jawline and laterally from the corner of the mouth to the tragus. The area "Face" will not include surface area of the lips, scalp, ears, or neck but will include the eyelids and nose.
- F/N-BSA includes the BSA of the face and neck.
- BSA of the hands, forearms and elbows will include BSA affected with vitiligo in those aforementioned areas.
- BSA (total body) will include all areas of the body affected with vitiligo.

5.2.3. Vitiligo Area Scoring Index (VASI)

Areas affected by depigmentation due to vitiligo will be assessed using the VASI, which is a quantitative clinical tool that is based on a composite estimate of the overall area of vitiligo patches at baseline and the degree of macular repigmentation within these patches over time. The reliability and validity of F-VASI and T-VASI instruments as measures of treatment efficacy were confirmed (Rosmarin 2020).

VASI is measured by percentage of vitiligo involvement (% of BSA) and the degree of depigmentation. The percentage of BSA (hand unit) vitiligo involvement is estimated by the Investigator using the Palmar Method. Hand unit is based on subject's hand size. The Investigator uses his/her hand to mimic the subject's hand size to evaluate percentage of BSA vitiligo involvement.

The following VASI scoring will be completed per the Schedule of Visits and Assessments (Section 1.3).

- F-VASI: The area "Face" is defined as the area included in the validation of F-VASI (Rosmarin 2020), with the additional inclusion of the eyelids. "Face" is defined as the area on the forehead to the original hairline, on the cheek to the jawline vertically to the jawline and laterally from the corner of the mouth to the tragus. The area "Face" will not include surface area of the lips, scalp, ears, or neck but will include the eyelids and nose.
- F/N-VASI: Includes the VASI of the face and neck
- FOREARM-VASI: Includes VASI (total score) of the Forearms and Elbows
- HAND-VASI: Includes VASI of the hands only

- T-VASI: Includes VASI of the following 6 separate and mutually exclusive sites: (1) head/neck, (2) hands, (3) upper extremities (excluding hands), (4) trunk, (5) lower extremities (excluding feet), and (6) feet.

The degree of depigmentation foreach vitiligo involvement site is determined and estimated to the nearest of the following percentages: 0, 10%, 25%, 50%, 75%, 90%, or 100%. At 100% depigmentation, no pigment is present; at 90%, specks of pigment are present; at 75%, the depigmented area exceeds the pigmented area; at 50%, the depigmented and pigmented area are equal; at 25%, the pigmented area exceeds the depigmented area; at 10%, only specks of depigmentation are present.

The VASI is then derived by multiplying the values assessed for the vitiligo involvement by the percentage of affected skin for each site and summing the values of all sites together.

The percentage of vitiligo involvement is estimated in hand units by the same investigator during the entire course of the study.

5.2.4. Vitiligo Quality of Life (VitiQoL)

The Vitiligo Quality of Life (VitiQOL) will be completed according to the Schedule of Visits and Assessments (Section 1.3). The VitiQOL is an instrument designed to assess disease specific health-related quality of life (HRQL) in patients suffering from vitiligo and also provide an objective measure of disease status, burden of disease, and treatment outcome (Appendix 2). It consists of 16-item questionnaire with a 7-point numerical scale from 0 - Not at all to 6 - All of the time.

5.2.5. Vitiligo Noticeability Scale (VNS)

The Vitiligo Noticeability Scale (VNS) is a 5-point scale which compares vitiligo from before treatment to how noticeable the vitiligo is at the time the VNS is performed. The VNS will be completed by subjects with respect to vitiligo on the facial target patch. The target patch on the face is selected by the subjects as being the patch that they would most like to see an improvement in. The photos taken of the facial target patch at the Baseline visit prior treatment and at the subsequent visits will be used as reference for the assessment (Appendix 3).

5.2.6. Facial Static Investigator Global Assessment (FsIGA)

The Facial Static Investigator Global Assessment (FsIGA) is a global score of vitiligo severity for the face only. The outcome measure incorporates location, distribution, size, depigmentation within lesions and presence or absence of signs of activity. Examination of skin should be performed with both normal lighting and Woods lamp (Appendix 4).

5.2.7. Patient Global Impression of Change-Vitiligo (PaGIC-V)

The PaGIC-V is an assessment of improvement by the subject and is to be evaluated in this study **specifically with respect to facial vitiligo**. It is a 7-point scale comparing facial vitiligo at baseline with the subject's treated facial vitiligo at the study visit. (Appendix 5)

5.3. Other Evaluations

5.3.1. Medical Photography

Digital Photography will be conducted at all sites for all subjects according to the Schedule of Visits and Assessment (Section 1.3). Photos will be taken of the facial target patch at the Baseline visit prior treatment and at the subsequent visits as reference for the VNS assessment. Fixed, multi-angle photos will be taken at select sites for additional evaluation.

5.3.2. Pharmacokinetics Assessment

PK sampling will be performed according to the Schedule of Visits and Assessments (Section 1.3) for all subjects at all sites:

- PK will be evaluated through trough/pre-dose sampling at Baseline, Week 4, Week 12, and Week 24.

Subjects should apply investigational product 11-12 hours before the PK collection time.

PK samples will be collected while the subject is having safety labs drawn at applicable visits. The PK samples will be completed prior to investigational product application in the clinic. Ensure investigational product is not applied in the area where PK will be drawn.

5.4. Final Study Visit

The final study visit will take place at approximately Week 25. The procedures performed during this visit are as described in the Schedule of Visits and Assessments (Section 1.3). A 7-day scheduling window is allowed for this visit. Adverse events will be recorded as reported by the subject and followed to resolution (as necessary).

5.5. Early Termination Visit

If a subject is withdrawn or wishes to exit the study prior to the final study visit, an early termination visit will be scheduled. This visit should include the procedures and assessments that would be performed at the Week 24 visit as described in the Schedule of Visits and Assessments (Section 1.3).

5.6. Unscheduled Visit

Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted in the judgement of the Investigator.

The following information will be collected for all subjects:

- Concomitant medications/procedures
- AEs
- F-VASI, F/N-VASI, FOREARM-VASI (forearms and elbows), HAND-VASI, and T-VASI

5.7. Adverse Events

5.7.1. Adverse Event Definition

An adverse event (AE) means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug or device related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product or device, whether or not related to the medicinal (investigational) product or device.

The definition of an AE includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition has increased in severity, frequency, and/or duration or has an association with a worse outcome. A pre-existing condition that has not worsened during the study or involves an intervention, such as elective cosmetic surgery or a medical procedure while on study, is not considered an AE.

Adverse events resulting from device deficiency will also be reported. A device deficiency is inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling.

Irradiated site reactions will be considered adverse events if they exceed the expected irradiation reaction per the Investigator's discretion, require medical intervention (e.g. treatment with medication or dressings prescribed or applied by a physician) or discontinuation of phototherapy treatment.

5.7.2. Serious Adverse Event

The Investigator is responsible for ensuring that all serious adverse events observed by the clinical staff or reported by the subject that occur after signing of the informed consent through 30 days after the last day of the application of the investigational product or the end of study (whichever is later) are recorded in the subject's medical record and are submitted per SAE reporting requirements.

All SAEs will be reported to the Sponsor (or delegate) within 24 hours of becoming aware of the event, whether or not the serious events are deemed IP related. All serious event reporting will adhere to ICH E6: Guideline for Good Clinical Practice and ICH E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.: The ERB/IRB will be notified of the Alert Reports as per HC, FDA, ICH and the IRB/ERB's policies and procedures. Refer to the Safety Reporting Instructions for SAE reporting.

An SAE is any AE that in the view of either the PI or Sponsor, results in any of the following outcomes: Death, a life threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such medical events include allergic bronchospasm requiring intensive

treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Life threatening is defined as an AE that in the view of the PI or Sponsor, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

Hospitalization does not include the following:

- Rehabilitation facilities, hospice facilities or respite care (e.g., caregiver relief)
- Nursing homes or skilled nursing facilities
- Emergency room visits
- Same day surgeries (as outpatient/same day/ambulatory procedures)
- <24 hour admissions for observation or evaluation

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition that did not worsen
- Hospitalizations for cosmetic elective surgery, social, and/or convenience admissions
- Pre-planned treatments or surgical procedures should be noted in the history documentation for the individual subject
- Diagnostic and therapeutic procedures, such as surgery, should not be reported as AEs; however, the medical condition for which the procedure was performed should be reported if it occurs during the reporting period and meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as an AE, and the resulting appendectomy should be recorded as treatment of the AE.

Unexpected is defined as an AE that is not listed in the IB or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the general investigational plan or elsewhere in the current study documentation.

If an SAE occurs to a subject on this study, contact the Medical Monitor within one business day of knowledge of event.

The definitions and reporting requirements of Health Canada/the Food and Drug Administration (FDA)/ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2A will be adhered to. If any AEs are serious, as defined by ICH Guidelines for Clinical Safety, required procedures will be followed.

5.7.3. Suspected Unexpected Serious Adverse Reaction (SUSAR)

This is defined as a serious adverse reaction, the nature or severity of which is not consistent with the known study treatment information. A serious event or reaction is not defined as a SUSAR when: 'it is serious but expected' or it does not fit the definition of an SAE, whether expected or not.

5.7.4. Safety Review with Subject

At each follow-up visit, subjects will be queried with an open-ended question such as: 'How have you been feeling since your last visit?' Additionally, the study staff will review subject diaries and, if it appears that a potential AE was recorded, study staff will query the subject and determine if an AE occurred.

Where appropriate, medical test(s) and/or examination(s) will be performed to document resolution and/or outcome of event(s).

5.7.5. Adverse Event Reporting

The Investigator is responsible for ensuring that all adverse events observed by the clinical staff or reported by the subject that occur after baseline the first application of investigational product through the end of the study are recorded in the subject's medical record and the eCRF.

AEs (whether serious or non-serious) and clinically significant abnormal laboratory test value(s) will be evaluated by the PI and treated and/or followed up for up to 30 days after end of treatment or until the symptoms or value(s) return to normal, or acceptable levels, as judged by the PI.

The Investigator will review each event and assess its relationship to investigational product treatment (unrelated, unlikely, possibly, probably, likely) or phototherapy treatment (unrelated, likely). Each sign or symptom reported will be graded on the NIH NCI CTCAE (Version 5.0) toxicity grading scale 5-point severity scale (Grade 1, 2, 3, 4 and 5). The date and time of onset, time relationship to drug dosing and/or phototherapy treatment, duration, and outcome of each event will be noted.

The relationship of each AE to the **investigational product** will be assessed using the following definitions:

Unrelated	The AE must clearly be caused by the subject's clinical state, or the study procedure/conditions. Definitely not related to drug. Temporal sequence of AE onset relative to administration of drug not reasonable. Another obvious cause of an AE.
Unlikely	Time sequence is unreasonable. There is another more likely cause for an AE.
Possibly	Corresponds to what is known about the drug. Time sequence is reasonable. Could have been due to another equally, likely cause.

Probably	Is a known effect of the drug. Time sequence from taking drug is reasonable. Ceases on stopping the drug. Cannot be reasonably explained by the known characteristics of the subject's clinical state.
Likely	Is a known effect of the drug (e.g., listed in Physicians' Desk Reference, Compendium of Pharmaceuticals and Specialties, IB). Time sequence from taking drug is reasonable. Event stops upon stopping drug, event returns upon restarting drug.

The relationship of each AE to the **phototherapy treatment** will be assessed using the following definitions:

Unrelated	The AE must clearly be caused by the subject's clinical state, or the study procedure/conditions. Definitely not related to phototherapy treatment. Temporal sequence of AE onset relative to phototherapy treatment not reasonable. Another obvious cause of an AE.
Likely	Is a known effect of the phototherapy treatment (e.g., listed in Fitzpatrick's Dermatology, 9th Edition). (Kang 2019) Time sequence from the phototherapy treatment is reasonable. Event stops upon cessation of phototherapy treatment, event returns upon restarting phototherapy treatment.

The following CTCAE toxicity grading scale 5-point severity scale definitions for rating maximum severity will be used:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.*
Grade 3	Severe or medically significant but not immediately life-threatening; Hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.** Note**:** An experience may be severe but may not be serious, e.g., severe headache).
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

Note: A semi-colon indicates 'or' within the description of the grade.

* Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The Investigator is responsible for the assessment of all adverse events to determine if the event is related to the Investigational Product, Phototherapy Treatment, or both. AEs will be coded using the most current MedDRA® version available at the start of the study (e.g., 21.0 or higher).

5.8. Reporting Pregnancy

During the study, all subjects should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period). If pregnancy is confirmed, Investigational Product must be discontinued immediately, the subject should be referred to an obstetrician experienced in reproductive toxicity for evaluation and counseling, and the subject should be followed until conclusion of the pregnancy. Subject may be required to sign a separate informed consent form to obtain pregnancy follow-up information, per local requirements.

The Investigator is responsible for reporting all available pregnancy information on the pregnancy report and submitting to the Medical Monitor within 24 hours of becoming aware of the event, although pregnancy itself is not considered an AE. Follow-up information detailing the outcome of the pregnancy and the health of the newborn should be reported as it becomes available. Any pregnancy resulting in a congenital abnormality or birth defect of the newborn, or neonatal death occurring within 30 days of the birth must be reported as a SAE, regardless of causality. Any infant death that occurs after the 30-day reporting period that the Investigator suspects is related to Investigational Product must also be reported as an SAE.

Partner pregnancies of a male subject will be reported.

5.9. Treatment Stopping Rules

If a subject has non-cutaneous adverse events of concern, clinically significant laboratory values or any condition that the Investigator determines could possibly be related to the investigational product, the Investigator should immediately contact the Medical Monitor to discuss if the subject should be discontinued from treatment with investigational product.

Treatment for any individual subject should be interrupted if the Investigator observes the following:

- If a subject develops an application site reaction with the clinical appearance of an 'irritation reaction', and with a severity of a Dermal Response Score of 5 (erythema, edema, and papules) on Local Tolerability Assessment (Section 5.1.8), treatment should be interrupted for up to one week and may then be resumed if the reaction has, in the opinion of the Investigator, adequately resolved.

For application site reactions treatment should be discontinued:

- If the application site reaction reoccurs, treatment should be discontinued permanently, and the subject followed until the reaction resolves.

Treatment for any individual subject will be discontinued if the subject experiences:

- A serious adverse event (SAE) or a clinically significant non-serious AE which in the opinion of the Principal Investigator or Medical Monitor warrants discontinuation from the study for that subject's well-being.
- A treatment-emergent severe (Grade 3) laboratory abnormality (confirmed by repeat sample) which in the opinion of the Principal Investigator or Medical Monitor warrants discontinuation from the study for that subject's well-being.
- A severe infection (Grade 3 or higher)
- An ischemic or thromboembolic cardiovascular event (regardless of Grade)
- A severe adverse event within the system-organ class of Cardiac Disorders (Grade 3 or higher)

As noted above, study treatment must be discontinued immediately in the event of a female subject's pregnancy.

In the event of a medical emergency where unblinding is required to provide medical care to the subject, refer to the most current IRT plan and Breaking Treatment Codes (Section 4.4.1). Contact the Medical Monitor and the Sponsor promptly.

6. STATISTICAL METHODS

Data will be handled and processed according to the Contract Research Organization's Standard Operating Procedures, which are written based on the principles of GCP.

6.1. Statistical Methods

The methodology presented below is a summary of the more detailed analysis plan that will be presented in the Statistical Analysis Plan (SAP). The SAP will be finalized before the database is locked and unblinded. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

All statistical processing will be performed using SAS® (Version 9.4) unless otherwise stated.

Descriptive statistics will be used to provide an overview of the safety, efficacy, and pharmacokinetic results. For categorical parameters, the number and percentage of subjects in each category will be presented. The denominator for percentage will be based on the number of subjects appropriate for the purpose of analysis. For continuous parameters, descriptive statistics will include n (number of subjects), mean, standard deviation (SD), median, minimum, and maximum.

Missing efficacy data for F-VASI will be imputed using multiple imputation.

For statistical comparisons other than those for the primary and hierarchical secondary endpoints, the overall 0.05 significance level will be used and no adjustments will be made for multiple comparisons.

6.1.1. Pharmacokinetics Assessment

Plasma pre-dose concentrations will be compared between treatment groups to evaluate potential differences.

6.1.2. Determination of Sample Size

The primary statistical comparison will be to compare

- ARQ-252 cream 0.3% in combination with phototherapy vs. vehicle cream in combination with NB-UVB
- ARQ-252 cream 0.3% in combination with phototherapy vs. ARQ-252 cream 0.3% in combination with sham phototherapy at the 5% significance level.

A sample size of 500 subjects will provide approximately 84% power to detect an ARQ-252 cream 0.3% in combination with phototherapy response rate of at least 50% vs. a vehicle cream in combination with phototherapy response of rate of 30% and approximately 84% power to detect an ARQ-252 cream 0.3% in combination with phototherapy rate of at least 50% vs. an ARQ-252 cream 0.3% in combination with sham phototherapy rate of 30% using a stratified Cochran-Mantel-Haenszel test conducted at the 0.025 alpha level for each comparison. A drop out rate of 15% at 24 weeks is assumed.

Upon successful testing for the comparisons above, a hierarchical testing scheme will be used to test the following secondary comparisons:

- ARQ-252 cream 0.3% in combination with phototherapy vs. vehicle cream BID in combination with the sham phototherapy
- ARQ-252 cream 0.3% in combination with sham phototherapy vs. vehicle cream BID in combination with the sham phototherapy
- Vehicle cream BID in combination with phototherapy vs. vehicle cream BID in combination with the sham phototherapy

Assuming a Vehicle cream BID in combination with the sham phototherapy rate of no more than 5%, these comparisons are expected to have at least 74% power. These comparisons will be made at either the 0.025 or 0.05 level, depending on the outcome of the primary statistical comparisons.

6.1.3. Subjects to Analyze

Three analysis populations will be defined:

- The Safety population will include all subjects who are enrolled and received at least one confirmed dose of investigational product. This population will be used for all safety analyses and will be defined separately for each treatment arm.
- The Intent-to-Treat (ITT) will include all subjects randomized in the study. This population will be the primary analysis for the analysis of efficacy endpoints.

- The PK population will include all subjects who are randomized and receive at least one application of investigational product and have at least one analyzed PK sample.

6.1.4. Background and Demographic Characteristics

Demographics, baseline disease characteristics, baseline height, weight, and BSA will be summarized descriptively for all enrolled subjects.

6.1.5. Study Disposition

The number of subjects randomized, receiving IP, completing study, and withdrawing prematurely (with reason for withdrawal) will be summarized by treatment group.

6.1.6. Investigational Product Application Compliance

The number of subjects with important protocol deviations and/or eligibility deviations will be summarized by category and by treatment group.

6.2. Efficacy Evaluation

Efficacy endpoints were evaluated by an independent rater as described in Section 5.2.1.

6.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint will be the proportion of subjects achieving F-VASI75 (≥ 75% improvement from baseline in Facial Vitiligo Area Scoring Index (F-VASI) score) at Week 24.

The primary endpoint of 'Proportion of subjects achieving F-VASI75 (≥ 75% improvement from baseline in Facial Vitiligo Area Scoring Index (F-VASI) score) at Week 24 will be analyzed using a Cochran-Mantel-Haenszel test stratified by the stratification factors study site and Fitzpatrick Skin Type (I-III vs. IV-VI). The analysis will be performed on the Intention-to-Treat (ITT) population and missing data will be imputed using multiple imputation.

6.2.2. Secondary Efficacy Endpoints

Continuous secondary endpoints will be analyzed using Analysis of Covariance with treatment and stratification factor as independent variables. Binary secondary endpoints will be analyzed similarly to the primary endpoint.

The secondary efficacy endpoints will include:

- Proportion of subjects achieving F-VASI75 (≥ 75% improvement from baseline in F-VASI score) at visits prior to Week 24.
- Percent change from baseline in F-VASI score at all visits.
- Percent change from baseline in facial body surface area (F-BSA) at all visits.
- Proportion of subjects achieving F-VASI50 (≥ 50% improvement from baseline in F-VASI score) at all visits.

- Proportion of subjects achieving F-VASI90 (≥ 90% improvement from baseline in F-VASI score) at all visits.
- Proportion of subjects in each category of VNS at specified visits.
- Change from Baseline in the VNS at specified visits.
- Change from Baseline in the VitiQoL at specified visits.
- Patient Global Impression of Change-Vitiligo (PaGIC-V), proportion of patients in each PaGIC-V category at specified visits.
- Proportion of subjects who report PaGIC-V of very much improved or much improved during the treatment period.
- Time to achieve F-VASI50.
- Time to achieve F-VASI75.
- Time to achieve FsIGA of clear or almost clear (0 or 1).
- FsIGA of clear or almost clear (0 or 1).
- FsIGA of clear or almost clear (0 or 1) plus 2-grade improvement from baseline.
- Time to achieve a PaGIC-V of very much improved or much improved.

The binary secondary endpoints will be analyzed using a Cochran-Mantel-Haenszel test stratified by study site, age ≤30 or >30 years, and Fitzpatrick Skin Type (I-III vs. IV-VI).

6.2.3. Exploratory Endpoints

- Percent change from baseline in combined face and neck body surface area (F/N-BSA) at all visits.
- Percent change from baseline in surface area BSA (hands/forearms/elbows) at all visits.
- Percent change from baseline in BSA affected across all treatable sites (face, neck, hands, forearms, elbows) at all visits.
- Proportion of subjects achieving F/N-VASI50 (≥ 50% improvement from baseline in F/N-VASI score) at all visits.
- Proportion of subjects achieving F/N-VASI75 (≥ 75% improvement from baseline in F/N-VASI score) at all visits.
- Proportion of subjects achieving F/N-VASI90 (≥ 90% improvement from baseline in F/N-VASI score) at all visits.
- Percent change from baseline in FOREARM-VASI (forearms/elbows) score at all visits.
- Percent change from baseline in HAND-VASI (hands only) score at all visits.

- Serum levels of ARQ-252.
- The proportions of subjects who maintain 80% treatment compliance with both application of ARQ-252 cream 0.3% or vehicle cream and phototherapy or sham phototherapy up through 24 weeks.

6.3. Safety Evaluation

Descriptive statistics will be calculated for safety data and presented by visit and treatment group for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data. Summaries of local tolerability will be presented by visit and treatment group.

6.3.1. Adverse Events

All AEs occurring during the study will be recorded and classified on the basis of MedDRA terminology for the safety population. AEs will be summarized by treatment group, the number of subjects reporting AEs, system organ class, preferred term, severity, relationship, and seriousness.

Serious adverse events (SAEs) will be listed by subject. SAEs will be summarized by treatment group, severity, and relationship to study treatment. For AEs, each subject will be counted only once within a system organ class or a preferred term using the event with the greatest relationship and greatest severity.

All information pertaining to AEs noted during the study will be listed by subject, detailing the verbatim description given by the Investigator, preferred term, system organ class, start date, stop date, severity, action taken regarding IP, corrective treatment, outcome, and IP and/or phototherapy relatedness. The event onset will also be shown relative (in number of days) to date of first application.

In addition, a listing of subjects who prematurely discontinue from the IP due to adverse events will also be provided.

6.3.2. Local Tolerance Assessment

For the Investigator's and Subject's assessment, the numeric application site reaction scores will be summarized individually by using number and percentage of subjects by visit, as well as mean/median scores.

6.3.3. Medical History and Physical Examinations

Clinically significant changes observed during physical examination will be captured as adverse events and included in AE tabulations.

6.3.4. Clinical Laboratory Results and Vital Signs

All clinical laboratory results and ECG measurements and their change from Baseline (pre dose), will be summarized descriptively by parameter, along with time point of collection.

A shift table describing out-of-normal range shifts will be provided for clinical laboratory results.

6.3.5. Prior and Concomitant Medications

Prior and concomitant medication information for all enrolled/randomized subjects will be presented in electronic datasets. Summary tables will be presented by World Health Organization-Anatomical Therapeutic Chemical Classification System (WHO-ATC) therapeutic category and product.

6.3.6. Pharmacokinetic Analysis

Plasma drug concentrations at pre-dose will be summarized using descriptive statistics.

A manual for blood sampling, collection, processing, and sample shipment will be provided in a separate document.

7. STUDY ADMINISTRATION

7.1. Ethics

7.1.1. Ethics Review Board

Before enrollment of subjects into the study, the current protocol and ICF will be reviewed and approved by an appropriate IRB or IEC, as required by FDA (21 CFR § 56), Health Canada, ICH GCP regulations and other local/regional regulatory requirements. A letter documenting the IRB or IEC approval must be received by the Sponsor (or delegate) before the initiation of the study at a clinical site. Amendments to the protocol will be subject to the same requirements as the original protocol.

The Investigator, Sponsor, or designee will submit a progress report at least once yearly to the IRB or IEC. However, the frequency of these reports will depend on IRB or IEC requirements. As soon as possible after completion or termination of the study, the Investigator will submit a final report to the IRB or IEC per the IRB or IEC requirements, and in compliance with FDA, Health Canada, local and regional regulations and ICH GCP guidelines.

The Investigator, the Sponsor, or designee shall promptly notify the IRB or IEC of any SAEs, SUSARs, or any other information that may affect the safe use of the investigational products during the study, per the IRB or IEC local requirements, and in compliance with FDA and Health Canada regulations and ICH GCP guidelines.

7.1.2. Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, the principles of the Tri Council Policy Statement (TCPS), the ethical principles set forth in the Declaration of Helsinki, and the ICH harmonized tripartite guideline regarding GCP (E6 (R2), Nov 2016) and the applicable regulations of the country(ies) in which the trial is conducted.

7.1.3. Subject Information and Consent

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the subjects in non-technical terms. Subjects will be required to read, sign and date a current version of the IRB/EC approved ICF summarizing the discussion prior to enrollment and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Subjects will be given a signed copy of their ICF.

7.2. Study Monitoring

Prior to the initiation of the clinical investigation, Sponsor representatives or designees will visit the clinical site where the investigation is to be conducted. Sponsor representatives shall ensure that the Investigator understands the investigational status of the investigational product, all requirements of the investigation to be undertaken, and all of his/her responsibilities as an Investigator. Sponsor representatives will also visit the clinical site at appropriate intervals as required to ensure compliance with the protocol and to verify the accuracy and completeness of data reported on the CRFs. The Study Director or designees shall be available for consultation with the Investigator and serve as liaisons between the clinical site and the Sponsor.

The Sponsor or authorized designees may inspect all documents and records required to be maintained by the Investigator, including but not limited to medical records (office, clinic, or hospital) and investigational product dispensation logs for the subjects in this clinical investigation. The Investigator must permit access to such records. The Investigator must obtain, as part of informed consent, permission for an authorized representative of the Sponsor, or regulatory authorities, to review, in confidence, any records identifying subjects.

7.3. Study Completion/Termination

7.3.1. Study Completion

The study is considered completed with the last visit of the last subject participating in the study. The final data from the investigational site will be sent to the Sponsor (or designee) after completion of the final subject visit at that site, in the time frame specified in the Clinical Trial Agreement.

7.3.2. Study Termination

The Sponsor reserves the right to close the investigational site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Investigational sites will be closed upon study completion. An investigational site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed. The Investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of an investigational site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the Investigator.
- Discontinuation of further IP development

7.4. Data Quality Assurance

In order to ensure the collection of accurate, consistent, complete, and reliable data during this clinical study, Sponsor representatives or designees may conduct audits of participating clinical study sites at appropriate intervals throughout the study. The results of these periodic clinical study site audits may be subject to review by independent auditors at completion of the clinical investigation.

The Clinical Study Report will undergo QC review by the Clinical Research Organization's Quality Assurance (QA) department.

All clinical data will undergo a quality control check prior to clinical database lock. Edit checks are performed for appropriate databases as a validation routine to check for missing data, data inconsistencies, data ranges etc. Corrections are made prior to database lock.

7.5. Data Handling and Record Keeping

During the clinical study, the Investigator will maintain adequate records, including medical records, records detailing the progress of the study for each subject, laboratory reports, signed informed consent forms, investigational product disposition records, correspondence with the ERB/IRB and Study Monitor/Sponsor, AE reports, and information regarding subject discontinuation and completion of the clinical investigation.

All required study data will be recorded on CRFs. Any change of data will be recorded on the audit trail and a reason for the change will be entered.

The Principal Investigator must retain all documentation relating to the study for a period of at least 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation. If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is less than 2 years.

7.6. Protocol Amendments and Deviations

No change or amendment to this protocol may be made by the Investigator or Sponsor after the protocol has been agreed to and signed by all parties unless such change(s) or amendment(s) has (have) been agreed upon by the Investigator and Sponsor. Any change agreed upon will be recorded in writing, and the written amendment will be signed by the Investigator and Sponsor. Institutional review board approval is required prior to the implementation of an amendment,

unless overriding safety reasons warrant immediate action, in which case the IRB(s) will be promptly notified.

No deviation from the protocol will be made except to protect the life or physical well-being of a subject in an emergency. Except in such emergencies, prior approval of the Sponsor, and the IRB, is required before deviations from the planned protocol. All protocol deviations that occur during the study will be documented and reported to Sponsor and to the IRB(s), if applicable, according to regulations. Further details about the documentation, evaluation, and follow-up of protocol deviations are detailed in this study's clinical monitoring plan.

No waivers to inclusion/exclusion criteria will be granted; subjects need to meet all criteria, exactly as specified, to be enrolled. Additionally, prospective deviations from the protocol or investigational plan are not permitted except to protect the life or physical well-being of a subject in an emergency. Deviations that occur unintentionally or are the result of action by the subject must be documented and reported to the IRB(s), if applicable, according to regulations. Further details about the documentation, evaluation, and follow-up of protocol deviations are detailed in this study's clinical monitoring plan.

7.7. Confidentiality and Privacy

The Investigator must assure that subjects' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code and any other unique identifier(s) as allowed by local law (such as date of birth) will be recorded on any form or biological sample submitted to the Sponsor.

The Investigator agrees that all information received from Arcutis Biotherapeutics, Inc., including but not limited to the Investigator's Brochure, this protocol, CRF/eCRF, the IP, and any other study information, remain the sole and exclusive property of Arcutis Biotherapeutics, Inc. 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 Arcutis Biotherapeutics, Inc. 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.

7.8. Conflict of Interest

All study Investigators will provide documentation of their financial interest or arrangements with Arcutis Biotherapeutics, Inc., or proprietary interests in the investigational product under study. This documentation must be provided prior to the Investigator's participation in the study. All Investigators with reported conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this study.

7.9. Report Format

According to the ICH Harmonized Tripartite Guideline (Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use M4 and the ICH M2 Expert Working Group), the final report will be written according to the ICH E3 Guideline (Structure and Content of Clinical Study Reports).

7.10. Publication Policy

The Sponsor is supportive of publishing clinical trial findings. Any form of publication that is derived from this study must be submitted to Arcutis Biotherapeutics, Inc. for review and approval. The process of coordinating publication efforts is detailed in the Clinical Trial Agreement.

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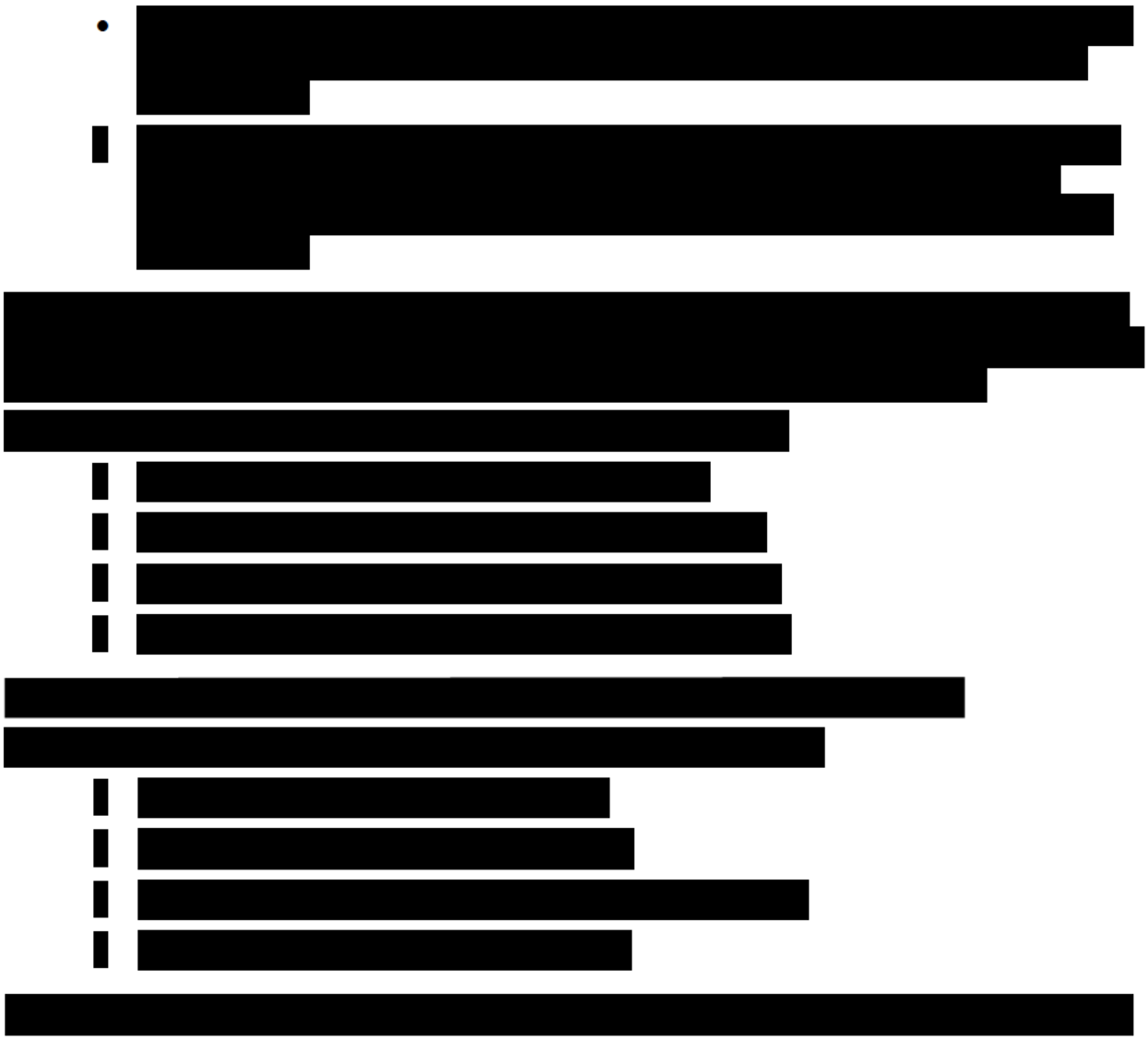
9. APPENDICES

APPENDIX 1. VITILIGO NB-UVB TREATMENT PROTOCOL



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APPENDIX 2. VITILIGO QUALITY OF LIFE QUESTIONNAIRE

VitiQoL

The aim of these questions is to measure how much your skin has affected you over the past month.

During the past month,	Not at all ↓			•			All of the time ↓
1. Have you been bothered by the appearance of your skin condition?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
2. Have you felt frustrated about your skin condition?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
3. Has your skin condition made it hard to show affection?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
4. Has your skin condition affected your daily activities?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
5. When you were talking to someone, have you worried about what they may be thinking of you?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
6. Have you been afraid that people will find fault with you?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
7. Have you felt embarrassed or self-conscious because of your skin?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
8. Has your skin condition influenced the clothes you wear?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
9. Has your skin condition affected your social or leisure activities?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
10. Has your skin condition affected your emotional well-being?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
11. Has your skin condition affected your overall physical health?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
12. Has your skin condition affected your grooming practices (i.e. hairstyle, use of cosmetics)?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
13. Has your skin condition affected your sun protection efforts during recreation (i.e. limiting exposure time during peak sun hours, seeking shade, wearing hat, long sleeves or pants)?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
14. Has your skin condition affected your chances for making new friends?	☐0	☐1	☐2	☐3	☐4	☐5	☐6
15. Have you worried about progression or spread of disease to new areas of the body?	☐0	☐1	☐2	☐3	☐4	☐5	☐6

Please check how severe you currently feel your skin condition is:	No skin involvement ↓			•			Most severe case ↓
16. Severity of skin condition.	☐0	☐1	☐2	☐3	☐4	☐5	☐6

Have you answered every item? Yes ☐ No ☐

Questions 7,8 and 9 ©A Y Finlay, G K Khan, April 1992, modified and used with permission

The validation of this instrument is described in (Lilly 2013).

APPENDIX 3. VITILIGO NOTICABILITY SCALE (VNS)

The Vitiligo Noticeability Scale (VNS) is a 5-point scale which compares vitiligo from before treatment to how noticeable the vitiligo is at the time the VNS is performed. The VNS will be completed by subjects with respect to vitiligo on the facial target patch. The target patch on the face is selected by the subjects as being the patch that they would most like to see an improvement in. The photos taken of the facial target patch at the Baseline visit prior treatment and at the subsequent visits will be used as reference for the assessment.

"Compared to before treatment, how noticeable is the vitiligo now?

More noticeable (1)

As noticeable (2)

Slightly less noticeable (3)

A lot less noticeable (4)

No longer noticeable (5)

- VNS score of 1 or 2 = treatment not successful
- VNS score of 3 = treatment partially successful
- VNS score of 4 or 5 = treatment successful

Validation of this instrument is described in (Batchelor 2016).

APPENDIX 4. FACIAL STATIC INVESTIGATOR GLOBAL ASSESSMENT (FsIGA)

Facial Static Investigator Global Assessment (FsIGA) Outcome Measure

Examination of skin should be performed with both normal lighting and a Woods lamp

0 - Clear- No signs of vitiligo

1 - Almost clear- Faint, barely detectable loss of pigmentation mainly located on the forehead, periocular skin, lips and/or limited areas; approximately 90% pigmentation within lesions; no or rare signs of Koebner phenomenon, confetti-like or trichrome lesions may be present

2 - Mild vitiligo- Mild loss of pigmentation mainly located on the forehead, periocular skin, lips, and/or limited areas; approximately 75% pigmentation within lesions; few signs of Koebner phenomenon, confetti-like or trichrome lesions may be present

3 - Moderate vitiligo- Moderate loss of pigmentation affecting several areas of the face with large patches; approximately 50% pigmentation within lesions; a moderate number of signs of Koebner phenomenon, confetti-like or trichrome lesions may be present

4 - Severe vitiligo- Extensive loss of pigmentation affecting most areas of the face; approximately 25% or less pigmentation within lesions; many signs of Koebner phenomenon, confetti-like or trichrome lesions affecting several areas of the body may be present

Score	Short Descriptor	Detailed Descriptor
0	Clear	No signs of vitiligo
1	Almost Clear	Faint, barely detectable loss of pigmentation mainly located on the forehead, periocular skin, lips, and/or limited areas; approximately 90% pigmentation within lesions; no or rare signs of Koebner phenomenon, confetti-like or trichrome lesions may be present
2	Mild Vitiligo	Mild loss of pigmentation mainly located on the forehead, periocular skin, lips, and/or limited areas; approximately 75% pigmentation within lesions; few signs of Koebner phenomenon, confetti-like or trichrome lesions may be present

Score	Short Descriptor	Detailed Descriptor
3	Moderate Vitiligo	Moderate loss of pigmentation affecting several areas of the face with large patches; approximately 50% pigmentation within lesions; a moderate number of signs of Koebner phenomenon, confetti-like or trichrome lesions may be present
4	Severe Vitiligo	Extensive loss of pigmentation affecting most areas of the face; approximately 25% or less pigmentation within lesions; many signs of Koebner phenomenon, confetti-like or trichrome lesions affecting several areas of the body may be present

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APPENDIX 5. PATIENT GLOBAL IMPRESSION OF CHANGE-VITILIGO (PAGIC-V)

The PaGIC-V is an assessment of improvement by the subject, and is to be evaluated in this study **specifically with respect to facial vitiligo**. It is a 7-point scale comparing facial vitiligo at baseline with the subject's treated facial vitiligo at the study visit.

The subject will answer the following:

Since the start of the treatment you've received in the study, the vitiligo on your face treated with the study drug is:

(1) very much improved

(2) much improved

(3) minimally improved

(4) no change

(5) minimally worse

(6) much worse

(7) very much worse