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Protocol Title:	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
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Approvals

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Document History

Not applicable.

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List of Abbreviations

Abbreviation	Definition
aCRF	annotated case report form
ADR	adverse drug reactions
AE	adverse event
AESI	adverse events special interest
ANCOVA	analysis of covariance
ATC	anatomical therapeutic chemical
BID	Twice daily
BLQ	below limit of quantification
BMI	body mass index
CI	confidence interval
CRF	case report form
CS	clinically significant
CSR	clinical study report
COVID-19	Novel coronavirus disease
DBL	database lock
DBP	diastolic blood pressure
DLT	dose limiting toxicity
DMC	data monitoring committee

Abbreviation	Definition
DOB	date of birth
DSMB	data safety monitoring board
DSUR	development safety update report
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EMA	European medicines agency
FDA	food and drug administration
FSIGA	Facial Static Investigator Global Assessment
GCP	good clinical practice
HR	heart rate
IB	investigator's brochure
IP	investigational product
IRB	institutional review board
IRR	infusion related reactions
IRT	interactive response technology
ITT	intent-to-treat
LLOQ	lower limit of quantification
MedDRA	medical dictionary for regulatory activities

Abbreviation	Definition
MI	multiple imputation
MMRM	mixed model for repeated measurements
MTD	maximum tolerated dose
NA	not applicable
NCS	non-clinically significant
PAGIC	Patient Global Impression of Change
PD	protocol deviation
PK	pharmacokinetic
PKAP	pharmacokinetic analysis plan
PP	per-protocol
RR	respiratory rate or relative rate
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SOC	system organ class
SOP	standard operating procedure
SUSAR	suspected, unexpected, serious adverse (drug) reaction

Abbreviation	Definition
TEAE	treatment-emergent adverse event
VASI	Vitiligo Area Scoring Index
VITIQOL	Vitiligo Quality of Life Questionnaire
VNS	Vitiligo Noticeability Scale
WHO-DD	world health organization drug dictionary

1. Overview

This statistical analysis plan (SAP) describes the planned analysis and reporting for Arcutis Biotherapeutics, Inc. protocol number 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), dated 14-Apr-2021 Amendment Version 1 (US) and 30-Apr-2021 Amendment Version 1 (CAN). Reference materials for this statistical plan include the protocol and the accompanying sample data collection documents. Operational aspects related to collection and timing of planned clinical assessments are not repeated in this SAP unless relevant to the planned analysis.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA), European Medicines Agency (EMA), and International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Statistical Principles in Clinical Trials (ICH, 1998). All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association (ASA, 2018) and the Royal Statistical Society (RSS, 2014), for statistical practice.

The planned analyses identified in this SAP may be included in clinical study reports (CSRs), regulatory submissions, or future manuscripts. Also, post-hoc exploratory analyses not necessarily identified in this SAP may be performed to further examine study data. Any post-hoc or unplanned, exploratory analysis performed will be clearly identified as such in the final CSR.

Upon sponsor discretion, this study was terminated before the enrolled subjects could finish their treatment period. The statistical plan described hereafter is an *a priori* plan. It will be approved before any inferential or descriptive analysis of data pertaining to Arcutis Biotherapeutics, Inc.'s study ARQ-252-213.

2. Study Objectives and Endpoints

2.1. Study Objectives

2.1.1. Primary Objective

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

2.1.2. Secondary Objectives

The secondary objective of this study is 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.

2.2. Study Endpoints

2.2.1. Efficacy Endpoints

Upon sponsor discretion, this study was terminated before the enrolled subjects could finish their treatment period. As a result, only descriptive summaries are provided for in Facial Vitiligo Area Scoring Index (F-VASI), and no additional efficacy analyses are conducted.

2.2.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint of this study is proportion of subjects achieving F-VASI75 (≥ 75% improvement from baseline F-VASI score) at Week 24.

2.2.1.2. Secondary Efficacy Endpoint(s)

The secondary efficacy endpoints of this study include the following:

- 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 Vitiligo Noticeability Scale (VNS) at specified visits.
- Change from Baseline in the VNS at specified visits.
- Change from Baseline in the Vitiligo-Specific Quality of Life Instrument (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.

2.2.1.3. Exploratory Efficacy Endpoint(s)

The exploratory efficacy endpoints of this study include the following:

- 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.

2.2.2. Safety Endpoints

The safety endpoints of this study include the following and will be conducted:

- Adverse events (AEs)
- Local tolerability assessments
- Clinical laboratory parameters
- Vital signs

- Physical examinations
- 12-lead electrocardiograms (ECGs)
- Prior and concomitant medications

3. Overall Study Design and Plan

This is a 24-week, parallel group, double blind, vehicle-controlled study for the treatment of subjects with non-segmental facial vitiligo. This study was planned to include both male and female adults having a facial BSA ≥ 0.25% and F-VASI ≥ 0.25. A total of 500 subjects were planned to be randomized. After having met all inclusion criteria, and none of the exclusion criteria, subjects were to be randomized in a 3:3:3:1 ratio as mentioned below in Section 3.4. Screening for up to 5 weeks followed by 24 weeks of treatment phase was planned for this study. In addition to the study drug ARQ-252 cream and vehicle cream, subjects were randomized to receive Daavlin series NB-UVB active or sham units. Subjects have to record the date and time each dose has been applied, any missed doses, and any additional comments. There was a follow-up visit approximately 1 week after treatment has been completed.

Upon the sponsor discretion, this study was terminated and none of the subjects could finish the entire treatment period. All the subjects that were currently enrolled have been early terminated and subjects that are in screening have been screen failed. Emergency unblinding was performed after following Premier Research SOPs.

3.1. Overall Design

3.2. Sample Size and Power

The primary statistical comparisons 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 was planned to 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 was 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.

3.3. Study Population

The study population consists of male and female adults (>18 y/o) with facial non-segmental vitiligo having F-BSA ≥ 0.25% and F-VASI ≥ 0.25, with a maximum BSA (total body inclusive of the face, whether or not in areas to be treated in this study) of 15%.

3.4. Treatments Administered

Subjects who meet the eligibility criteria will be randomized to 1 of the 4 following treatment groups in a 3:3:3:1 ratio:

- ARQ-252 cream 0.3% BID with NB-UVB phototherapy
- ARQ-252 cream 0.3% BID with sham NB-UVB phototherapy
- Vehicle cream BID with NB-UVB phototherapy
- Vehicle cream BID with sham NB-UVB phototherapy

3.5. Method of Assigning Subjects to Treatment Groups

Subjects will be randomized and assigned to treatment arm in a 3:3:3:1 ratio according to a computer-generated randomization list. Randomization will be stratified by study site and FitzPatrick skin type (I-III or IV-VI), with at least 50% of subjects having Fitzpatrick skin type IV-VI.

3.6. Blinding and Unblinding

The study was planned to be double-blinded, therefore neither the subjects nor the Investigator, Independent Rater, or clinical site personnel were aware of which investigational product (ARQ- 252 0.3% cream or vehicle cream) or NB-UVB phototherapy unit (Active or Sham) the subject receives. However, upon the sponsor discretion, the study was terminated and treatment unblinding was performed following Premier Research SOPs.

3.7. Schedule of Events

A detailed schedule of events for the study is provided in Table 1.

Table 1: Schedule of Events

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 surgicalhistory	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								

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**
Follicle-StimulatingHormone (FSH)[n]	X								
PK Sampling[o]		X	X		X			X	
NB-UVB Phototherapy inclinic[p]		X							
Return of USB stick to sitefor 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 the protocol.

[e] Vitiligo Area Scoring Index (VASI) per the protocol: 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 the protocol.

[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 the protocol.

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.

[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 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 willbe 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.

4. Statistical Analysis and Reporting

4.1. Introduction

Data processing, tabulation of descriptive statistics, calculation of inferential statistics, and graphical representations will primarily use SAS (release 9.4 or higher). If the use of other software is warranted, the final statistical methodology report will detail what software was used for what purposes.

Continuous (quantitative) variable summaries will include the number of subjects (n) with non-missing values, mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum.

Categorical (qualitative) variable summaries will include the frequency and percentage of subjects who are in the particular category or each possible value. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the study population for the treatment group, unless otherwise specified. The denominator for by-visit displays will be the number of subjects in the relevant study population with non-missing data at each visit.

The minimum and maximum will be reported with the same degree of precision (i.e., the same number of decimal places) as the observed data. Measures of location (mean, median, Q1, and Q3) will be reported to 1 degree of precision more than the observed data and measures of spread (SD) will be reported to 2 degrees of precision more than the observed data.

Percentages will be presented to 1 decimal place, unless otherwise specified.

No formal hypothesis testing was done for this study.

4.2. Interim Analysis and Data Monitoring

No interim analyses are planned.

5. Analysis Populations

The following analysis populations are planned for this study:

- **Safety Population (SAF):** The Safety population includes all subjects who are enrolled and received at least 1 confirmed dose of investigational product (IP). This population will be used for all safety analyses.
- **Intent-To-Treat Population (ITT):** The ITT population includes all randomized subjects in the study. This population will be used for efficacy descriptive summaries along with disposition.
- **Pharmacokinetic Population (PK):** The PK population will include all subjects who are randomized and receive at least 1 application of IP and have at least 1 analyzed PK sample.

6. General Issues for Statistical Analysis

The study was terminated based on sponsor's decision. All the analysis are in descriptive nature. No formal test will be performed.

6.1. Statistical Definitions and Algorithms

6.1.1. Baseline

For assessments where time was recorded (e.g., ECG), the last observation recorded before the first application of study drug will be used as the baseline observation for all calculations of change from baseline. For assessments where time was not recorded, the last observation recorded on or before the day of first application of study drug will be used as the baseline observation for all calculations of change from baseline.

For subject tolerability assessments, baseline is derived as the last non-missing measurement taken on the day of first application of study drug.

6.1.2. Adjustments for Covariates

No adjustment for covariates will be made for this study. All the analyses are descriptive, and no subgroup analysis will be performed.

6.1.3. Multiple Comparisons

No adjustments will be made for multiple comparisons because there will be no formal hypothesis testing, nor any inferential statistical analyses, only descriptive summaries.

6.1.4. Handling of Dropouts or Missing Data

No inferential statistical analyses are planned for this study.

6.1.5. Analysis Visit Windows

Safety and efficacy data will not be windowed and will be analyzed as per the nominal visit present in the database.

6.1.6. Pooling of Sites

Not applicable.

6.1.7. Derived Variables

- **Weight of IP (g)** = dispensed tube weight – returned tube weight.

- **Number of expected IP applications** = calculated as 2 * (last treatment date - first treatment date + 1).
- **Number of IP applications** = number of expected IP applications – missed IP applications as collected in the case report form (CRF). As the time of missing dose is not captured in the CRF, only the dates will be used in determining number of missed doses; if 2 records exist for the same date, that will be considered as 2 missed IP applications.
- **Days on IP** = Calculated as last treatment date – first treatment date + 1. For subjects who are missing the date of last study drug application, for any reason, the last known contact date from subject visits CRF will be used in the calculation of treatment duration.
- **BMI (kg/m2)** = (weight in kg)/[(height in cm/100)2]. For all visits, baseline height will be used to derive BMI since height is collected only at baseline.
- **Change from baseline** = value at current time point – value at baseline.
- **Percent change from baseline** = (value at current time point – value at baseline)/value at baseline.
- **TEAE** = any AE with an onset date/time after the first application of IP. If time is unavailable, any AE occurring on or after the date of first application of IP will be considered treatment emergent.

6.1.8. Data Adjustments/Handling/Conventions

Upon the sponsor discretion, only safety and limited efficacy will be presented in Clinical Data Interchange Standards Consortium (CDISC) datasets. Data not subject to analysis according to this plan will not appear in any tables or graphs or listings or the CDISC datasets.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.1 thesaurus.

A treatment-related AE to study drug is any AE with a relationship to the study drug of possibly, probably, likely, or missing.

A treatment-related AE to phototherapy treatment is any AE with a relationship to the phototherapy treatment of likely or missing.

For partial AE and medication start dates:

- If the year is unknown, then do not impute the date but assign a missing value.
- If the year is known, but the month or month and day is unknown, then:
    - If the year matches the year of first dose date and the end date (if present) is after first dose date, then impute as the month and day of the first dose date.

- Otherwise, assign 01 January.

- If the year and month are known, but the day is unknown, then:
  - If the month and year match the month and year of the first dose date, then impute as the day of the first dose date.
  - Otherwise, assign 01.

For partial AE and medication end dates:

- If the year is unknown, then do not impute the date but assign as missing value.
- If the year is known, but the month or month and day is unknown, then:
  - If the year matches the year of the last date of the study (date of last contact if subject lost to follow-up; date of completion or early termination otherwise), then impute as the month and day of the last date of the study.
  - Otherwise, assign 31 December.
- If the year and month are known, but the day is unknown, then:
  - If the month and year match the month and year of the last date of the study, then impute as the day of the last date of the study.
  - Otherwise, assign the last day of the month.

7. Study Subjects and Demographics

7.1. Disposition of Subjects and Withdrawals

Disposition will include tabulations of the number of subjects randomized into each treatment group, the number of subjects who received treatment, subjects completing the study, tabulated reasons for discontinuation from the study overall and due to COVID-19 disruption, and number of subjects in each analysis population. Disposition will be summarized for all subjects who were entered into database by treatment group and overall.

7.2. Demographics and Other Baseline Characteristics

Summary statistics for age, age group (age ≤ 30, age > 30), gender (including child-bearing potential), race, ethnicity, height, weight, baseline disease characteristics (F-VASI, Fitzpatrick skin type), percent total BSA affected by vitiligo, percent BSA affected by vitiligo on face, and BMI will be presented by treatment group and overall.

For the continuous variables, the number of non-missing values and the mean, standard deviation, minimum, Q1, median, Q3, and maximum will be tabulated.

For the categorical variables, the counts and proportions of each value will be tabulated.

These analyses will be conducted for the Safety population.

7.3. Exposure and Compliance

The number of IP applications by each subject based on diary data will be summarized using descriptive statistics appropriate for continuous variables.

The amount of IP used by each subject based on tube weight will be summarized descriptively by treatment group using continuous methods.

The number of days on IP will be summarized descriptively by treatment group using continuous methods.

8. Efficacy Analysis

Due to the study termination, it was the sponsor decision to not execute any efficacy analyses. Though the protocol indicates primary and secondary endpoints, upon the sponsor decision only F-VASI summaries will be provided based on observed value. Hence, observed, change and percent change from baseline in F-VASI scores will be summarized descriptively by treatment group using ITT population.

9. Safety and Tolerability Analysis

Safety will be evaluated from reported AEs, physical examinations, local tolerability assessments, and changes in 12-lead ECGs, clinical laboratory values, and vital signs/weight. No inferential statistical tests will be performed.

All safety analyses will be performed on the Safety population.

9.1. Adverse Events

All AEs, TEAEs, and SAEs will be coded using the MedDRA dictionary version 23.1.

A TEAE is defined as an AE with an onset date/time on or after the first application of IP. An overall summary of TEAEs will be provided; this will present number and percent of subjects who reported at least 1 of the following: TEAE (including all TEAEs, TEAEs by maximum severity, and related TEAEs to study drug and phototherapy), SAE, discontinued the study due to a TEAE, discontinued the study drug due to a TEAE, and discontinued the phototherapy due to a TEAE.

The number and percent of subjects reporting TEAEs, grouped by MedDRA system organ class (SOC) and preferred term, will be tabulated by severity or greatest relationship to study drug and treatment group. In the case of multiple occurrences of the same TEAE within the same subject, each subject will only be counted once for each preferred term. In addition, summary by greatest relationship to the phototherapy treatment will be tabulated similarly.

In the summaries showing severity and relationship to study medication the event with the maximum severity (mild < moderate < severe < life-threatening < death) will be reported. If a particular event is missing the severity, then the strongest possible severity will be assumed for analysis (severity = severe).

In the AE data listings, all AEs will be displayed. Any AEs that are treatment emergent will be flagged.

9.1.1. Adverse Events Leading to Withdrawal

AEs leading to withdrawal of study drug will be flagged in the AE listing, displaying details of the event(s) captured on the CRF.

9.1.2. Deaths and Serious Adverse Events

No deaths occurred during the course of study.

9.2. Local Tolerability Assessments

The investigator's assessment of the application site reaction will be summarized by study visit and treatment group using both categorical methods (number and percentage of subject with each score) as well as continuous methods (e.g., mean, median, etc.). Categorical summaries will be provided for dermal response as well as other effects. No inferential statistical tests will be performed. This assessment should be performed prior to the application of IP in the study site. Subjects not meeting this condition on baseline visit are completely removed from the table summary.

The subject's assessment of the application site reaction will be summarized similarly. This assessment should be performed 10 – 15 minutes after the application of IP in the study site. Subjects not meeting this condition on baseline visit are completely removed from the table summary.

9.3. Clinical Laboratory Evaluations

Laboratory test results will be summarized descriptively by treatment and study visit as both observed values, changes, and percent changes from baseline values for continuous hematology, chemistry, and urinalysis results. Categorical urinalysis results will be summarized using frequencies by study visit and treatment.

Abnormal results will be flagged in the listings.

9.4. Vital Signs

Descriptive summaries of observed values, changes, and percent changes from baseline will be calculated for systolic blood pressure, diastolic blood pressure, heart rate, weight, BMI, and oral body temperature by treatment group and study visit.

9.5. 12-Lead Electrocardiograms

Descriptive summaries for observed values and change from baseline will be presented for 12-lead ECG measures of PR interval, QRS interval, QT interval, QTc interval (Fridericia's [QTcF] correction method), and heart rate. These summaries will be presented by study visit and treatment group.

The number and percentage of subjects with each ECG investigator interpretation (normal; abnormal, not clinically significant; or abnormal, clinically significant) will be displayed for each treatment group and study visit. If the interpretation results are different in CRF and external data, only the CRF data will be summarized in the tables. If the interpretation results are just collected in one source, that will be used for table summaries.

9.6. Physical Examination

The number and percentage of subjects with normal; abnormal, not clinically significant; or abnormal, clinically significant findings in the physical examination will be displayed at each study visit by body system and treatment group. Subjects having abnormal findings with description of Vitiligo are removed from table summary upon the sponsor request.

9.7. Concomitant Medications

Prior and concomitant medications will be summarized descriptively by treatment group, Anatomical Therapeutic Chemical (ATC) Class Level 4, and Preferred Term using counts and percentages.

Prior medications will be presented separately from concomitant medications. Medications that started before the first application of IP will be considered prior medications whether or not they were stopped before the first application of study drug. Any medications continuing or starting after the first application of study drug will be considered to be concomitant. If a medication starts before the first application of study drug and continues after the first application of study drug it will be considered both prior and concomitant.

Medications will be coded using WHODrug Enhance Global B3G, version September 2020.

10. Changes from Planned Analysis

This study was planned for 24 weeks to evaluate safety and efficacy ARQ-252 Cream 0.3% in Subjects with Non-Segmental Facial Vitiligo. However, upon the sponsor discretion the study

terminated and all the subjects that were currently enrolled are early terminated. Due to this decision, the following actions were taken which deviates from the planned analyses in the protocol:

- Emergency unblinding was done after following Premier Research SOPs.
- Only summary statistics are provided for F-VASI and other safety endpoints.
- No statistical testing is performed and none of secondary endpoints are summarized.
- The SAP and shells are developed to provide only summary statistics and frequency distributions.

11. Other Planned Analysis

11.1. Pharmacokinetic Analysis

Plasma drug concentrations will be summarized using descriptive statistics by treatment group and time point.

12. References

ASA. (2018) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, April 2018. http://www.amstat.org/about/ethicalguidelines.cfm

ICH (1998). ICH Harmonised Tripartite Guideline. Statistical Principles for Clinical Trials E9; 1998. https://database.ich.org/sites/default/files/E9_Guideline.pdf

RSS. (2014) The Royal Statistical Society: Code of Conduct, 2014. https://rss.org.uk/about/policy-and-guidelines/code-of-conduct/.