Statistical Analysis Plan

Study Title:	**A Phase 2, 4-Week, Parallel Group, Double Blind, Vehicle-Controlled Study of the Safety and Efficacy of ARQ-151 Cream 0.05% and ARQ-151 Cream 0.15% Administered QD in Adolescent and Adult Subjects with Atopic Dermatitis**
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This statistical analysis plan will be reviewed and revised as needed. The most recent version will replace the previous version in place.

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ABBREVIATIONS

AD	atopic dermatitis
AE	adverse event
ANCOVA	analysis of covariance
ATC	anatomical therapeutic chemical
AUC	Area under the curve
BSA	body surface area
CI	confidence interval
C_{max}	Maximum Concentration
CMH	Cochran Mantel Haenszel
CRO	contract research organization
C-SSRS	Columbia Suicide Severity Rating Scale
EASI	Eczema Area and Severity Index
EASI50	improvement of at least 50% in the Eczema Area and Severity Index score
EASI75	improvement of at least 75% in the Eczema Area and Severity Index score
ECG	electrocardiogram
ET	early termination
IGA	Investigator's Global Assessment
IP	Investigational product
IWRS	Internet-based response system
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat (population)
MMRM	mixed model repeated measures
PHQ-8	Patient Health Questionnaire - 8
PK	pharmacokinetic
PP	per-protocol (population)
PR	PR interval
PT	preferred term
QD	Quaque die, once daily
QRS	QRS interval
QT	QT interval
QTcB	Bazett's correction formula for QT interval
QTcF	Fridericia's correction formula for QT interval
RR	RR interval
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis system®
SD	standard deviation
SOC	system organ class
TEAE	treatment emergent adverse event
TLF	tables, listings, and figures
vIGA-AD	Validated Investigator Global Assessment-Atopic Dermatitis
WHO-DD	World Health Organization Drug Dictionary

WI-NRS Worst Itch Numeric Rating Scale

1 INTRODUCTION

This statistical analysis plan (SAP) describes the planned analysis and reporting for Arcutis, Inc. clinical protocol ARQ-151-212. The analyses described in the SAP are based upon the protocol Amendment 2.0 dated August 5th 2019.

This SAP has been developed prior to database lock, final unblinding, and final analyses. All final analyses will be performed after the clinical trial data are entered into the database, any discrepancies in the data are resolved, the database is locked, and following the signature of the SAP.

Analyses related to PK data are not covered in this SAP and will be described in a separate document.

2 STUDY OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Safety	Safety endpoints
To assess the safety of ARQ-151 cream 0.05% vs ARQ-151 cream 0.15% vs vehicle administered QD x 4 weeks to adolescent and adult subjects with mild to moderate atopic dermatitis.	• Incidence of local and non-local treatment-emergent adverse events (TEAEs) • Change from baseline in vital signs • Change from baseline in clinical laboratory test results • Change from baseline in electrocardiograms (ECG) • Patient Health Questionnaire – 8 (PHQ-8) and Columbia Suicide Severity Rating Scale (C-SSRS) assessments • Local tolerability assessments Subset analysis by age group (adolescents and adults) will also be conducted.
Efficacy	Efficacy endpoints
To assess the efficacy of ARQ-151 cream 0.05% vs ARQ-151 cream 0.15% vs vehicle administered QD x 4 weeks to adolescent and adult subjects with mild to moderate atopic dermatitis.	**Primary:** • Change from baseline in Eczema Area and Severity Index (EASI) Total Score at Week 4

	Secondary: • Percent change from baseline in EASI Total Score at each study visit • Change from baseline in EASI Total Score at weeks 1 and 2 • Achievement of a 75% or greater improvement in EASI (EASI75) score from baseline to each study visit • Achievement of a 50% or greater improvement in EASI (EASI50) score from baseline to each study visit • Change from baseline in BSA involvement at each study visit • Change from baseline in WI-NRS pruritus score at each study visit • Achievement of a ≥4-point improvement from Baseline in WI-NRS pruritus score at each study visit for subjects with a Baseline WI-NRS ≥ 4 Subset analysis by age group (adolescents and adults) and baseline EASI score ('2' (mild) or '3' (moderate)) will also be conducted.
Pharmacokinetic	Pharmacokinetic endpoints (not covered in this SAP)
To evaluate the systemic exposure and characterize the plasma pharmacokinetic (PK) profile of ARQ-151 cream 0.05% and 0.15% and its major N-oxide metabolite, in adolescent and adult subjects with mild to moderate atopic dermatitis.	• Plasma levels of circulating roflumilast and its major N-oxide metabolite • Exposure of roflumilast and its major N-oxide metabolite (as evidenced by the C_{max} and AUC) for subjects who have serial PK data.

3 STUDY DESIGN

3.1 Overall Design

This is a phase 2, parallel group, double blind, vehicle-controlled study of ARQ-151 cream 0.15% and ARQ-151 cream 0.05% QD applied for 4 weeks to adolescent and adult subjects with 1.5% to 35% BSA of mild to moderate atopic dermatitis. A subset of subjects that consented under the previous amendment will have serial PK testing, while only trough PK sampling will be performed for all new subjects enrolled under protocol amendment 2.0.

A total of up to approximately 90 to 105 subjects will be enrolled at approximately 30 study sites in the United States and Canada. Subjects will be adolescent (12-17 y/o) or adult (≥18 y/o) males or females with atopic dermatitis. Subjects must have a vIGA-AD of Mild ('2') or Moderate ('3') at Baseline. Subjects must have at least 1.5% and no more than 35% BSA of atopic dermatitis (excluding scalp, palms, and soles). All atopic dermatitis lesions on a subject will be treated including the face, trunk, genitals/skin folds, or limbs (excluding the scalp). The palms and soles will be treated but will not be counted towards any measurements of efficacy (EASI, BSA).

Subject participation involves a minimum of 5 clinic visits including Screening, Baseline, Week 1, Week 2, and Week 4. For the subset of subjects enrolled under amendment 1.0 and consented to participate in serial PK sampling, 2 additional clinic visits include the 24-hour PK sample collection after Baseline on Day 2 and on Day 16. The interval between the Screening and Baseline visits could be up to 4 weeks, therefore the anticipated maximum duration of subject participation is ~8 weeks.

3.2 Schedule of Events

Table 1 provides a description of the procedures planned at each visit.

Table 1: Study Events Flow Chart

Study Procedure	Screen	Baseline Day 1	Day 2, 24-hour PK Collection	Wk 1 Day 8	Wk 2 Day 15	Day 16, 24-hour PK Collection	Wk 4 Day 29
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Visit Window	**-4 weeks**			**+/- 3 days**	**+/- 3 days**		**+/- 3 days**
Informed consent	X						
Demographics	X						
Medical and surgical history	X						
Physical examination[a]	X	X					X
I/E criteria	X	X					
Hematology, Serum Chemistries, and Urine Analysis	X	X					X
12 lead ECG	X						X
Vital signs, height, weight[b]	X	X		X	X		X
vIGA-AD[c], EASI[c], BSA[c]	X	X		X	X		X
WI-NRS pruritus[d]	X	X		X	X		X
Local Tolerability Assessment[e]		X		X	X		X
PHQ-8, C-SSRS	X	X		X	X		X
Optional photography[f]		X		X			X
Serum pregnancy test	X						
Urine pregnancy test[g]		X		X	X		X
PK draws[h]		X	X		X	X	X
Drug/vehicle application in clinic[i]		X		X	X		
Dispense study medication kit[j]		X		X	X		
Dispense/review diary		X		X[o]	X		X[n]
Weigh study medication kit[k]		X		X	X		X
Compliance calculation[l]		X		X	X		X
Adverse event assessment[m]	X	X	X	X	X	X	X
Concomitant medications	X	X		X	X		X

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

[b] Height will be collected at Screening only. Weight will be collected at all study visits. Subject to void prior to weight being taken. Remove any jackets, outerwear and shoes. Remove any objects of significant weight (i.e. cell phones, wallet, key chains). A 5% weight loss should be reported to the medical monitor.

[c] vIGA-AD will be a 5-point scale ranging from clear (0) to severe (4) and is evaluated for the entire body except the scalp, palms, and soles. EASI takes into account overall severity of erythema, infiltration/papulation, excoriation, and lichenification, in addition to extent of BSA affected. The 4 clinical signs will be graded on a 4-point scale (0 [absent] to 3 [severe]) for 4 body regions (head and neck, upper extremities, lower extremities, and trunk). Total EASI score will be

calculated as a sum of scores of all 4 body regions. EASI total score will range from 0 (absent) to 72 (severe). Total BSA affected by AD will be determined for all body surfaces except the scalp, palms and soles. vIGA-AD should be completed prior to other physician assessments.

[d.] Subjects will complete the WI-NRS pruritus questionnaire.

[e.] Local tolerability assessments should be recorded prior to study drug application for the Investigator assessment of skin irritation (Berger and Bowman skin irritation score) and 10-15 minutes post-drug application for the subject's '0-3' burning/stinging assessment.

[f] Photography of AD lesion(s) selected by the Investigator will be performed at some investigational sites. Photography will be optional. All efforts will be made to de-identify the subjects.

[g] 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.

[h] For the subset of subjects who enrolled under the previous protocol amendment and agreed to the serial PK: on the first day of dosing, PK draws will be done pre-dose (within 1-hour) and at 1, 2, 4, 6 (all ± 20 min) and 24 hours (± 2 hr) post-dose administration. On Day 15, PK draws will be taken at pre-dose (within 1-hour), 1, 2, 4, 6 (all ± 20 min) and 24 hours (± 2 hr) post dose administration. For other subjects: PK draws will be collected at Days 1 and 29. The draws will be pre-dose, ≤ 60 minutes before drug application in the clinic. Ensure study medication is not applied in the area where PK will be drawn. Note: Day 2 and Day 16 visits for 24-hour PK collection only apply to the subset of subjects who agree to the serial PK.

[i] Subjects to apply assigned IP in clinic at every visit.

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

[k.] The entire kit should be weighed and recorded at every visit. See IP Handling Manual for details.

[l] Compliance calculation is described in the IP Handling Manual

[m] Any emergent AEs will be followed in the clinic for up to one month at the Investigator's discretion until resolved or otherwise judged as clinically stable.

[n] On Day 29, no further IP will be applied or dispensed.

[o] On Day 8, dispensing of IP is optional. Site should review IP kit to ensure sufficient IP is available until the next visit and only dispense additional IP if needed.

3.3 Treatment

The treatment groups are:

- ARQ-151 cream 0.05% applied QD (once a day) for 4 weeks
- ARQ-151 cream 0.15% applied QD for 4 weeks
- Matching Vehicle cream applied QD for 4 weeks

3.4 Randomization, Replacement, and Unblinding Procedures

3.4.1 Randomization

Subjects will apply ARQ-151 cream 0.15% QD or ARQ-151 cream 0.05% QD or vehicle cream QD. Assignment of drug or vehicle will be made at a 1:1:1 ratio and stratified based on vIGA-AD score of '2' (mild) or '3' (moderate) according to a computer-generated randomization list. Randomization will take place at Baseline after the subject has been found to be fully eligible for participation. Kits containing tubes of study medication will be assigned to each subject using an internet-based response system (IWRS). A subject may receive more than one kit for the treatment period. The kits and tubes are blinded and each kit is numbered with a unique kit number.

This is a double-blind study, therefore neither the subjects nor the Investigator and clinical personnel will be aware of which treatment an individual has received.

3.4.2 Replacement

Subjects that withdraw or are discontinued from the study prior to Final Study Visit, may be replaced.

3.4.3 Unblinding

This is a double-blind study, therefore neither the subjects nor the Investigator and clinical personnel will be aware of which treatment an individual has received until after the database lock. The SAP and the study populations for analysis will be finalized prior to database lock and unblinding occurs.

3.5 Changes to the Analysis from the Protocol

The primary method of handling of missing data will be the MMRM method without explicit imputations for missing data as opposed to a multiple imputation technique.

The PHQ-8 scoring in the protocol describes "Severe Depression" as any score between 20 and 27. The PHQ-8 score has a maximum result of 24, The category has been corrected in section 13.6 to a score between 20-24.

4 POPULATIONS FOR ANALYSIS

4.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) population will include all randomized subjects. All subjects will be analyzed according to the treatment group to which they were randomized, regardless of treatment received.

4.2 Per-Protocol Population

The Per-Protocol (PP) Population will include all subjects who are in the safety population, are at least 80% compliant with study medication and do not miss more than 3 consecutive doses, and show no other major deviations (a deviation that affects the interpretation of the primary efficacy outcome; Section 6.6) from the study protocol .

Prior to the database lock, major protocol deviation will be defined and reviewed by the sponsor and the CRO in charge of the study follow-up in a blinded fashion. Subjects with major protocol deviations will be excluded from the PP population.

All subjects will be analyzed according to the actual treatment they received.

4.3 Safety Population

The Safety population will include all subjects who are enrolled and received at least one confirmed dose of study medication. Subjects will be analyzed according to the majority of the treatment applications received regardless of the treatment group to which they were randomized.

4.4 Pharmacokinetic Population

The PK population will include all subjects with serial PK data, receiving the active drug, with sufficient plasma concentrations of roflumilast and its major N-oxide metabolite to define a profile, as determined by the pharmacokineticist.

5 GENERAL CONSIDERATIONS

Formats and layouts of tables, listings, and figures (TLF) will be provided in a separate document (output general layout is described in Appendix 1).

5.1 Sample Size

There are approximately 90-105 subjects planned for this study. A subset of approximately 18 adults will receive serial PK sampling.

Approximately 30-35 subjects will receive ARQ-151 cream 0.05% QD; approximately 30-35 subjects will receive ARQ-151 cream 0.15% QD; approximately 30-35 subjects will receive vehicle QD.

A sample size of 27 per arm will provide at least 80% power to detect a difference in the mean change from baseline in EASI Total Score of 35% at week 4 (for each ARQ-151-treated group versus vehicle-treated group), assuming a pooled standard deviation (SD) of 40%, with a two-sided $\alpha = 0.05$. This is based on a 2-sample t-test. This includes P value adjustment for multiplicity using Bonferroni correction. With a 10-25% dropout rate, the sample size for the study would be increased to 30-35 subjects per arm (90-105 subjects total).

Change from baseline in EASI Total Score at week 4 is expected to provide more statistical power than percent change from baseline in EASI Total Score at this timepoint (which is a secondary endpoint) and has been chosen as the primary endpoint.

This sample size is considered adequate for PK and safety evaluation.

5.2 Baseline

Unless otherwise specified, baseline value will be defined as the last non missing assessment prior to or on the first study treatment dose date (including unscheduled assessments). If the last non missing assessment is performed on the same date as the first study treatment and time is not available, the assessment will be considered as baseline, except for adverse events (AEs) and medications starting on the first study treatment dose date which will be considered post-baseline.

5.3 Reference Start Date and Analysis Day

Analysis day will be calculated from the first study treatment date (day 1) and will be used to show start/end day of assessments or events.

In the situation where the assessment/event date is partial or missing, Analysis day will be missing.

5.4 Windowing Conventions

Statistical Windows have been proposed for early termination (ET) visits in this study:

	Day 1 (Baseline)	Day 8	Day 15	Day 29

Visit	1	4	5	7
Statistical Window	Latest pre-dose measurement	[Day 2; day 11]	[Day 12 – Day 21]	[Day 22 – D32]

If there is more than one assessment for a given timepoint and analysis visit, the assessment closest to the target day will be considered. If there is more than one assessment with the same target date, then the scheduled assessment result will be considered.

5.5 Descriptive Statistics

All continuous variables will be summarized by presenting the number of subjects, mean, SD, median, minimum, and maximum. Categorical variables will be presented as frequencies and percentages. Summary tables will be presented by treatment and visit, when applicable.

Change from baseline will be calculated as:

Assessment value at post-baseline visit X – Baseline value.

Percent change from baseline will be calculated as:

(Assessment value at post-baseline visit X – Baseline value) / Baseline value * 100.

5.6 Handling of Retests, Unscheduled Visits, and Early Termination Data

When retests measurements are done, the retest measurement will be considered for the summary analysis. All data from retest visits will be listed.

Unscheduled measurements will not be summarized in by-visit summary tables or figures. However, they will be included in shift summary tables. All data from unscheduled visits will be listed.

Early Termination (ET) visit assessments will be re-mapped according to the windowing conventions in section 5.4.

5.7 Software Version

All analyses will be performed using SAS® software Version 9.4 or higher.

6 STATISTICAL CONSIDERATIONS

6.1 Adjustments for Covariates

For the efficacy parameters analyzed using a mixed-effects model for repeated measures (MMRM), the corresponding baseline value and the stratification factor vIGA-AD score ("2" (mild) or "3" (moderate)) will be included as covariates in the statistical model.

6.2 Handling of Dropouts or Missing data

See Appendix 2 for handling of completely or partially missing dates for prior and concomitant medications and adverse events.

The primary method of handling of missing data will be the MMRM method without explicit imputations for missing data. A sensitivity analysis will be carried out on the primary endpoint using the last observation carried forward (LOCF) as an imputation for missing data. Only post-baseline values will be carried forward.

For secondary endpoints involving proportions, missing data at any post-baseline assessment will be imputed using LOCF and they will then be determined as a responder or non-responder based on the LOCF value.

6.3 Interim Analysis and Data Monitoring

No interim analysis is planned for this study.

6.4 Multicenter Studies

This is a multicenter study. Since randomization is not stratified by site, subjects will be analysed as if from a single center (i.e. all sites are combined).

6.5 Statistical Tests

Unless otherwise specified, all statistical tests will be two-sided and will be performed with a significance level of 0.05. Confidence intervals (CIs) will be two-sided with 95% coverage.

6.6 Multiple Comparisons/Multiplicity

The statistical test for each ARQ-151 dose level for the primary endpoint of Eczema Area and Severity Index (EASI) will be two-sided and will be performed with a significance level of 0.05 using Dunnett's method to control the overall alpha level.

No adjustments will be made to account for multiplicity in secondary and exploratory endpoints and multiple assessments through time in the same subjects. P-values presented for these endpoints will be nominal p-values.

6.7 Examination of Subgroups

Subset analysis by age group (adolescents and adults) will be conducted for both safety and efficacy data. Subset analysis by vIGA-AD strata ("2" (mild) and "3" (moderate)) will also be conducted on the primary and secondary efficacy endpoints. Details on these analyses are described in Sections 12.1, 12.2, and 13.

7 STUDY SUBJECTS

7.1 Disposition of Subjects

All subjects who provide informed consent will be accounted for in this study. The number of subjects screened and subjects rescreened will be presented. Screen failures and the reason for screen failure will be presented for all screened subjects except for those who were rescreened and did not fail the second screening. Moreover, the number of subjects randomized and included in each analysis population will be presented. Study completion status and the reason for study discontinuation will also be presented. The percentage of subjects with screen failures will be calculated using the number of subjects screened as denominator. The percentage of screen failure by reasons will be calculated using the number of screen failures as denominator. The percentage of subjects with study discontinuation will be calculated by reasons using the number of subjects who did not complete study as denominator. Otherwise, percentages will be calculated using the number of subjects randomized as denominator. Number of days in the study will be calculated as follows and summarized:

$$\text{Number of days in study} = \text{Date of completion/discontinuation} - 1^{st} \text{ dose date} + 1$$

A listing of subject's disposition will be provided. Information on first screening for subjects who were rescreened, including the rescreened subject identifier, will be presented under the first screening subject identifier. A listing of subject's randomization information and a listing of subjects included in each of the study populations will also be provided.

7.2 Protocol Deviations

The number of events and the number and percentage of subjects with at least one major protocol deviation will be summarized by deviation category using the safety population. A listing of all

protocol deviations will also be provided. The number of events and the number and percentage of subjects with at least one important protocol deviation will be summarized by deviation category using the safety population. A listing of subjects with inclusion and exclusion criteria deviations will also be provided. This listing will identify important and major protocol deviations.

An important protocol deviation is a deviation that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being. A major protocol deviation is a deviation that is likely to affect the primary efficacy data (Total EASI score).

8 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographics and baseline characteristics will be summarized with descriptive statistics using the safety population. The list of demographics and baseline characteristics to be summarized will include:

- Age (years) – calculated relative to date of consent
- Sex
- Ethnicity
- Race
- Baseline Height (cm)
- Baseline Weight (kg)
- Baseline EASI
- Baseline vIGA-AD
- Baseline BSA Involvement
- WI-NRS Pruritus Score

A listing of all demographics and baseline characteristics will be provided.

9 SURGICAL AND MEDICAL HISTORY

Surgical and Medical history will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA), Version 22.0.

Surgical and medical history will be summarized by system organ class (SOC) and preferred term (PT) using the safety population. A subject who experienced the same surgical and medical history event multiple times will be counted only once for the corresponding PT. Similarly, if a subject experienced multiple surgical and medical history events within the same SOC, the subject will be counted only once for that SOC. Surgical and medical history events will be sorted alphabetically by SOC and within each SOC the PT will be presented by decreasing order.

A listing of all surgical and medical history events will be provided.

10 PRIOR AND CONCOMITANT MEDICATIONS

Medications will be coded according to the World Health Organization Drug Dictionary (WHO-DD), GLOBAL B3 March 1, 2019.

Prior medications are defined as any medication started and discontinued prior to the first study treatment dose. Concomitant medications are defined as any medication taken after the first study treatment dose, including those starting prior to the first study treatment date and continuing past that date. See Appendix 2 for handling of completely or partially missing dates for prior and concomitant medications.

Incidence of prior and concomitant medications will be tabulated by anatomical therapeutic chemical (ATC) level 3 and PT using the safety population. A subject with the same medication taken multiple times will be counted only once for the corresponding PT. Similarly, if a subject has taken more than one medication within the same ATC level, then the subject will be counted only once for that ATC. Prior and concomitant medications will be sorted alphabetically by ATC level and within each ATC level the PT will be presented by decreasing order.

A listing of all prior and concomitant medications will be provided.

11 STUDY TREATMENT EXPOSURE AND TREATMENT COMPLIANCE

A summary of exposure related to ARQ-151 cream and the vehicle will be presented using the safety population. It will include descriptive statistics on the number of days treated, as well as the number of treatment applications, for each treatment group.

For each treatment, compliance will be calculated as follows:

$$\frac{\text{Number of treatment applications}}{\text{Number of expected treatment applications}} \times 100$$

Since the study treatment is applied once daily, the number of expected treatment applications is 28 for all subjects. Descriptive statistics for the compliance as well as the number of missed applications, subjects with $< 80\%$ and $\geq 80\%$ compliance will be presented by treatment. Furthermore, the incidence of subjects who missed more than 3 consecutive doses and compliant subjects will be presented by treatment.

A subject will be considered compliant with the dosing regimen if the subject applies at least 80% of the expected applications during the study drug application period and does not miss more than 3 consecutive doses.

Exposure and compliance, including compliance collected at each clinic visit, will be displayed in a listing of study treatment administration by subject, for each treatment. A listing of drug accountability including the tube number, dispensed and returned weight will also be provided.

12 EFFICACY ANALYSIS

12.1 Primary Efficacy Endpoint

The Eczema Area and Severity Index (EASI) is a static assessment to measure the severity and extent of atopic dermatitis. EASI combines the assessment of the severity of lesions and the area affected into a single score in the range 0 (no disease) to 72 (maximal disease).

The body is divided into four sections (head (h) (10% of a person's skin); arms (a) (20%); trunk (t) (30%); legs (l) (40%)). Each of these areas is scored by itself, and then the four scores are combined into the final EASI.

For each section, the percent of area (A) of skin involved is estimated and then transformed into a grade from 0 to 6 (A):

0. 0% of involved area
1. < 10% of involved area
2. 10–<30% of involved area
3. 30–<50% of involved area
4. 50–<70% of involved area
5. 70–<90% of involved area
6. 90–100% of involved area

EASI is evaluated for the entire body except the scalp, palms, and soles.

Within each area, the severity is estimated by four clinical signs: Redness (erythema, inflammation), Thickness (induration, papulation, swelling – acute eczema), Scratching (excoriation), and Lichenification (lined skin, furrowing, prurigo nodules – chronic eczema). Severity parameters are measured on a scale of 0 to 3, from none to severe.

To calculate the EASI, the sum of the severity rating for the four clinical signs are multiplied with the numerical value of the area affected and with the various percentages of the four body areas (see Appendix 3). The score will be set to missing in case of at least one missing value.

Descriptive statistics on EASI total score will be presented by visit for each treatment group. Change from baseline and percentage change from baseline will be also summarized.

Primary Endpoint Analysis

The primary efficacy endpoint is change from baseline in EASI Total Score at Week 4.

The primary efficacy endpoint will be analyzed using a MMRM analysis on change-from-baseline EASI with subject as a random effect and vIGA-AD strata, visit, treatment group, and interaction term for treatment-by-visit as fixed effects and baseline EASI as a fixed covariate. An unstructured variance-covariance matrix will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. The primary treatment comparisons will be the contrast between each dose of ARQ-151 with the Vehicle at Week 4.

Sensitivity Analyses
The interaction term baseline value-by-treatment will also be included in a supportive statistical model.

Missing data is handled using MMRM without explicit imputations for missing data. To assess robustness of the primary method of analysis via MMRM, a sensitivity analyses using LOCF will be performed.

The primary efficacy analysis will be performed using the ITT population and the PP population will be used as supportive analysis.

Subgroup Analyses
An analysis of variance (ANCOVA) will be performed using LOCF to handle missing data, where the absolute change from baseline or the percent change from baseline in EASI score at Week 4 will be the dependent variable, the treatment group, vIGA-AD strata and age group (adolescents or adults) will be fixed effects. Treatment effect per age group and vIGA-AD strata will be presented.

12.2 Secondary Endpoints

Eczema Area and Severity Index (EASI)

EASI score (as a secondary endpoint) will be assessed as:

- Percent change from baseline in EASI Total Score at each study visit
- Change from baseline in EASI Total Score at Weeks 1 and 2
- Proportion of subjects with a 75% or greater improvement in Eczema Area and Severity Index (EASI75) score from baseline to each study visit
- Proportion of subjects with a 50% or greater improvement in Eczema Area and Severity Index (EASI50) score from baseline to each study visit
- Proportion of subjects with a 90% or greater improvement in Eczema Area and Severity Index (EASI90) score from baseline to each study visit
- Proportion of subjects with a 100% or greater improvement in Eczema Area and Severity Index (EASI100) score from baseline to each study visit

Body Surface Area (BSA)

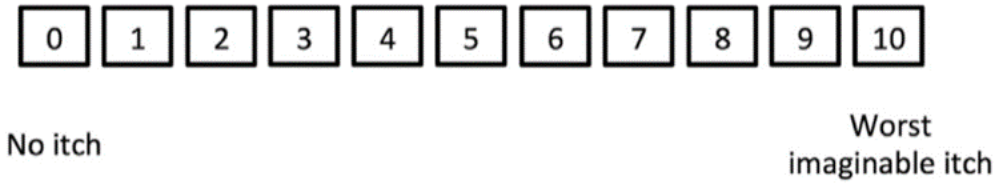
The BSA affected by atopic dermatitis will be determined by the subject's hand method, where the subject's hand (including fingers) surface area is assumed to equal 1% of BSA.

BSA will be assessed as:

- Change from baseline in BSA involvement at each study visit

Worst Itch Numerical Rating Scale (WI-NRS)

The WI-NRS has been developed as a simple, single item to assess the patient-reported severity of this symptom at its highest intensity during the previous 24-hour period. The WI-NRS will be determined by asking the subject's assessment of worst itch over the past 24 hours. The scale is from '0 to 10' ("no itch" to "worst imaginable itch"). Subjects will complete the WI-NRS pruritus assessment.



WI-NRS will be assessed as:

- Change from baseline in WI-NRS pruritus score at each study visit
- ≥4-point improvement from Baseline in WI-NRS pruritus score at each study visit for subjects with a Baseline WI-NRS ≥ 4
- ≥4-point improvement from Baseline in WI-NRS pruritus score at each study visit for subjects with a Baseline WI-NRS ≥ 6

Secondary Endpoint Analysis

Descriptive statistics will be presented on all secondary endpoints by visit and treatment group.

A similar analysis approach as outlined for the primary endpoint will be used for all secondary continuous efficacy endpoints. The comparisons of each dose of ARQ-151 with the vehicle will be presented.

For categorical efficacy endpoints involving proportions (e.g. achievement of a 75% or greater improvement in EASI score from baseline at each study visit), a Cochran Mantel Haenszel test (CMH) controlling for the stratification variable will be performed. The comparisons of each dose of ARQ-151 with the vehicle will be presented.

Subgroup analyses by vIGA-AD strata and age-group will be performed on all secondary endpoints.

12.3 Exploratory Endpoints

Validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD)

The vIGA-AD is a static evaluation of qualitative overall atopic dermatitis severity. This global assessment scale is an ordinal scale with five severity grades (reported only in integers of 0 to 4). Each grade is defined by a distinct and clinically relevant morphologic description that minimizes inter-observer variability (see Appendix 4). vIGA-AD is evaluated for the entire body except the scalp, palms, and soles.

vIGA-AD will be assessed as:

- Proportion of subjects with vIGA-AD score of 'clear' or 'almost clear' at each study visit
- Proportion of subjects with vIGA-AD score of 'clear' or 'almost clear' with a 2-point improvement from baseline at each study visit
- Change from baseline in vIGA-AD score at each study visit

Exploratory Endpoint Analysis

Descriptive statistics will be presented on vIGA-AD by visit and treatment group.

A similar analysis approach as outlined for the primary endpoint will be used for the change from baseline in vIGA-AD. The comparisons of each dose of ARQ-151 with the vehicle will be presented.

For categorical efficacy endpoints involving proportions (e.g. proportion of subjects with vIGA-AD score of "clear" or "almost clear" at each study visit), a Cochran Mantel Haenszel test (CMH) controlling for the stratification variable will be performed. The comparisons of each dose of ARQ-151 with the vehicle will be presented.

13 SAFETY ANALYSIS

All safety analyses will be conducted using the safety population. Safety analyses will be presented for all subjects combined, and for adults and adolescents separately. No formal inferential statistics will be performed on safety assessments.

13.1 Adverse Events

Adverse events (AEs) will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA), Version 22.0.

A treatment emergent adverse event (TEAE) is defined as an AE that started post application of study medication at the baseline visit or was present at treatment initiation but worsened during treatment, through study completion. See Appendix 2 for handling of completely or partially missing dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified as treatment emergent.

An overall summary table of adverse events will be provided. The number of events and the number and percentage of subjects who experienced AE, TEAE, TEAE by greatest reported relationship, TEAE by highest reported severity, related TEAE by highest reported severity, serious AE (SAE), serious TEAE, TEAE leading to study drug discontinuation, TEAE leading to study discontinuation, and AE leading to death will be presented.

Unless otherwise specified, a subject experiencing the same TEAE multiple times will be counted only once for the corresponding PT. Similarly, if a subject experiences multiple TEAEs within the same SOC, the subject will be counted only once for that SOC. TEAEs will be sorted by decreasing order of SOC and within each SOC the PT will be presented by decreasing order.

Frequency and percentage of subjects who experience TEAE will be summarized by SOC and PT within SOC.

Frequency and percentage of subjects who experience TEAE will be summarized by SOC, PT, and relationship. A treatment-related TEAE is defined as any TEAE that is assessed by the investigator as likely, probably, or possibly related to study treatment. TEAE that is assessed as unrelated or unlikely will be defined as not treatment-related. If a subject experiences more than one TEAE within different relationship categories within the same SOC/PT, only the worst case (greatest reported relationship) will be reported. A TEAE with an unknown relationship will be considered as treatment-related.

Frequency and percentage of subjects who experience TEAE will be summarized by SOC, PT, and severity (mild/moderate/severe). A severe adverse event is defined as any adverse events with a severity grade of 3 or higher. If a subject experiences more than one TEAE within different severity categories within the same SOC/PT, only the worst case (highest reported severity) will be reported. TEAE with an unknown severity will be considered as severe.

Frequency and percentage of subjects who experience TEAE will be summarized by SOC, PT, relationship, and severity (mild/moderate/severe). Each subject will be counted only once within a SOC or PT by using 1) the greatest reported relationship followed by 2) the highest reported intensity.

Frequency and percentage of subjects who experience a serious TEAE will be summarized by SOC and PT within SOC. Furthermore, frequency and percentage of subjects who experience a TEAE at the application site will be summarized by SOC and PT within SOC.

Listings of all AEs, all AEs leading to death, all serious AEs, all TEAEs leading to study or study drug discontinuation will be provided.

13.2 Clinical Laboratory

Descriptive statistics will be presented for data related to chemistry, hematology, and urinalysis. Change from baseline values will be presented for each post-baseline assessment. Frequencies and percentages for each result will be provided for qualitative urinalysis data.

Shift tables from baseline to the worst post-baseline assessment describing shifts to abnormality will be provided as well. Only subjects with a baseline result and a post-baseline result for the parameter will be considered.

Separate listings of all data for chemistry, hematology, urinalysis, and pregnancy tests will be provided.

Laboratory data will be presented in SI units.

13.3 Vital Signs

Descriptive statistics will be presented for data related to vital signs (systolic blood pressure diastolic blood pressure, heart rate, body temperature, and weight). Change from baseline values will be presented for each post-baseline assessment.

A shift table identifying subjects who gain or lose >5% body weight over the course of the study will be provided. Only subjects with a baseline result and a result at the specified visit for the parameter will be considered.

A listing of all vital sign assessments will be provided.

13.4 Electrocardiogram (ECG)

Descriptive statistics will be presented for data related to ECGs (heart rate, RR duration, PR interval, QRS interval, QT interval, QTcB interval, and QTcF interval). Change from baseline values will be presented for each post-baseline assessment.

Shift tables from baseline to the worst post-baseline assessment describing shifts to abnormality for investigator overall interpretation will be provided as well.

A listing of the ECG assessments will be provided.

13.5 Local Tolerability Assessments

Investigator Local Tolerability Assessments

Local tolerability assessed by the investigator will be summarized by treatment and visit for dermal response on an 8-point scale (0-7). Furthermore, the frequency of subjects with each dermal response score as well as other effects (A to G) will be summarized by treatment and visit.
A sensitivity analysis of investigator local tolerability assessments will be conducted in which data from study sites 19, and 21 will be excluded. Due to a misunderstanding of the data collection form, data from both of these sites were initially assessed as disease assessments rather than local tolerability assessments. Data were updated after correct understanding of the CRF was attained, however, the effect of this post facto update of these data will be evaluated with this sensitivity analysis.

A listing of investigator local tolerability assessments will be provided.

Subject Local Tolerability Assessments

Local tolerability assessed by the subject will be summarized by treatment and visit for tolerability grading on a 4-point scale (0-3). Furthermore, the frequency of subjects with each tolerability score will be summarized by treatment and visit.

A listing of subject local tolerability assessments will be provided.

13.6 Patient Health Questionnaire Depression Scale (PHQ-8)

The Patient Health Questionnaire Depression Scale is an 8 question Assessment (see Appendix 5).

The PHQ-8 score is the sum of the responses for the 8 questions, each question ranging from 0 (Not at all) to 3 – (Nearly every day). Five severity categories of depression are defined as follows:

- None – Minimal depression (1 to 4)
- Mild depression (5 to 9)
- Moderate depression (10 to 14)
- Moderately severe depression (15 to 19)
- Severe depression (20 to 24)

The score will be set to missing in case of at least one missing value. The PHQ-8 score will be summarized by treatment and visit. Furthermore, the frequency of subjects within each severity category will be summarized by treatment and visit.

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

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a questionnaire used for suicide assessment developed by multiple institutions, including Columbia University (see Appendix 6). A listing of the C-SSRS assessments will be provided. In addition, a listing of data will be provided for all subjects who answer 'Yes' to any question on the C-SSRS questionnaire.

14 APPENDICES

Appendix 1 Output Conventions

TLF will be generated using SAS® and will be displayed on letter size paper with landscape orientation, 1-inch margins, and 9 pt Courier New font.

The header section will comprise the sponsor's name, the protocol number, the delivery description, the data cut-off date (if applicable), the TLF number, the TLF title, the analysis population, and the page number (Page X of Y). The footer section will include the TLF footnotes, the CRO's name, the date and time of the execution of the program, the reference listings and the name of the program.

P-values equal to and above 0.001 will be reported to 3 decimal places; p-values less than 0.001 will be reported as "<0.001"; p-values greater than 0.999 will be reported as ">0.999".

The mean, median, and quantiles will be displayed to one more decimal place than the original value; minimum and maximum will keep the same number of decimal places as the original value; SD, standard error, and CI will be displayed to two more decimal places than the original value. If derived parameters are to be summarized, the number of decimals of the derived values is to be chosen on a case-by-case basis, but the rule above applies.

For categorical summary tables, percentages will be reported to one decimal place. Percentages between 0 and 0.1 (both exclusive) will be displayed as "<0.1". The denominator for each percentage will be the number of subjects within the population per treatment group unless otherwise specified.

Listings will be ordered by treatment group, subject number, date, and visit (where applicable). Imputed dates and imputed missing data will not be presented in the listings.

Dates & Times Format

Date and time (if available) will be presented in the format yyyy-mm-dd/hh:mm.

Presentation of Treatment Groups

When applicable, study treatments will be represented as follows in the different outputs:

Study Treatment Full Names	Study Treatment Output Names
ARQ-151 cream 0.05%	ARQ-151 0.05%
ARQ-151 cream 0.15%	ARQ-151 0.15%
Vehicle	Vehicle

Appendix 2 Algorithm for Imputation of Start/End Date of Adverse Events and Prior/Concomitant Medications

Event Start Date Imputation

- Imputation of event end date should be done before imputation of event start date.
- Completely missing: Impute to the first study treatment date.
- Missing day and month: Impute to January 1st, unless year is the same as year of first study treatment dose then impute to the first study treatment date.
- Missing day: Impute to the 1st of the month, unless month and year are the same as month and year of first study treatment dose then impute to the first study treatment date.
- If imputed event start date is after event end date (imputed or not), set the event start date to the imputed event end date.

Event End Date Imputation

- Completely missing (and not flagged as "ongoing"): Impute to the last contact date.
- Missing day and month: Impute to December 31st, unless year is the same as last contact date then impute to the last contact date.
- Missing day: Impute to the last day of the month, unless year and month are the same as year and month of last contact date then impute to the last contact date.

Appendix 3 EASI Scoring Tool

Eczema Area and Severity Index (EASI) case report form - age≥8 years

Area of Involvement: Each body region has potentially 100% involvement. Score **0 to 6** based on the following table:

% involvement	0	1-9%	10 - <30%	30 - <50%	50 - <70%	70 - <90%	90 - 100%
Region score	0	1	2	3	4	5	6

Severity of Signs: Grade the severity of each sign on a scale of **0 to 3**:

0	None
1	Mild
2	Moderate
3	Severe

- ✓ Take an average of the severity across the involved area.
- ✓ Half points (1.5 and 2.5) may be used. 0.5 is not permitted – if a sign is present it should be at least mild (1)

Scoring table:

Body region	Erythema (0-3)	Edema/ Papulation (0-3)	Excoriation (0-3)	Lichenification (0-3)	Region score (0-6)	Multiplier	Score per body region
Head/neck	(+	+	+	)	x	X 0.1	
Trunk	(+	+	+	)	x	X 0.3	
Upper extremities	(+	+	+	)	x	X 0.2	
Lower extremities	(+	+	+	)	x	X 0.4	
The final EASI score is the sum of the 4 region scores:							_____ (0-72)

Appendix 4 vIGA-AD

Validated Investigator Global Assessment scale for Atopic Dermatitis

vIGA-AD™

Instructions:

The IGA score is selected using the descriptors below that best describe the overall appearance of the lesions at a given time point. It is not necessary that all characteristics under Morphological Description be present.

Score	Morphological Description
0 – Clear	No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting). Post-inflammatory hyperpigmentation and/or hypopigmentation may be present.
1 – Almost clear	Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification. No oozing or crusting.
2 – Mild	Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification. No oozing or crusting.
3 – Moderate	Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing and crusting may be present.
4 – Severe	Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification. Disease is widespread in extent. Oozing or crusting may be present.

Notes:

1. In indeterminate cases, please use extent to differentiate between scores.

For example:

- *Patient with marked erythema (deep or bright red), marked papulation and/or marked lichenification that is limited in extent, will be considered "3 – Moderate".*

2. Excoriations should not be considered when assessing disease severity.

Appendix 5 PHQ-8

SMRC Self-Management Resource Center

Personal Health Questionnaire Depression Scale (PHQ-8)

Over the **last 2 weeks**, how often have you been bothered by any of the following problems?
*(circle **one** number on each line)*

How often during the past 2 weeks were you bothered by...	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself, or that you are a failure, or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3

Scoring

If two consecutive numbers are circled, score the higher (more distress) number. If the numbers are not consecutive, do not score the item. Score is the sum of the 8 items. If more than 1 item missing, set the value of the scale to missing. A score of 10 or greater is considered major depression, 20 or more is severe major depression.

Appendix 6 Columbia-Suicide Severity Rating Scale (C-SSRS)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline/Screening Version

Version 1/14/09

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

Disclaimer:

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

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

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION		
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Lifetime: Time He/She Felt Most Suicidal**	**Past __ Months**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…and I would never go through with it."* ***Have you been thinking about how you might do this?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them."* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
INTENSITY OF IDEATION		
The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe). Ask about time he/she was feeling the most suicidal. Lifetime - ***Most Severe Ideation:*** _____ ***Type # (1-5)*** _____ ***Description of Ideation*** Past X Months - ***Most Severe Ideation:*** _____ ***Type # (1-5)*** _____ ***Description of Ideation***	Most Severe	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**	**Past __ Years**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent) If yes, describe:	**Yes** ☐ **No** ☐ Total # of Attempts _____	**Yes** ☐ **No** ☐ Total # of Attempts _____
Has subject engaged in Non-Suicidal Self-Injurious Behavior?	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐

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

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

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

Disclaimer:

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

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

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

SUICIDAL IDEATION

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

Since Last Visit

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

If yes, describe:

Yes ☐ **No** ☐

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

If yes, describe:

Yes ☐ **No** ☐

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

If yes, describe:

Yes ☐ **No** ☐

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

If yes, describe:

Yes ☐ **No** ☐

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

If yes, describe:

Yes ☐ **No** ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e., 1-5 from above, with 1 being the least severe and 5 being the most severe).

Most Severe Ideation: _____ _____

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

Most Severe

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

____

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

____

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

____

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

____

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

____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** ☐ **No** ☐ Total # of Attempts _____ **Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐
Suicide:	**Yes** ☐ **No** ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
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