Statistical Analysis Plan

A Phase 3 Multi-Center, Open Label Study Evaluating the Long Term Safety of SB204 Once Daily in the Treatment of Acne Vulgaris

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Contents

Abbreviations

Abbreviation	Definition
AE	Adverse Event
ATC	Anatomical and Therapeutic Class
ET	Early Termination
g	gram
IRB	Institutional Review Board
LTS	Long-Term Safety
MedDRA	Medical Dictionary for Regulatory Activities
NOVAN	Novan, Inc.
OCP	Oral Contraceptive Pill
PT	Preferred Term
SAE	Serious Adverse Event
SAF	Safety Population
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Events
UPT	Urine Pregnancy Test
WHO	World Health Organization
WOCBP	Women of Child-Bearing Potential

1 Introduction

This document presents the statistical analysis plan (SAP) for Novan Inc., Protocol No. NI-AC303: A Phase 3 Multi-Center, Open Label Study Evaluating the Long Term Safety of SB204 Once Daily in the Treatment of Acne Vulgaris.

The SAP provides the detailed description of the planned statistical analysis of data from protocol NI-AC303.

2 Study Objectives

The primary objective of this study is to evaluate the safety of SB204 4% once daily in subjects with acne vulgaris for up to 40 weeks of treatment. The Week 12 visit from the pivotal studies (NI-AC301 and NI-AC302) will serve as the Baseline Visit for this study.

2.1 Safety Endpoints

Safety endpoints will include adverse events, changes in physical examination and changes in vital sign measurements. Any clinically significant changes noted during the physical exam as well as from the vital sign measurements will be recorded as adverse events and included in the comparison. Urine pregnancy tests in women of child-bearing potential will be conducted at each visit.

2.2 Tolerability Endpoints

The cutaneous tolerability assessments include the investigator's assessment of erythema, scaling, dryness, and the subject's report of pruritus and burning/stinging based on the preceding 24 hours.

2.3 Extent of Exposure

Duration, days of, and extent of exposure for each subject will be determined based on the stop and start dates of use of SB204, the total number of days of study drug application, and the areas treated (face, upper back, upper chest, and shoulders).

2.4 Efficacy Endpoints

Efficacy endpoints will include absolute and percent change in inflammatory and non-inflammatory facial area lesion counts from baseline at each study visit.

3 Study Design

3.1 Study Design

This is a multi-center, open label long-term safety (LTS) study to be conducted in approximately 600 subjects with acne vulgaris. Subjects will be enrolled into the study from approximately 100

sites in North America. Subjects eligible to enroll in this study will have completed one of the Phase 3 pivotal studies with SB204, NI-AC301 or NI-AC302, and meet study inclusion and exclusion criteria.

Subjects who satisfy the entry criteria at the Baseline visit will be enrolled to receive open-label SB204. Investigational drug will be delivered from a double barrel single pump dispenser. The pump dispenses product (NVN1000 Gel and a hydrogel) from two chambers which will be mixed together quickly (about 5 seconds) by the subject and applied once daily to the acne affected areas identified by the Investigator. Areas that could be treated include the face, upper chest, upper back and shoulders. No other acne treatments will be permitted during the study.

Subjects will return for post-baseline evaluation at Weeks 4, 12, 24, 36 and 40/ET.

3.2 Study Treatment

The amount of SB204 per application will vary depending on the areas to be treated as shown in Table 1 below. Subjects are allowed to specify 'Other'. If the other specification is jaw or neckline, it is assumed that the same pump stroke used to apply drug to face is being used for the jaw and/or neckline application. One pump stroke will likely be used for each application area. For example, application to the face, upper back and upper chest will require up to 2.7 g (three (3) pump strokes).

Table 1: Dosing Amount by Area

Area (BSA)	Number of Pump Strokes	Amount of Product
Face, including jaw line and or neck if indicated	1	0.9 g
Upper Back	1	0.9 g
Upper Chest	1	0.9 g
Shoulders	1	0.9 g

3.3 Study Schedule

Study visits should occur at approximately the same time of day throughout the study.

PROCEDURES	**Visit 1[1]** **Baseline (Day 0)**	**Visit 2[3] Week 4 ±5 days (Day 28)**	**Visit 3 Week 12 ±7 days (Day 84)**	**Visit 4 Week 24 ±7 days (Day 168)**	**Visit 5 Week 36 ±7 days (Day 252)**	**Visit 6[4] Week 40/ET ±7 days (Day 280)**
Informed Consent/Assent	X					
Demographics	X[2]					
Medical History	X					
Medication History	X					
Inclusion/Exclusion Criteria	X					
Brief Physical Examination	X[2]					X
Urine Pregnancy Test (all WOCBP)	X[2]	X	X	X	X	X
Blood Pressure and Pulse	X[2]	X	X	X	X	X
Lesion Counts	X[2]	X	X	X	X	X
Cutaneous Tolerability Evaluation	X[2]	X	X	X	X	X
Instruct on Study Drug Application and Provide Subject Instructions	X					
Record application areas since last visit		X	X	X	X	X
Study Drug Dispensed/Retraining on mixing and application	X	X	X	X	X	
Study Drug Collected		X	X	X	X	X
Subject Study Drug Use Reviewed		X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X

[1]Data for the Baseline Visit for this study will be the Week 12 data from the Phase 3 pivotal study for completing, eligible subjects.
[2]Demographics and assessments from the Week 12 visit from the preceding Phase 3 study including the physical examination, blood pressure and pulse, UPT, tolerability, and lesion counts do not need to be repeated.
[3]All visit dates are in reference to Baseline, e.g., Visit 2 occurs four weeks (28 days) after Baseline visit.
[4]All Week 40 procedures should be completed for subjects who prematurely discontinue, if possible.

3.4 Concomitant Medication

Subjects will be permitted to apply non-comedogenic moisturizer or sunscreen on an as-needed basis. Moisturizer must not contain antibacterials and the subject must not change moisturizer and/or sunscreen used during the course of the study. If used, moisturizers and sunscreen must be applied at least 30 minutes after study drug application.

Subjects must not have used anti-acne treatments including topical or systemic antibiotics or retinoids (as described in Section 3.7.3 of the protocol) prior to Baseline. These medications are also prohibited during the trial. Short term courses of antibiotics (≤ 14 days) for non-acne related illnesses and inhaled or intranasal steroids are permitted during the trial.

Subjects may not be concurrently on drugs associated with exacerbating acne vulgaris (see Appendix 16.1 of the protocol). Subjects must not participate in a different interventional research study during the study period.

Any medication/therapy used by the subject following first application of study product will be considered a concomitant medication/therapy (e.g., aspirin, acetaminophen, birth control pills, vitamins, etc.). Every attempt should be made to keep concomitant medication/therapy dosing constant during the study. Any change to concomitant medications/therapies should be noted on the subject's study record and in the study database. When applicable, an AE should be completed for any subject starting a concomitant medication/therapy after enrollment into the study.

3.5 Populations

3.5.1 Safety Population

The safety population (SAF) will include all subjects that have received at least one dose of SB204. For the summaries, we are defining two subject categories, based on the subject's status at the start of the LTS:

- SB204 Experienced: subjects allocated to SB204 in the previous study
- SB204 Naïve: subjects allocated to vehicle in the previous study

3.6 Sample Size

The main objective of this study is to evaluate the long term safety of SB204, therefore, no sample size or power calculations were performed.

4 Statistical Methodology

4.1 Planned Analyses

All statistical processing will be performed using statistical analysis software (SAS®) unless otherwise stated. Safety analyses will be performed using the safety population.

Continuous data will be summarized with sample size (N), mean, median, standard deviation, minimum and maximum. Categorical data will be summarized with N, frequency counts, and percentages, based on N.

4.2 Disposition of Subjects

The number of subjects in the Safety Population, who completed the study and the reasons for any premature discontinuation from the study, will be presented. Listings will indicate whether subjects met all inclusion and exclusion criteria, and, if not, which criteria were not met.

A summary and a listing of protocol deviations will be presented.

4.3 Baseline and Demographic Characteristics

Subject baseline and demographic characteristics, including age, race, ethnicity, and gender, will be summarized, as well as which previous Novan study the subject was enrolled in (NI-AC301 or NI-AC302) and previous treatment assignment (SB204 or Vehicle).

For female subjects the following summaries will be included: child-bearing potential, contraceptive use at baseline. Medical history will be summarized for each treatment group by SOC and PT and presented in listings. Adverse events ongoing at end of pivotal study will be carried forward to this study, will not be considered treatment-emergent for this study, and will be summarized separately by SOC, PT, and relatedness.

4.4 Extent and Duration of Exposure

Summaries of the duration of exposure, days of exposure, and extent of exposure (calculated total grams) to study drug will be presented, overall and by whether previously randomized to SB204 (SB204 experienced) or randomized to Vehicle (SB204 naïve). This information plus study drug management details will be listed as well. All exposure endpoints will take into account whether the subject received SB204 in the previous study (NI-AC301 or NI-AC302).

Duration of exposure will be defined as:

Date of Last Drug Administration – Date of First Drug Administration + 1 day

Where date of first drug administration is the date of first treatment in the previous pivotal study for subjects randomized to SB204 in the previous study, and date of first dose in the LTS for subjects randomized to vehicle in the previous study.

Days of exposure will be defined as the total number of days that the subject reported taking study medication, and includes the days of exposure to SB204 in the previous study (NI-AC301 or NI-AC302) if applicable.

Extent of exposure will be based on the number of areas treated (face, upper back, and/or upper chest/shoulders, and any other areas reported) and the number of days with treatment. For subjects randomized to SB204 in the previous studies, drug was only applied to the face so for the days of exposure from the previous studies, it will be assumed that there is only one area of application, i.e. the face.

Each application is equal to 0.9 g. Extent of exposure is estimated as the sum of application areas (face only=1, face and chest=2, etc.) times the number of days of application to those areas times 0.9g. For example, a subject who applies 200 applications to the face only will have extent of exposure = 180g, while a subject who applies 100 applications to the face and 50 applications to the upper back will have extent of exposure = 135 g. The maximum extent of exposure would be: [0.9 grams x number of days on treatment in previous study] + [0.9 grams x 4 areas x number of LTS days on treatment]. Most subjects will have less exposure than this, so extent of exposure will be categorized logically depending on actual distribution of subjects. Initially, quartiles will considered.

4.5 Safety

4.5.1 Adverse Events

All AEs that occur during the study or continue after enrollment into this study will be recorded and classified on the basis of Medical Dictionary for Regulatory Activities (MedDRA) terminology version 18.1. Adverse events ongoing at end of the pivotal study will be carried forward to this study, will not be considered treatment-emergent for this study, and will be summarized separately by SOC, PT, and relatedness. Treatment-emergent AEs (TEAEs) will be defined as AEs reported on or after the first day of enrollment in this long term safety study.

All information pertaining to an AE noted during the study will be listed by subject, detailing verbatim term given by the Investigator or designee, preferred term, system organ class (SOC), onset date, resolution date, severity, seriousness, action taken, outcome, and drug relatedness. The event onset will also be shown relative (in number of days) to date of first dose in this study.

Treatment-emergent AEs will be summarized by the number of subjects reporting a TEAE, SOC, preferred term, severity, relationship to study drug (causality), and seriousness. When summarizing AEs by severity and relationship, each subject will be counted only once, within a system organ class or a preferred term, by using the event with the highest severity and greatest relationship within each classification.

Serious AEs will be summarized by severity, and relationship to study drug, and individual SAEs will be listed by subject. In addition, a list of subjects who prematurely discontinue study drug due to an AE, had AEs leading to treatment modification, and AEs that resulted in death will be provided.

Adverse events will also be summarized by windows of duration of exposure to study drug to determine if there is a safety signal due to duration of exposure. The windows of exposure will include but are not limited to: 1) within the first 24 hours (i.e. Day 1 of the LTS study), 2) up to 1 month (i.e. 2-30 days), 3) up to 3 months (i.e. 31-90 days), 4) up to 6 months (i.e. 91-180 days) and 5) up to 12 months (i.e. 181-365 days).

Adverse event incidence will also be summarized by the extent of exposure categories (in grams) as described in section 4.4.

4.5.2 Prior and Concomitant Medications

Medications will be mapped to their corresponding thesaurus terms (ATC Class and Preferred Term) according to the World Health Organization (WHO) Drug Dictionary, Version Mar2016. A summary of concomitant medications, sorted by ATC Class 2 and Preferred Term, will be provided. A listing of prior and concomitant medications will be presented, as well a listing of any prohibited medications used during the study.

4.5.3 Physical Examination

The results of the physical exams will be presented in a listing. Clinically significant changes from Baseline will be documented as an AE.

4.5.4 Vital Signs

Blood pressure and pulse will be summarized from Baseline through Week 40/ET. Additionally, change from Baseline in vital signs will be summarized at Week 4, 12, 24, 36, and 40/ET. Clinically significant changes from Baseline will be documented as an AE.

4.5.5 Urine Pregnancy Tests

Urine pregnancy tests results for WOCBP will be presented in data listings by subject.

4.6 Tolerability

Distribution and shift in cutaneous tolerability assessments (erythema, scaling, dryness, pruritus, burning/stinging) will be summarized from Baseline to Week 40/ET.

4.7 Efficacy Analysis

The facial area inflammatory and non-inflammatory lesion counts will be summarized at each evaluation from Baseline through Week 40/ET. Absolute and percent change in inflammatory and non-inflammatory lesion counts will be summarized at Weeks 4, 12, 24, 36 and 40/ET. The absolute and percent change in inflammatory non-inflammatory lesion counts will also be summarized by prior treatment (SB204 experienced, SB204 naïve).

4.8 Deviations from SAP

Any deviations from the original statistical plan will be described and justified in the final clinical study report.

Protocol: NI-AC303

A Phase 3 Multi-Center, Open Label Study Evaluating the Long Term Safety of SB204 Once Daily in the Treatment of Acne Vulgaris.

Mock Data Displays- Tables
Version 1.0
Date: 12Apr2017

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Contents

Table 14.1.1.1
Subject Disposition
Safety Population

	SB204 (N=XXX)
SAF Population	xx (xx.x)
Treatment-naïve at enrollment	xx (xx.x)
Previously on SB204 at enrollment	xx (xx.x)
Completed Study	xx (xx.x)
SB204 Experienced	xx (xx.x)
SB204 Naïve	xx (xx.x)
Discontinued Early	xx (xx.x)
Primary Reason for Study Discontinuation [a]	
Adverse Events	xx (xx.x)
Lack of Efficacy as Determined by Investigator	xx (xx.x)
Withdrawal by Subject	xx (xx.x)
Physician Decision	xx (xx.x)
Protocol Violation	xx (xx.x)
Lost to Follow-up	xx (xx.x)
Pregnancy	xx (xx.x)
Worsening of Condition	xx (xx.x)
Other	xx (xx.x)

Notes: Safety (SAF) Population includes all subjects that have been dispensed study drug and received at least one dose of SB204.
Unless stated otherwise, denominator is the number of subjects in safety population.
[a]Denominator is the number of subjects who were randomized.
Source: Listing xx.x.x.x.x, Program: xxxxx.sas, Output: T_xx.x_x_x_xxxx.rtf, Generated on: DDMMMYYYY HH:MM

Table 14.1.1.2
Summary of Protocol Deviations
Safety Population

Protocol Deviations	SB204 (N=XXX)
Subjects with Any Protocol Deviation	xxx (xx.x)
Deviation A	xxx (xx.x)
…	
Deviation B	xxx (xx.x)
…	
Deviation C	xxx (xx.x)
Etc.	

Note (s): Percentages are based on the number of subjects in safety population.
Reference: Listing 16.2.x

Table 14.1.2.1
Demographics
Safety Population

	SB204 Experienced (N=XXX)	SB204 Naïve (N=XXX)	Overall (N=XXX)
Age (years)			
n	xxx	xxx	xxx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x
Min, Max	x.x, xx.x	x.x, xx.x	x.x, xx.x
Age Group			
Juvenile (Age <18 years)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Adult (Age 18+ years)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Race			
White	xx (xx.x)	xx (xx.x)	xx (xx.x)
Black or African American	xx (xx.x)	xx (xx.x)	xx (xx.x)
American Indian or Alaska Native	xx (xx.x)	xx (xx.x)	xx (xx.x)
Native Hawaiian or Other Pacific Islander	xx (xx.x)	xx (xx.x)	xx (xx.x)
Asian	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ethnicity			
Hispanic or Latino	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not Hispanic or Latino	xx (xx.x)	xx (xx.x)	xx (xx.x)
Sex			
Male	xx (xx.x)	xx (xx.x)	xx (xx.x)
Female	xx (xx.x)	xx (xx.x)	xx (xx.x)
Previously in Study			
NI-AC301	xx (xx.x)	xx (xx.x)	xx (xx.x)
NI-AC302	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note(s): Percentages are based on the number of subjects in safety population. Age is based on the date of informed consent from the previous study (NI-AC301 or NI-AC302); LTS = Long Term Safety Study.
Source: Listing xx.x.x.x.x, Program: xxxxx.sas, Output: T_xx.x_x_x_xxxx.rtf, Generated on: DDMMMYYYY HH:MM

Table 14.1.2.2
Child Bearing Potential and Contraceptive Use (Females Only)
Safety Population

	SB204 (N=XXX)
If Female, of Childbearing Potential?	
Yes	xx (xx.x)
No	xx (xx.x)
If No to Childbearing Potential, Why	
Post-Menopausal	xx (xx.x)
Hysterectomy or Bilateral Oophorectomy	xx (xx.x)
Surgically Sterilized	xx (xx.x)
If Yes to Childbearing Potential, Primary Method of Birth Control	
Oral Contraceptive	xx (xx.x)
Intra-Uterine Device	xx (xx.x)
Condom with Spermicide	xx (xx.x)
Diaphragm with Spermicide	xx (xx.x)
Implant	xx (xx.x)
Nuvaring	xx (xx.x)
Medroxyprogesterone Injection	xx (xx.x)
Transdermal Patch	xx (xx.x)
Abstinence	xx (xx.x)
Other	xx (xx.x)

Note(s): Percentages are based on the number of female subjects in Safety population.
Source: Listing xx.x.x.x.x, Program: xxxxx.sas, Output: T_xx.x_x_x_xxxx.rtf, Generated on: DDMMMYYYY HH:MM

Table 14.1.3
Medical History by System Organ Class and Preferred Term
Safety Population

Body System Class Preferred Term	SB204 (N=XXX)
Subject with Any Medical History	xx (xx.x)
System Organ Class 1	xx (xx.x)
Preferred Term 1	xx (xx.x)
Preferred Term 2	xx (xx.x)
……	
Preferred Term n	xx (xx.x)
……	
System Organ Class n	xx (xx.x)
Preferred Term 1	xx (xx.x)
Preferred Term 2	xx (xx.x)
……	
Preferred Term n	xx (xx.x)
	xx (xx.x)
System Organ Class q	xx (xx.x)
Preferred Term 1	xx (xx.x)
Preferred Term 2	xx (xx.x)
……	

Note(s): All investigator terms were coded using MedDRA dictionary version 18.1.
Source: Listing xx.x.x.x.x, Program: xxxxx.sas, Output: T_xx.x_x_x_xxxx.rtf, Generated on: DDMMMYYYY HH:MM

Table 14.1.4
Adverse Events Ongoing at the Start of the Study by System Organ Class, Preferred Term, and Extent of Exposure
Safety Population

System Organ Class Preferred Term	SB204 Experienced (N=XXX)	SB204 Naïve (N=XXX)	Overall (N=XXX)
Number of Subjects with at Least One Event	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of Events	xx	xx	xx
System Organ Class 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
System Organ Class 2	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note(s): Adverse event terms were coded using MedDRA dictionary version 18.1. Subjects are counted once within each level of summary.
Source: Listing xx.x.x.x.x, Program: xxxxx.sas, Output: T_xx.x_x_x_xxxx.rtf, Generated on: DDMMMYYYY HH:MM

Programmer Note: Order SOC by decreasing frequency and preferred term by decreasing frequency within SOC based on overall incidence.

Table 14.1.5
Concomitant Medications by WHO Drug Class and WHO Drug Preferred Name
Safety Population

Drug Class Preferred Name	SB204 (N=XXX)
Subjects Who Took at Least One Concomitant Medication	xx (xx.x)
Drug Class 1	xx (xx.x)
Preferred Name 1	xx (xx.x)
Preferred Name 2	xx (xx.x)
Preferred Name 3	xx (xx.x)
etc.	xx (xx.x)
Drug Class 2	xx (xx.x)
Preferred Name 1	xx (xx.x)
Preferred Name 2	xx (xx.x)
Preferred Name 3	xx (xx.x)
etc.	xx (xx.x)
Drug Class 3	xx (xx.x)
Preferred Name 1	xx (xx.x)
Preferred Name 2	xx (xx.x)
……	xx (xx.x)

Note(s): Subjects are counted only once at each level of summarization.
Concomitant medications are all medications taken during the study period, including those started before but ongoing at first dose. All medications were coded using WHO Drug dictionary version March 2016.
Source: Listing xx.x.x.x.x, Program: xxxxx.sas, Output: T_xx.x_x_x_xxxx.rtf, Generated on: DDMMMYYYY HH:MM

Programmer's Note(s): Continue with all drug classes and preferred names which appear in the data. Sort drug classes and within drug classes, preferred terms by decreasing overall frequency.

Table 14.2.1.
Summary of Duration and Extent of Drug Exposure
Safety Population

	SB204 Experienced (N=XXX)	SB204 Naïve (N=XXX)	Overall (N=XXX)
Overall Duration of Exposure (Days)			
Number of Subjects with Exposure	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x
Min, Max	x.x, xx.x	x.x, xx.x	x.x, xx.x
Unknown			
Days of Exposure			
n	xx	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x
Min, Max	x.x, xx.x	x.x, xx.x	x.x, xx.x
Unknown			
Areas of Application			
Face	xx (xx.x)	xx (xx.x)	xx (xx.x)
Upper Back	xx (xx.x)	xx (xx.x)	xx (xx.x)
Upper Chest	xx (xx.x)	xx (xx.x)	xx (xx.x)
Shoulders	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	xx (xx.x)	xx (xx.x)	xx (xx.x)
Extent of Exposure (grams)			
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x
Min, Max	x.x, xx.x	x.x, xx.x	x.x, xx.x
Unknown	xx (xx.x)	xx (xx.x)	xx (xx.x)
1-100 grams	xx (xx.x)	xx (xx.x)	xx (xx.x)
>100-330 grams	xx (xx.x)	xx (xx.x)	xx (xx.x)
>330-675 grams	xx (xx.x)	xx (xx.x)	xx (xx.x)
>675 grams	xx (xx.x)	xx (xx.x)	xx (xx.x)

Notes: All exposure endpoints includes exposure to SB204 from the previous study (NI-AC301 or NI-AC302), if applicable.
Duration of Exposure = Date of Last Drug Administration – Date of First Drug Administration + 1 day.
Days of exposure will be defined as the total number of days that the subject reported taking study medication.
Areas of application indicate if the subject ever applied drug to that area. Each subject is counted only once per area.
Extent of exposure is determined as: 0.9 grams times the number of application areas times the number of days applied.
Application to neck and jawline are considered part of application to the face when determining extent of exposure.
Source: Listing xx.x.x.x.x, Program: xxxxx.sas, Output: T_xx.x_x_x_xxxx.rtf, Generated on: DDMMMYYYY HH:MM

Table 14.2.2.1
Inflammatory Lesion Counts by Study Visit (Face Only)
Safety Population

		SB204 (N=XXX)		
Visit	Statistic	Count	Absolute Change from Baseline	Percent Change from Baseline
Baseline	N	XX		
	Mean	XX.X		
	SD	XX,XX		
	Median	XX		
	Min. to Max.	XX to XX		
Week 4	N	XX	XX	XX
	Mean	XX.X	XX.X	XX.X
	SD	XX,XX	XX,XX	XX,XX
	Median	XX	XX,X	XX,X
	Min. to Max.	XX to XX	XX to XX	XX to XX
Week 12	N	XX	XX	XX
	Mean	XX.X	XX.X	XX.X
	SD	XX,XX	XX,XX	XX,XX
	Median	XX	XX,X	XX,X
	Min. to Max.	XX to XX	XX to XX	XX to XX
Etc.				

Source: Listing xx.x.x.x.x, Program: xxxxx.sas, Output: T_xx.x_x_x_xxxx.rtf, Generated on: DDMMMYYYY HH:MM

Programming Note: Repeat table for Non-Inflammatory Lesions:

Table 14.2.2.2 Non-Inflammatory Lesion Counts by Study Visit (Face Only) Safety Population

Table 14.2.3.1
Inflammatory Lesion Counts (Face Only) by Prior Treatment and Study Visit
Safety Population

		SB204 Experienced (N=XXX)			SB204 Naïve (N=XXX)		
Visit	Statistic	Count	Absolute Change from Baseline	Percent Change from Baseline	Count	Absolute Change from Baseline	Percent Change from Baseline
Baseline	N	XX			XX		
	Mean	XX.X			XX.X		
	SD	XX,XX			XX,XX		
	Median	XX			XX		
	Min. to Max.	XX to XX			XX to XX		
Week 4	N	XX	XX	XX	XX	XX	XX
	Mean	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	SD	XX,XX	XX,XX	XX,XX	XX,XX	XX,XX	XX,XX
	Median	XX	XX,X	XX,X	XX	XX,X	XX,X
	Min. to Max.	XX to XX	XX to XX	XX to XX	XX to XX	XX to XX	XX to XX
Week 12	N	XX	XX	XX	XX	XX	XX
	Mean	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	SD	XX,XX	XX,XX	XX,XX	XX,XX	XX,XX	XX,XX
	Median	XX	XX,X	XX,X	XX	XX,X	XX,X
	Min. to Max.	XX to XX	XX to XX	XX to XX	XX to XX	XX to XX	XX to XX
Etc.							

Source: Listing xx.x.x.x.x, Program: xxxxx.sas, Output: T_xx.x_x_x_xxxx.rtf, Generated on: DDMMMYYYY HH:MM

Programming Note: Repeat table for Non-Inflammatory Lesions:

Table 14.2.3.2 Non-Inflammatory Lesion Counts (Face Only) by Prior Treatment and Study Visit Safety Population

Table 14.3.1.1
Cutaneous Tolerability Evaluation – Erythema - Summarized by Study Visit (Face Only)
Safety Population

Study Visit	SB204 (N=XXX)
Baseline	
0 – None	xx (xx.x)
1 – Mild	xx (xx.x)
2 – Moderate	xx (xx.x)
3 - Severe	xx (xx.x)
Missing	xx (xx.x)
Week 4	
0 – None	xx (xx.x)
1 – Mild	xx (xx.x)
2 – Moderate	xx (xx.x)
3 - Severe	xx (xx.x)
Missing	xx (xx.x)
Week 12	
0 – None	xx (xx.x)
1 – Mild	xx (xx.x)
2 – Moderate	xx (xx.x)
3 - Severe	xx (xx.x)
Missing	xx (xx.x)
Week 24	
0 – None	xx (xx.x)
1 – Mild	xx (xx.x)
2 – Moderate	xx (xx.x)
3 - Severe	xx (xx.x)
Missing	xx (xx.x)
Week 36	
0 – None	xx (xx.x)
1 – Mild	xx (xx.x)
2 – Moderate	xx (xx.x)
3 - Severe	xx (xx.x)
Missing	xx (xx.x)
Week 40\ET	
0 – None	xx (xx.x)
1 – Mild	xx (xx.x)
2 – Moderate	xx (xx.x)
3 - Severe	xx (xx.x)
Missing	xx (xx.x)

Note: Baseline is the Week 12 assessment from the previous study (NI-AC301 or NI-AC302).
Source: Listing xx.x.x.x.x, Program: xxxxx.sas, Output: T_xx.x_x_x_xxxx.rtf, Generated on: DDMMMYYYY HH:MM

Using shell 14.3.1.1, repeat table for the following:

Table 14.3.1.2 Cutaneous Tolerability Evaluation – Scaling - Summarized by Study Visit Safety Population

Table 14.3.1.3 Cutaneous Tolerability Evaluation – Dryness - Summarized by Study Visit Safety Population

Table 14.3.1.4 Cutaneous Tolerability Evaluation – Pruritus - Summarized by Study Visit Safety Population

Table 14.3.1.5 Cutaneous Tolerability Evaluation – Burning/Stinging - Summarized by Study Visit Safety Population

Table 14.3.2.1
Shift from Baseline in Cutaneous Tolerability Evaluation – Erythema, by Study Visit (Face Only)
Safety Population

Study Visit / Cutaneous Tolerability Score	Cutaneous Tolerability Score at Baseline				
	0 - None	1 - Mild	2 - Moderate	3 - Severe	Missing
Week 4					
0 – None	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
1 – Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
2 - Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
3 – Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Week 12					
0 – None	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
1 – Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
2 - Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
3 – Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Week 24					
0 – None	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
1 – Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
2 - Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
3 – Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Week 36					
0 – None	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
1 – Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
2 - Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
3 – Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Week 40					
0 – None	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
1 – Mild	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
2 - Moderate	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
3 – Severe	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Missing	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note: Baseline is the Week 12 assessment from the previous study (NI-AC301 or NI-AC302).
Source: Listing xx.x.x.x.x, Program: xxxxx.sas, Output: T_xx.x_x_x_xxxx.rtf, Generated on: DDMMMYYYY HH:MM

Using shell 14.3.2.1, Repeat table for the following:

Table 14.3.2.2 Shift from Baseline in Cutaneous Tolerability Evaluation – Scaling - Summarized Continuously by Study Visit Safety Population

Table 14.3.2.3 Shift from Baseline in Cutaneous Tolerability Evaluation – Dryness - Summarized Continuously by Study Visit Safety Population

Table 14.3.2.4 Shift from Baseline in Cutaneous Tolerability Evaluation – Pruritus - Summarized Continuously by Study Visit Safety Population

Table 14.3.2.5 Shift from Baseline in Cutaneous Tolerability Evaluation – Burning/Stinging - Summarized Continuously by Study Visit Safety Population

Table 14.3.3.1
Treatment Emergent Adverse Events (TEAE) Overview
Safety Population

Number of Subjects with	SB204 Experienced (N=XXX)	SB204 Naïve (N=XXX)	Overall (N=XXX)
Any TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of TEAEs	xx	xx	xx
Treatment-Related TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of Treatment-Related TEAEs	xx	xx	xx
TEAE Leading to Treatment Modification	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of TEAE Leading to Treatment Modification	xx	xx	xx
Treatment-Related TEAE Leading to Treatment Modification	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of TRTEAE Leading to Treatment Modification	xx	xx	xx
TEAE Leading to Treatment Discontinuation	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of TEAE Leading to Treatment Discontinuation	xx	xx	xx
Treatment-Related TEAE Leading to Treatment Discontinuation	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of TRTEAE Leading to Treatment Discontinuation	xx	xx	xx
Serious TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of Serious TEAEs	xx	xx	xx
Treatment-Related Serious TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of Treatment-Related Serious TEAEs	xx	xx	xx
TEAE Leading to Death	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of TEAE Leading to Death	xx	xx	xx
Treatment-Related TEAE Leading to Death	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of Treatment-Related TEAE Leading to Death	xx	xx	xx

Note: TEAE onset is based on the start of treatment in the LTS. Adverse events were coded using MedDRA 18.1.
TR=Treatment-Related.
Source: Listing xx.x.x.x.x, Program: xxxxx.sas, Output: T_xx.x_x_x_xxxx.rtf, Generated on: DDMMMYYYY HH:MM

Table 14.3.3.2.1
Treatment Emergent Adverse Events (TEAE) by System Organ Class, Preferred Term, and Duration of Exposure
Safety Population

System Organ Class Preferred Term	Within 24 hours (N=XXX)	Within 2-30 days (N=XXX)	Within 31-90 Days (N=XXX)	Within 91-180 Days (N=XXX)	Within 181-365 Days (N=XXX)	Overall (N=XXX)
Number of Subjects with at Least One TEAE	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of Events	xx	xx	xx	xx	xx	xx
System Organ Class 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
System Organ Class 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note(s): Adverse event terms were coded using MedDRA dictionary version 18.1. Subjects are counted once within each level of summary. Duration of exposure is based on date of first dose of SB204, which could be in the previous study (NI-AC301 or NI-AC302).
Source: Listing xx.x.x.x.x, Program: xxxxx.sas, Output: T_xx.x_x_x_xxxx.rtf, Generated on: DDMMMYYYY HH:MM

Programmer Note: Order SOC by decreasing frequency and preferred term by decreasing frequency within SOC based on overall incidence.

Table 14.3.3.2.2
Treatment Emergent Adverse Events (TEAE) by System Organ Class, Preferred Term, and Extent of Exposure
Safety Population

System Organ Class Preferred Term	1-100 grams (N=XXX)	>100-330 grams (N=XXX)	>330-675 grams (N=XXX)	>675 Grams (N=XXX)	Overall (N=XXX)
Number of Subjects with at Least One Event	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Number of Events	xx	xx	xx	xx	xx
System Organ Class 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
System Organ Class 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 1	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term 2	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Note(s): Adverse event terms were coded using MedDRA dictionary version 18.1. Subjects are counted once within each level of summary. TEAE onset is based on the start of treatment in the LTS. Extent of exposure is based on first exposure to SB204 – which could be in the previous study (NI-AC301 or NI-AC302).
Source: Listing xx.x.x.x.x, Program: xxxxx.sas, Output: T_xx.x_x_x_xxxx.rtf, Generated on: DDMMMYYYY HH:MM

Programmer Note: Order SOC by decreasing frequency and preferred term by decreasing frequency within SOC based on overall incidence.

Using shells 14.3.3.2.1 and 14.3.3.2.2, repeat for the following:

Table 14.3.3.3.1 Treatment-Related Emergent Adverse Events by System Organ Class, Preferred Term, and Duration of Exposure Safety Population

Table 14.3.3.3.2 Treatment-Related Emergent Adverse Events by System Organ Class, Preferred Term, and Extent of Exposure Safety Population

Programmer's Note: subset on TEAEs related to study treatment.

Table 14.3.3.4.1 Treatment Emergent Adverse Events Leading to Treatment Modification by Duration of Exposure Safety Population

Table 14.3.3.4.2 Treatment Emergent Adverse Events Leading to Treatment Modification by Extent of Exposure Safety Population

Programmer's Note: subset on TEAEs leading to treatment modification. Add the following footnote:

Note: Treatment modification includes reduction, interruption, or discontinuation of Study Drug

Table 14.3.3.5.1 Treatment-Related Treatment Emergent Adverse Events Leading to Treatment Modification by Duration of Exposure Safety Population

Table 14.3.3.5.2 Treatment-Related Treatment Emergent Adverse Events Leading to Treatment Modification by Extent of Exposure Safety Population

Programmer's Note: subset on Treatment-Related TEAEs leading to treatment modification. Add the following footnote:

Note: Treatment modification includes reduction, interruption, or discontinuation of Study Drug.

Table 14.3.3.6.1 Treatment Emergent Adverse Events Leading to Discontinuation of Study Drug by Duration of Exposure Safety Population

Table 14.3.3.6.2 Treatment Emergent Adverse Events Leading to Discontinuation of Study Drug by Extent of Exposure Safety Population

Programmer's Note: subset on TEAEs leading to discontinuation of Study Drug.

Table 14.3.3.7.1 Treatment-Related Treatment Emergent Adverse Events Leading to Discontinuation of Study Drug by Duration of Exposure Safety Population

Table 14.3.3.7.2 Treatment-Related Treatment Emergent Adverse Events Leading to Discontinuation of Study Drug by Extent of Exposure Safety Population

Programmer's Note: subset on Treatment-Related TEAEs leading to discontinuation of Study Drug.

Table 14.3.3.8.1 Treatment Emergent Serious Adverse Events by System Organ Class, Preferred Term, and Duration of Exposure Safety Population

Table 14.3.3.8.2 Treatment Emergent Serious Adverse Events by System Organ Class, Preferred Term, and Extent of Exposure Safety Population

Programmer's Note: subset on Serious TEAEs.

Table 14.3.3.9.1 Treatment-Related Treatment Emergent Serious Adverse Events by System Organ Class, Preferred Term, and Duration of Exposure Safety Population

Table 14.3.3.9.2 Treatment-Related Treatment Emergent Serious Adverse Events by System Organ Class, Preferred Term, and Extent of Exposure Safety Population

Programmer's Note: subset on Treatment-Related Serious TEAEs.

Table 14.3.3.10.1 Treatment Emergent Adverse Events Leading to Death by Duration of Exposure Safety Population
Table 14.3.3.10.2 Treatment Emergent Adverse Events Leading to Death by Extent of Exposure Safety Population

Programmer's Note: subset on TEAEs with fatal outcome.

Table 14.3.3.11.1 Treatment-Related Treatment Emergent Adverse Events Leading to Death by Duration of Exposure Safety Population

Table 14.3.3.11.2 Treatment-Related Treatment Emergent Adverse Events Leading to Death by Extent of Exposure Safety Population

Programmer's Note: subset on treatment related TEAEs with fatal outcome.
.

Table 14.3.3.13
Summary of Treatment Emergent Adverse Events (TEAE) by Highest Severity, System Organ Class and Preferred Term
Safety Population

System Organ Class Preferred Term	Severity	SB204 (N=XXX)
Subjects with at least one event	Mild	xx (xx.x)
	Moderate	xx (xx.x)
	Severe	xx (xx.x)
Number of events	Mild	xx
	Moderate	xx
	Severe	xx
System Organ Class 1	Mild	xx (xx.x)
	Moderate	xx (xx.x)
	Severe	xx (xx.x)
Preferred Term 1	Mild	xx (xx.x)
	Moderate	xx (xx.x)
	Severe	xx (xx.x)

Note(s): TEAE onset is based on the start of treatment in the LTS. Adverse event terms were coded using MedDRA dictionary version 18.1. Subjects are counted once within each level of summary. If a subject has multiple events, the event with highest severity will be considered.
Source: Listing xx.x.x.x.x, Program: xxxxx.sas, Output: T_xx.x_x_x_xxxx.rtf, Generated on: DDMMMYYYY HH:MM

Programmer Note: Order SOC by decreasing frequency and preferred term by decreasing frequency within SOC based on overall incidence.

Using shell 14.3.3.13, repeat table for the following:

Table 14.3.3.14 Summary of Treatment-Related Emergent Adverse Events (TEAE) by Severity, System Organ Class and Preferred Term Safety Population

Programmer's Note: subset on related TEAEs

Table 14.3.4
Summary of Vital Signs
Safety Population

<Parameter> (<units>)

	SB204 (N=XXX)	
Timepoint	Actual	Change from Baseline
Baseline		
n	xx	
Mean (SD)	xx.x (xx.xx)	
Median	xx.x	
Min, Max	xx, xx	
Missing	xx	
Week 4		
N	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x
Min, Max	xx, xx	xx, xx
Missing	xx	xx
Week 12		
n	xx	xx
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x
Min, Max	xx, xx	xx, xx
....		xx

Note(s): Baseline is defined as the Week 12 assessment from the previous study (NI-AC301 or NI-AC302).
Source: Listing xx.x.x.x.x, Program: xxxxx.sas, Output: T_xx.x_x_x_xxxx.rtf, Generated on: DDMMMYYYY HH:MM

Programmer Note: Include all vital signs parameters (e.g. SBP, DBP, Pulse) and all available post-baseline visits. Missing not presented if no missing values.

Protocol: NI-AC303

A Phase 3 Multi-Center, Open Label Study Evaluating the Long Term Safety of SB204 Once Daily in the Treatment of Acne Vulgaris.

Mock Data Displays - Figures
Version 1.0
Date: 12Apr2017

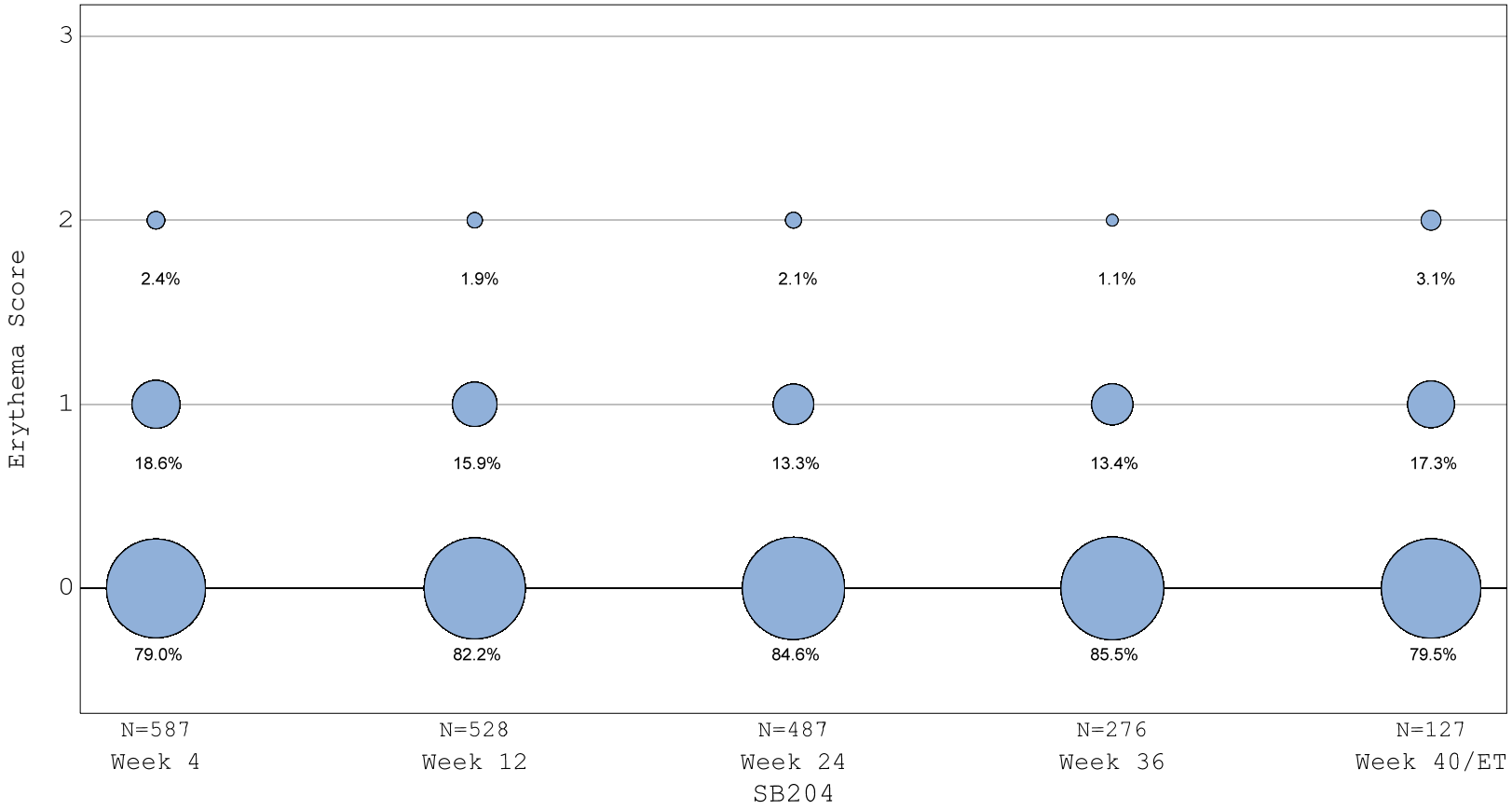
Prepared for:
Novan Inc.
4105 Hopson Road
Morrisville, NC 27560

Prepared by:
Chiltern International
4000 CentreGreen Way, Suite 300, Cary, NC, 27513, United States

Contents

Figure 14.1.1 Distribution of Erythema Scores by Treatment and Visit
Safety Population

Figure 14.1.1
Distribution of Erythema Scores by Treatment and Visit
Safety Population



Using shell for Figure 14.1.1, repeat for the following:

Figure 14.1.2 Distribution of Dryness Scores by Treatment and Visit, Safety Population

Figure 14.1.3 Distribution of Scaling Scores by Treatment and Visit, Safety Population

Figure 14.1.4 Distribution of Pruritus Scores by Treatment and Visit, Safety Population

Figure 14.1.5 Distribution of Burning/stinging Scores by Treatment and Visit, Safety Population

Figure 14.2.1 Average Change from Baseline in Inflammatory Lesion Count (Face only) Over Time
Safety Population

Figure 14.2.1
Average Change from Baseline in Inflammatory Lesion Count Over Time
Safety Population

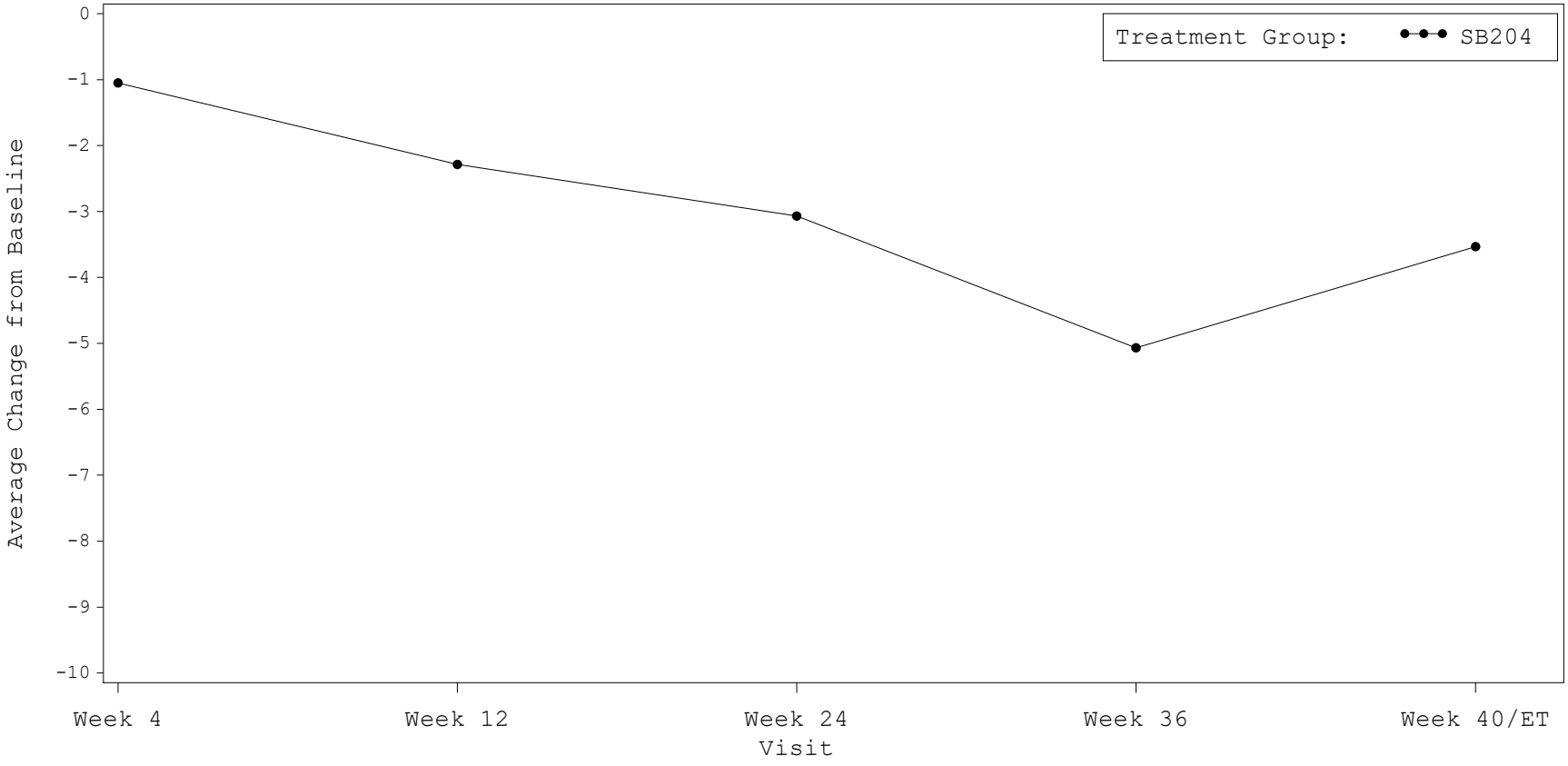
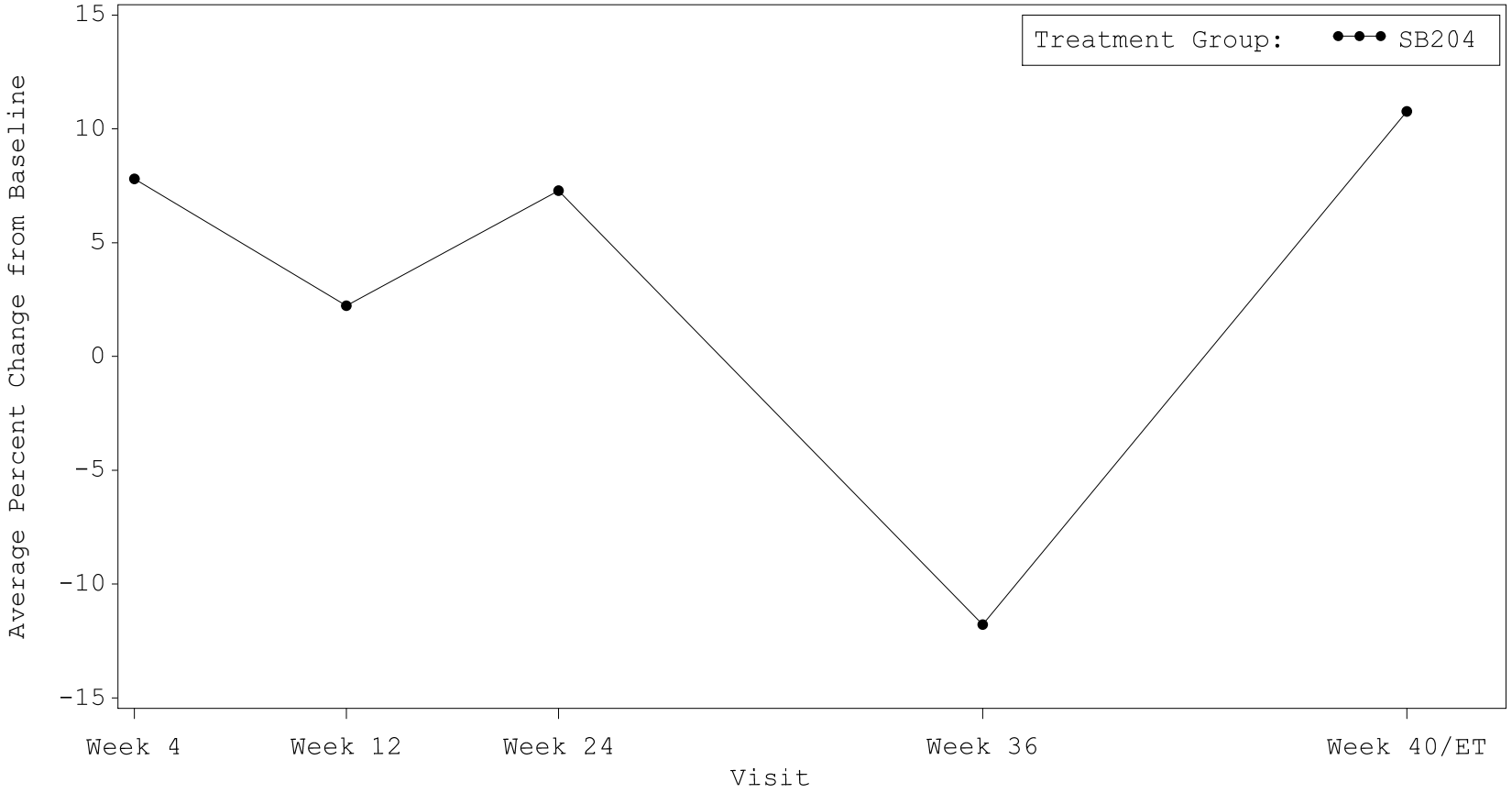


Figure 14.2.2 Average Percent Change from Baseline in Inflammatory Lesion Count (Face only) Over Time
Safety Population

Figure 14.2.2
Average Percent Change from Baseline in Inflammatory Lesion Count Over Time
Safety Population



Using shell for Figure 14.2.1, repeat for the following:

Figure 14.3.1 Average Change from Baseline in Non-Inflammatory Lesion Count (Face only) Over Time, Safety Population

Using shell for Figure 14.2.2 repeat for the following:

Figure 14.3.2 Average Percent Change from Baseline in Non-Inflammatory Lesion Count (Face only) Over Time, Safety Population

Protocol: NI-AC303

A Phase 3 Multi-Center, Open Label Study Evaluating the Long Term Safety of SB204 Once Daily in the Treatment of Acne Vulgaris.

Mock Data Displays- Listings
Version 1.0
Date: 12Apr2017

Prepared for:
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4105 Hopson Road
Morrisville, NC 27560

Prepared by:
Chiltern International
4000 CentreGreen Way, Suite 300, Cary, NC, 27513, United States

Table of Contents

Listing 16.2.1.1
Subject Disposition
Safety Population

Previous Study	Previous Treatment Group	Subject ID	Met All Inc/Exc Criteria	Date of: Informed Consent	Date of Completion or Discontinuation	Reason for Discontinuation
xxxxxxx	xxxxxxx	xxxxxxx	Yes	DDMMMYYYY	DDMMMYYYY	Completed
xxxxxxxx	xxxxxxx	xxxxxxxx	Yes	DDMMMYYYY	DDMMMYYYY	Withdrawal by Subject

s<nnn>xxxx yyyymmddthh:mm

Programmer's Note(s): This listing will be sorted by previous study number and then by Subject ID.

Listing 16.2.2
Protocol Violations/Deviations
Safety Population

Subject ID	Date of Violation/ Deviation /Day	Type of Violation	Details of Violation/Deviation
xxxxxxx	DDMMMYYYY/xx	ICF Issue	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
xxxxxxxx	DDMMMYYYY/xx	Assessment not Performed per Protocol	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
xxxxxxxx	DDMMMYYYY/xx	Non-compliance with IP	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Note(s): *Day = Day relative to the date of first dose of study medication.*
s<nnn>xxxx yyyymmddthh:mm

Programmer's Note(s): This and subsequent listings will be sorted by Subject ID.

Listing 16.2.3
Inclusion/Exclusion Criteria not Met
Safety Population

Subject ID	Criteria Not Met	Description of Criteria
xxxxxxx	INCXX	XXXXXXXXXXXXXXXXXXXXX
xxxxxxxx	EXCLXX	XXXXXXXXXXXXXXXXXXXXX

Listing 16.2.4.1
Demographics
Safety Population

Subject ID	Study Center	Date of Birth	Age (years)	Gender	Ethnicity	Race
xxxxxxx	xxxxxxx	DDMMMYYYY	xx.x	Male	Not Hispanic or Latino	xxxxxx
xxxxxxxx	xxxxxxx	DDMMMYYYY	xx.x	Female	Not Hispanic or Latino	xxxxx
xxxxxxxx	xxxxxxx	DDMMMYYYY	xx.x	Female	Not Hispanic or Latino	Other: xxxxxx

Note(s): Age is calculated as the interval between date of birth and date of baseline visit from the previous study (NI-AC301 or NI-AC302).
s<nnn>xxxx yyyymmddthh:mm

Listing 16.2.4.2
Medical History
Safety Population

Subject ID	SOC / Preferred Term / Verbatim Term	Onset / End
xxxxxxx	Xxxxxxxx / Xxxxxxxx / xxxxxxxx	DDMMYYYY / DDMMYYYY
xxxxxxxx	Xxxxxxxx / Xxxxxxxx / xxxxxxxx	DDMMYYYY / Ongoing

Listing 16.2.4.3
Child Bearing Potential and Pregnancy Test Results
Safety Population (Females only)

Subject ID	Of Child-Bearing Potential?	If no, why?	If Yes, Method of Birth Control	Visit	Collection Date / Day	Pregnancy Test Result or Reason Not Done
XXXXXXX	Yes		XXXXXXXXXX	Baseline	DDMMMYYYY /XX	Negative
XXXXXXX	No	XXXXXXXXXXXX		Baseline	DDMMMYYYY /XX	Negative

Note(s): *Day = Day relative to the date of first day of LTS.*
s<nnn>xxxx yyyymmddthh:mm

Listing 16.2.4.4
Physical Exam
Safety Population

Subject ID	Visit	Date	Body System	Evaluation	Abnormality
XXXXXXX	Baseline	DDMMMYYYY	General Appearance	Normal	
			Respiratory	Normal	
			Cardiovascular	Normal	
			Other: XXXXXXXx	ANCS	XXXXXXXXXXXXXXXXXXXX
			General Appearance	ACS	XXXXXXXXXXXXXXXXXXX
	Week 40\ET	DDMMMYYYY			
			Respiratory	Normal	
			Cardiovascular	Normal	
	Etc.				
XXXXXXX	Baseline	DDMMMYYYY	General Appearance	Normal	
			Respiratory	Normal	

Note(s):ANCS = Abnormal, Not clinically significant; ACS = Abnormal, Clinically Significant. If a finding was determined to be clinically significant, it is also reported as an adverse event, or, if it occurred prior to study start, it is reported in medical history.
s<nnn>xxxx yyyymmddthh:mm

Listing 16.2.5
Study Drug Management
Safety Population

Subject ID	Visit	Date/ Day	Was Pump dispensed?	If yes, Pump number(s)	Was previous pump returned?	If no. Reason why:
xxxxxxx	Baseline	DDMMMYYYY/xx	Yes	XXXXXX		
	Week 4	DDMMMYYYY/xx	No		No	XXXXXXXXXX
	Week 12	DDMMMYYYY/xx	Yes	XXXXXX, XXXXX		
	Week 24	DDMMMYYYY/xx	Yes	XXXXXX, XXXXX, XXXXX		
	Week 36	DDMMMYYYY/xx	Yes	XXXXXX		
	Week 40	DDMMMYYYY/xx	Yes	XXXXXX		
Xxxxxxx	Baseline	DDMMMYYYY/xx	Yes	XXXXXX		
	Week 4	DDMMMYYYY/xx	Yes	XXXXXX		
	Week 12	DDMMMYYYY/xx	Yes	XXXXXX	Yes	
	Week 24	DDMMMYYYY/xx	Yes	XXXXXX		
	Week 36	DDMMMYYYY/xx	Yes	XXXXXX		
	Week 40	DDMMMYYYY/xx	Yes	XXXXXX		
xxxxxxx	Baseline	DDMMMYYYY/xx	Yes	XXXXXX		
	Week 4	DDMMMYYYY/xx	Yes	XXXXXX	Yes	
	Week 12	DDMMMYYYY/xx	Yes	XXXXXX		
	Week 24	DDMMMYYYY/xx	No			
	Week 36	DDMMMYYYY/xx	Yes	XXXXXX		
	Week 40	DDMMMYYYY/xx	Yes	XXXXXX		

Note(s): *Day = Day relative to the date of first day of LTS.*
s<nnn>xxxx yyyymmddthh:mm

Listing 16.2.6
Extent and Duration of Exposure
Safety Population

Subject ID	Visit	Date	Duration of Exposure (days)	Number of Doses Reported Missed	Days of Exposure	Extent of Exposure (grams)	Areas of Application				
							Face	Upper Back	Upper Chest	Shoulders	Other:
xxxxxxx	Week 4	DDMMMYYYY	XXX	XXX	XXX	XXX	x	X			
	Week 12	DDMMMYYYY	XXX	XXX	XXX	XXX		x		X	
	Week 24	DDMMMYYYY	XXX	XXX	XXX	XXX			x	X	
	Week 36	DDMMMYYYY	UNK	UNK	UNK	UNK				x	Neck and Jawline
	Week 40	DDMMMYYYY	XXX	XXX	XXX	XXX					
	Overall		XXX	UNK	UNK	UNK					
										x	XXXXXXXXX
Xxxxxxx	Week 4	DDMMMYYYY	XXX	XXX	XXX	XXX					
	Week 12	DDMMMYYYY	XXX	XXX	XXX	XXX					
	Week 24	DDMMMYYYY	XXX	XXX	XXX	XXX					
	Week 36	DDMMMYYYY	XXX	XXX	XXX	XXX					
	Week 40	DDMMMYYYY	XXX	XXX	XXX	XXX					
	Overall		XXX	XXX	XXX	XXX					

Note(s):
Duration of Exposure = (Date of next drug dispensation or if last dispensataion, date of last dose) – Date of Drug Dispensation + 1 day. Overall is based on the date of first dose of study drug, which could be from the previous study (NI-AC301 or NI-AC302).
Days of Exposure = Duration of exposure minus the number of days that the subject reported not taking study medication.
Extent of Exposure: Each application is equal to 0.9 g. Extent of exposure is estimated as the sum of application areas (face only=1, face and chest=2, etc) times the number of days of application to those areas times 0.9g. If the other specification is jaw or neckline, it is assumed that the same pump stroke used to apply drug to face is being used for the jaw and/or neckline application. For subjects randomized to SB204 in the previous studies, drug was only applied to the face so for the days of exposure from the previous studies, it will be assumed that there is only one area of application, i.e. the face.
UNK = Unknown: For subjects who are lost-to-follow-up or who did not return diaries but reported an unknown number of missed doses, duration of exposure and days of exposure for that visit interval are defined as unknown. Overall duration will be defined as above; days of exposure will remain unknown.
s<nnn>xxxx yyyymmddthh:mm

Listing 16.2.7.1.1
Lesion Counts (Face Only): Total Inflammatory and Non-Inflammatory Lesions
Safety Population

					Inflammatory Lesions			Non-Inflammatory Lesions		
Previous Study	Subject ID	Visit	Date	Counter's Initials	Count	Absolute Change from Baseline	Percent Change from Baseline	Count	Absolute Change from Baseline	Percent Change from Baseline
xxxxxxx	xxxxxxx	Baseline	DDMMMYYYY	XXXX	XX			XX		
		Week 4	DDMMMYYYY	XXXX	XX	XX	XX	XX	XX	XX
		Week 12	DDMMMYYYY	XXXX	XX	XX	XX	XX	XX	XX
		Week 24	DDMMMYYYY	XXXX	XX	XX	XX	XX	XX	XX
		Week 36	DDMMMYYYY	XXXX	XX	XX	XX	XX	XX	XX
		Week 40	DDMMMYYYY	XXXX	XX	XX	XX	XX	XX	XX
xxxxxxx	xxxxxxx	Baseline	DDMMMYYYY	XXXX	XX			XX		
		Week 4	DDMMMYYYY	XXXX	XX	XX	XX	XX	XX	XX
		Week 12	DDMMMYYYY	XXXX	XX	XX	XX	XX	XX	XX
		Week 24	DDMMMYYYY	XXXX	XX	XX	XX	XX	XX	XX
		Week 36	DDMMMYYYY	XXXX	XX	XX	XX	XX	XX	XX
		Week 40	DDMMMYYYY	XXXX	XX	XX	XX	XX	XX	XX

Note: Inflammatory Lesions includes: papules/pustules + nodules/cysts.
s<nnn>xxxx yyyymmddthh:mm

Listing 16.2.7.1.2
Lesion Counts (Face Only): Papules, Pustules, Nodules, and Cysts
Safety Population

Previous Study	Subject ID	Visit	Date	Counter's Initials	Papules/Pustules	Nodules/Cysts
xxxxxxx	xxxxxxx	Baseline	DDMMMYYYY	XXXX	XXX	XXX
		Week 4	DDMMMYYYY	XXXX	XXX	XXX
		Week 12	DDMMMYYYY	XXXX	XXX	XXX
		Week 24	DDMMMYYYY	XXXX	XXX	XXX
		Week 36	DDMMMYYYY	XXXX	XXX	XXX
		Week 40	DDMMMYYYY	XXXX	XXX	XXX
xxxxxxx	xxxxxxx	Baseline	DDMMMYYYY	XXXX	XXX	XXX
		Week 4	DDMMMYYYY	XXXX	XXX	XXX
		Week 12	DDMMMYYYY	XXXX	XXX	XXX
		Week 24	DDMMMYYYY	XXXX	XXX	XXX
		Week 36	DDMMMYYYY	XXXX	XXX	XXX
		Week 40	DDMMMYYYY	XXXX	XXX	XXX

Listing 16.2.7.3
Cutaneous Tolerability
Safety Population

Previous Study	Subject ID	Visit	Date	Erythema	Scaling	Dryness	Pruritus	Burning/ Stinging
xxxxxxx	xxxxxxx	Baseline	DDMMMYYYY	Mild	Mild	Moderate	None	None
		Week 4	DDMMMYYYY	Mild	Mild	Moderate	None	None
		Week 12	DDMMMYYYY	Mild	Mild	Moderate	None	None
		Week 24	DDMMMYYYY	Mild	Mild	Moderate	None	None
		Week 36	DDMMMYYYY	Mild	Mild	Moderate	None	None
		Week 40	DDMMMYYYY	Mild	Mild	Moderate	None	None
xxxxxxxx	xxxxxxxx	Baseline	DDMMMYYYY	Mild	Mild	Moderate	None	None
		Week 4	DDMMMYYYY	Mild	Mild	Moderate	None	None
		Week 12	DDMMMYYYY	Mild	Mild	Moderate	None	None
		Week 24	DDMMMYYYY	Mild	Mild	Moderate	None	None
		Week 36	DDMMMYYYY	Mild	Mild	Moderate	None	None
		Week 40	DDMMMYYYY	Mild	Mild	Moderate	None	None

Note(s): 0 = None, 1 = Mild, 2=Moderate, 3 = Severe.
s<nnn>xxxx yyyymmddthh:mm

Listing 16.2.7.4
Vital Signs
Safety Population

Previous Study	Subject ID	Visit	Date/ Day	Systolic BP (mmHg)	Diastolic BP (mmHg)	Pulse (bpm)	Evaluation	If Abnormal and Clinically Significant, provide MH or AE term
xxxxxxx	xxxxxxx	Baseline	DDMMMYYYY/xx	xxx	xxx	xxx	Normal	
		Week 4	DDMMMYYYY/xx	xxx	xxx	xxx	Abnormal, NCS	
		Week 12	DDMMMYYYY/xx	xxx	xxx	xxx	Normal	
		Week 24	DDMMMYYYY/xx	xxx	xxx	xxx	Normal	
		Week 36	DDMMMYYYY/xx	xxx	xxx	xxx	Normal	
		Week 40	DDMMMYYYY/xx	xxx	xxx	xxx	Normal	
xxxxxxxx	xxxxxxxx	Baseline	DDMMMYYYY/xx	xxx	xxx	xxx	Abnormal, CS	XXXXXXXXXXXXX

Note(s): *Day = Day relative to the first day of LTS.* NCS = Not clinically significant;
CS = Clinically Significant. If a post-baseline finding was determined to be clinically significant, it is also reported as an adverse event.
s<nnn>xxxx yyyymmddthh:mm

Listing 16.2.7.5
Concomitant Medications
Safety Population

Previous Study	Subject ID	Drug Class/ Preferred Name/ Reported Term	Indication	Start Date (Day)/ End Date (Day)	Dose (Unit) / Frequency / Route	If for AE or MH, Primary Term	Ongoing from Previous Study?
xxxxxxx	xxxxxxx	XXXXXXXXXXXXXX/ XXXXXXXXXXXXXX/ XXXXXXXXXXXXXX	Adverse Event	DDMMMYYYY (XX)/ Ongoing			
xxxxxxxx	xxxxxxxx	XXXXXXXXXXXXXX/ XXXXXXXXXXXXXX/ XXXXXXXXXXXXXX	Medical History	DDMMMYYYY (XX)/ DDMMMYYYY (XX)	XXX.X (XXXXX) / XXX / XXXXXXXXXX	XXXXXXXXX	Yes
xxxxxxx	xxxxxxx	XXXXXXXXXXXXXX/ XXXXXXXXXXXXXX/ XXXXXXXXXXXXXX	Prophylaxis	DDMMMYYYY (XX)/ DDMMMYYYY (XX)	XXX.X (XXXXX) / XXX / XXXXXXXXXX		
xxxxxxxx	xxxxxxxx	XXXXXXXXXXXXXX/ XXXXXXXXXXXXXX/ XXXXXXXXXXXXXX	Dietary Supplement	DDMMMYYYY (XX)/ DDMMMYYYY (XX)	XXX.X (XXXXX) / XXX / XXXXXXXXXX	XXXXXXXXX	No
xxxxxxxx	xxxxxxxx	XXXXXXXXXXXXXX/ XXXXXXXXXXXXXX/ XXXXXXXXXXXXXX	Contraception	DDMMMYYYY (XX)/ DDMMMYYYY (XX)	XXX.X (XXXXX) / XXX / XXXXXXXXXX		
xxxxxxxx	xxxxxxxx	XXXXXXXXXXXXXX/ XXXXXXXXXXXXXX/ XXXXXXXXXXXXXX	Other: XXXXXXXXXX	DDMMMYYYY (XX)/ DDMMMYYYY (XX)	XXX.X (XXXXX) / XXX / XXXXXXXXXX		

Note(s): *Day = Day relative to the first day of LTS.* Coding will be done using the WHO March 2016 dictionary. Drug Class corresponds to ACT level 2.
s<nnn>xxxx yyyymmddthh:mm

Listing 16.2.8.1
Adverse Events
Safety Population

Subject ID	Duration of Exposure (days)	Extent of Exposure (grams)	System Organ Class/ Preferred Term/ Reported Term	TEAE	First Dose Date/ Start Date/ End Date / (Days)	Cause Study Discon-tinuation?	Severity / Relationship	Action / Treatment / Final Outcome	SAE?	SAE Criteria
xxxxxxx	XX	XX.X	XXXXXXXXXXXXXXX / XXXXXXXXXXXXXX / XXXXXXXXXXXXXXX	Y	DDMMMYYY / DDMMMYYY / DDMMMYYYY / XX	No	Mild / Unlikely	Dose Not Changed / XXXXXXXX / XXXXXXXXXXX XX	No	
xxxxxxx	XX	XX.X	XXXXXXXXXXXXXXX / XXXXXXXXXXXXXX / XXXXXXXXXXXXXXX	Y	DDMMMYYY / DDMMMYYY / DDMMMYYYY / XX	Yes	XXXXXXX / XXXXXXX	XXXXXXXX / XXXXXXXX / XXXXXXXXXXX XX	Yes	XXXXXXXXXX XX

Note(s): TEAE=Treatment-emergent Adverse Event. TEAE onset is based on the start of treatment in the LTS. Days = (Adverse event end date – event start date)+1. *Adverse events were coded using MedDRA 18.1. Duration and extent of exposure are based on the date of first dose of study drug, which could from the previous study (NI-AC301 or NI-AC302).*
s<nnn>xxxx yyyymmddthh:mm

Repeat Listing 16.2.8.1 for:

Listing 16.2.8.2 Treatment-Emergent Adverse Events Leading to Discontinuation of Study Drug Safety Population
Listing 16.2.8.3 Treatment-Emergent Adverse Events Leading to Treatment Modification Safety Population
Listing 16.2.8.4 Treatment-Emergent Serious Adverse Events Safety Population
Listing 16.2.8.5 Treatment-Emergent Adverse Events Leading to Death Safety Population

Listing 16.2.9
Concomitant Medical and Surgical Procedures
Safety Population

Previous Study	Subject ID	Verbatim Term	Start Date (Day) / End Date (Day)	Was it for an AE/SAE?	Ongoing from Previous Study?
xxxxxxx	xxxxxxx	XXXXXXXXXXXXXXXXXXXXX	DDMMYYYY (XX) / DDMMYYYY (XX)	No	Yes
xxxxxxxx	xxxxxxxx	XXXXXXXXXXXXXXXXXXXXX	DDMMYYYY (XX) / Ongoing	No	No