STATISTICAL ANALYSIS PLAN - TEXT

Title:	**A PHASE 3 OPEN LABEL SAFETY STUDY OF A-101 TOPICAL SOLUTION FOR THE TREATMENT OF COMMON WARTS**
Protocol:	**A-101-WART-303**
Study Drug:	**A-101 45% Topical Solution**
Sponsors:	**Aclaris Therapeutics, Inc.**
Version (Date):	**V 1.0 (17 January 2020)**
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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Term
AE	Adverse Event
CBC	Complete Blood Count
CRF	Case Report Form
ID	Identification
ITT	Intent to Treat
LSR	Local Skin Reaction
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term
PWA	Physician's Wart Assessment
SAE	Serious Adverse Event
SAP	Statistical Analysis Alan
SOC	System Organ Class

INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide a description of the statistical analyses performed for the Phase 3 protocol, A-101-WART-303, Version 3 (14February2019).

1. STUDY OBJECTIVES

1.1 Primary Objective

The primary objective of this study is to evaluate the long-term safety of A-101 45% when applied twice weekly to common warts.

1.2 Secondary Objectives

The secondary objectives of this study include:

- Efficacy of A-101 45% in the treatment of recurrent and/or further treatments for new warts.
- Duration of response to A-101 45%.
- Onset of action of A-101 45%.

2. STUDY DESIGN

This is a Phase 3, open-label, long-term safety study of A-101 45% Topical Solution in subjects with common warts.

In order to be eligible for A-101-WART-303, subjects must have completed protocol treatment on either the A-101-WART-301 or A-101-WART-302 study.

Subjects that have complete clearance of all warts at the end of A-101-WART-301 or A-101-WART 302 may enter into the A-101-WART-303 study following completion of the Visit 1 assessments. These subjects will be followed every 6 weeks to assess for a recurrence or development of new common warts. If a recurrence occurs or a new wart develops these subjects may return to the investigational site to receive A-101 45% Topical Solution twice a week for an additional 8 weeks.

Subjects that have warts that have not cleared (or were not treated) at the completion of A-101WART-301 or A-101-WART-302 may enter into the A-101-WART-303 study following completion of the Visit 1 assessments will receive A-101 45% Topical Solution twice a week for 8 weeks. Subjects may continue to receive A-101 45% Topical Solution twice a week for 8 weeks if their warts are not clear at the end of the 8-week treatment period but the 8 weekly treatments must be initiated by Day 122.

Visit 1 of A-101-WART-303 can be the same day as Visit 13 of either A-101-WART-301 or A101-WART-302.

All subjects will be required to remain on study for a total of 6 months.

During the study, the investigator may identify from 1 to 6 common warts to be treated twice a week for up to 8 weeks (maximum of 16 treatment applications). An 8-week treatment course may be repeated.

Figure 1 below provides a graphical representation for treatment in this study.

Figure 1: WART 303 Study Diagram for Treatment

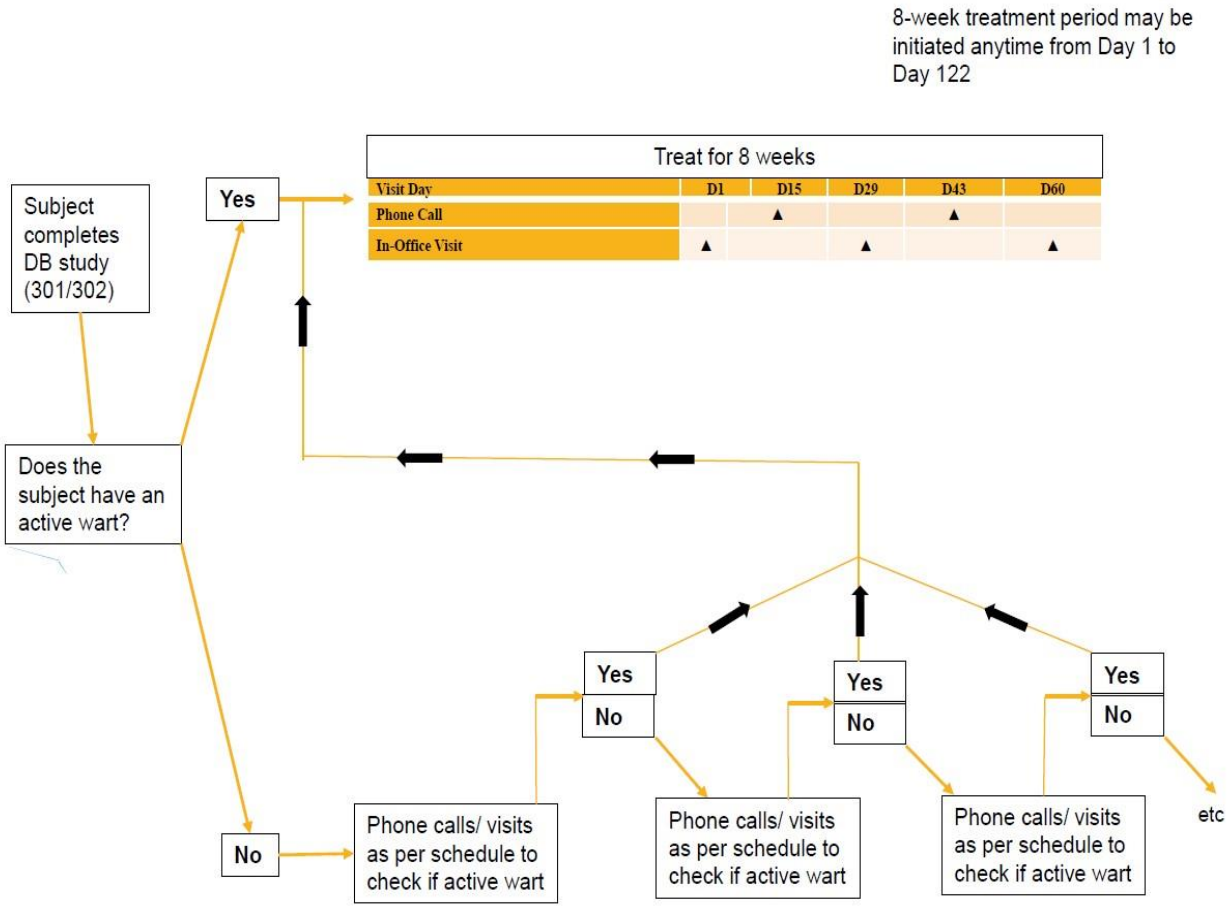

Table 2 and Table 3 provide complete list of protocol required study assessments.

Table 2: Study Procedures for Subjects with Common Warts at Visit 1

Visit	V1	V2	V3	V4	V5	V6	V7	V8
Visit Day	Day 1	Day 15	Day 29	Day 43	Day 60	Day 102	Day 144	Day 182
Visit Windows		+3 Days	+ 3 Days	+ 3 Days	+ 3 Days	+ 3 Days	+ 3 Days	+ 2 Days
In Office Visit	▲[1]		▲		▲			▲
Phone Call		▲[4]		▲[4]		▲[4]	▲[4]	
Informed Consent	▲							
Inclusion Criteria/Exclusion Criteria	▲							
Clinical Chem / CBC[2]								▲
Common Wart Identification	▲[3]							
Common Wart Dimensions	▲		▲		▲			▲
Physician's Wart Assessment	▲		▲		▲			▲
Local Skin Reactions	▲		▲		▲			▲

Visit	V1	V2	V3	V4	V5	V6	V7	V8
Study Medication Application[5]	▲	▲	▲	▲				
Study Medication Dispensing and Instructions for at home application	▲		▲		▲			
Concomitant therapies		▲	▲	▲	▲	▲	▲	▲
Adverse Events	▲	▲	▲	▲	▲	▲	▲	▲

[1] Visit 1 of A-101-WART 303 may occur on the same day as Visit 13 of A-101-WART 301 or A-101-WART 302.

[2] Subjects who do not have their Visit 1 assessment on Visit 13 of A-101-WART 301 or A-101-WART-302 will have to have a clinical chemistry and a complete blood count drawn and sent to the central laboratory for analysis. A complete blood count (including hematocrit, hemoglobin, platelet count, red blood cell count and morphology, white blood cell count and differential (absolute and %) including basophils, eosinophils, lymphocytes, monocytes and neutrophils and a clinical chemistry panel including albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), bicarbonate, calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid.

[3] Warts that are identified for treatment must meet the requirements as outlined in Section 9.1.

[4] Investigational site staff will be required to make a phone contact with the subject on Day 15, Day 43, Day 102 and Day 144 to assess for any safety issues and possible new concomitant medications the subject may have started taking. In addition, subjects are to ask if they have had any new warts develop since the last in office visit.

[5] Subjects over the age of 18 are to apply the A-101 study medication on the following days: Day 1, Day 4, Day 8, Day11, Day 15, Day 18, Day 22, Day 25, Day 29, Day 32, Day 36, Day 39, Day 43, Day 46, Day50 and Day 53. A window of +1 day is allowed. Subject between the ages of 1-17 will have their A-101 study medication applied by a parent or guardian. Parents/legal guardians of children must ensure that the child does not put the treated area in their mouth, or eyes, until completely dry after the application. If the treated area is not completely dry 10 minutes after the application, the area should be blotted dry.

Table 3 Safety Observation Assessments for Subjects that are Clear at Visit 1 and Remain Clear

Visit	V1	V2	V3	V4	V5
Treatment Day	Day 1	Week 6 (Day 42)	Week 12 (Day 84)	Week 18 (Day 126)	Week 26 (Day 182)
Window		+7 Days	+7 Days	+7 Days	+2 Days
In Office Visit	▲[1]				▲
Phone Call		▲[2]	▲[2]	▲[2]	
Informed Consent	▲				
Inclusion Criteria/Exclusion Criteria	▲				
Concomitant therapies		▲	▲	▲	▲
Adverse Events	▲	▲	▲	▲	▲

[1]Visit 1 of A-101-WART 303 may occur on the same day as Visit 13 of A-101-WART 301 or A-101-WART 302.

[2] Investigational site staff will contact via a documented phone call on Visit 2 Day 42, Visit 3 Day 84, Visit 4 Day 126 and Visit 5 Day 182. During the phone calls sites are to ask the subject if they have had any new warts develop or if a wart that was previously treated has recurred. If a subject has had a new wart develop or a previously treated wart has recurred, then the subject is to be scheduled for an in -office visit to start an 8-week treatment course with A-101 study medication. Subjects are to be instructed to contact the investigational site as soon as they think a new wart (or a recurrence) has developed. The 8-week treatment period can start no later than Day 102. Refer to Table 2 for the 8- week treatment schedule.

3. STATISTICAL METHODS

3.1 Analysis Populations

The populations used for analyses are defined as follows:

- All Enrolled Population: The All Enrolled population includes all subjects that signed informed consent.
- Safety Population: The Safety population includes all subjects who received at least one application of study medication.

Enrollment, disposition, demographics, and baseline characteristics summaries will be presented for All Enrolled Population.

The Safety population will be used for both efficacy and safety analyses and summaries.

All subjects will be included in the listings.

3.2 Treatment Groups and Data Presentation

This is an open-label study with only one treatment arm. Subjects who enter the study with a common wart receive study medication immediately. Subjects who enter the study with no common warts do not receive study medication at the start and will not be treated at all if they do not develop any common warts throughout the course of the study. In order to be eligible for this study, subjects must have completed protocol treatment on either the A-101-WART-301 or A-101-WART-302 study. Both WART-301 and WART-302 were double-blind studies where subjects were treated with either active A-101 45% topical solution or vehicle solution. To best account for all potential exposure to A-101 45%, summaries and analyses will take into consideration both the current open-label treatment status as well as the randomized treatment assignment from the subject's respective double-blind study. This classification precipitates the following four treatment groups.

- Open Label A-101 45%: Double-Blind A-101 45%
- Open Label A-101 45%: Double-Blind Vehicle
- Open Label Not Treated: Double-Blind A-101 45%
- Open Label Not Treated: Double-Blind Vehicle

Depending upon analysis population, data will be summarized into all or a subset of treatment groups indicated above. Summaries on All Enrolled Population will display all four treatment groups. Summaries on Safety Population will display only first two treatment groups.

All data listings will be sorted by treatment group and subject ID. Subject ID will identify site number and double-blind study subject participated prior to open label study

enrollment.

3.3 Study Day and Period Study Day

As shown in Figure 1, subjects can potentially take multiple courses of treatment throughout the study. Subjects entering the study with warts will receive treatment at study entry as shown in Table 2. Subjects who enter without any common warts do not receive study medication immediately and follow visit schedules shown in Table 3. If these subjects develop any wart during the study, they will then begin a treatment regimen and follow the visit schedule for treated subjects. Subjects can initiate a treatment regimen up to three times (cycles) throughout the course of the study up to day 122. To allow for comparisons referencing each treatment cycle, Study Day will be calculated in two ways. Study day is defined as the relative day in the study from time of enrollment (first dose if treated immediately). Period study day is defined as the relative day from the day of first dose within a treatment cycle.

3.4 Baseline and Analysis Visit

For the analysis of efficacy data, data will be assigned to an analysis visit within a treatment cycle based on period study day. These analysis visits are presented in Appendix A.

For subjects who are not treated, baseline values are non-missing values prior to the start of the study. For treated subjects, baseline values are last non-missing values prior to first application of study medication. For analysis by treatment cycle, baseline values are last non-missing values before the start of a treatment cycle.

3.5 Subject Enrollment and Disposition

The number of subjects enrolled to this study and their prior participation in double-blind studies will be presented by treatment status and double-blind treatment assignment. Study completion status and the reasons for discontinuation by major reason (lost to follow-up, adverse event, poor compliance etc.) will be presented for both All Enrolled Population and Safety Population by treatment group as defined in Section 3.2.

A listing will be provided of all subjects discontinued from the study after enrollment, broken down by previous double-blind study participated and study center, giving a subject identifier and the specific reason for discontinuation, and the duration of treatment before discontinuation.

3.6 Demographics and Other Baseline Characteristics

Descriptive summary statistics of demographic and other characteristics (Age, Sex, Race, Ethnicity, Height, Weight, and Fitzpatrick Skin Type) list characteristics inside parentheses) will be generated for All Enrolled Population. The n, mean, standard deviation, median, minimum, and maximum and/or frequency distributions will be reported, as appropriate.

3.7 Wart Characteristics at Study Entry and During the Study

Wart characteristics at study entry will be summarized descriptively for Enrolled Subjects. Summarized variables include identification of warts, wart dimension, and location (Hands, Feet, Elbows, Knees, Rest of Body). Wart Characteristics are also summarized during the study by treatment cycles for the Safety Population.

3.8 Prior and Concomitant Medications, Therapies and Procedures

Prior and concomitant medications are listed only. The period(s) (prior, on treatment, and post-therapy) in which the medications were administered will be flagged. These rules are explained in Data Handling and Programming Specification Document in detail. Medications are coded using the WHO Drug (March 2019).

3.9 Protocol Violations

Protocol violations will be identified prior to database lock to measure adherence to key aspects of the protocol (see Section 15 of the protocol for full definitions). Specific data fields that will be examined to identify protocol violations include inclusion/exclusion criteria and prohibited prior and concomitant medications as well as all deviations identified by the investigator. All protocol violations will be listed.

3.10 Efficacy Endpoints

The primary and secondary efficacy analyses will be carried out on the Safety Population. Efficacy summaries will be supported by listings.

Primary Efficacy Endpoint: Proportion of subjects who achieve complete clearance (PWA-0) of all identified warts at each analysis visit window by treatment group and treatment cycle.

Four secondary efficacy endpoints are:

- Durability of response: For subjects with all warts achieving a status of Clear (PWA=0), the number of weeks all warts remain clear by treatment group and treatment cycle.
- Mean per-subject percent of treated warts that are Clear (PWA=0) at each analysis visit by treatment group and treatment cycle.
- Proportion of subjects with a single wart at baseline whose wart is Clear (PWA=0) by analysis visit, treatment group, and treatment cycle.
- Median time to achieve onset of Clearance (PWA=0) for all treated warts by treatment group and treatment cycle.

3.10.1 Primary Efficacy Analysis - Complete Clearance of All Warts

The primary efficacy summary will tabulate the number and percent of subjects achieve complete clearance (PWA=0) at each analysis visit by treatment group. This analysis will also be done by treatment group and treatment cycle. Treatment cycle start date can vary from subject to subject so analysis visits will be derived from period study day as

described in Appendix A and Section 3.3. All efficacy analyses will be descriptive and there will be no formal statistical test to compare treatment groups.

Any identified common wart for a subject that has missing PWA data will be treated as not clear for the purpose of the primary efficacy analysis. A sensitivity analysis will be carried out using observed data.

3.10.2 Secondary Efficacy Analyses

3.10.2.1 Durability of Response

Difference in time to recurrence of wart by treatment group is summarized using Kaplan Meier analysis. This analysis will be done at overall study level and by treatment cycle.

- **Overall Study Level**: Time to recurrence will be presented graphically with a Kaplan Meier curve. For this analysis, time to first recurrence in the study will only be included for each subject. Subjects with no wart at the end of study will be censored. The proportion of subjects that remain clear of warts at the end of the study will also be presented.

- **By Treatment Cycle**: For this analysis, time to first recurrence in the treatment cycle will only be included for each subject. Subjects with no wart at the end of the treatment cycle will be censored.

Kaplan-Meier estimates and associated confidence intervals are obtained using SAS statements consistent with the following syntax:

```
PROC LIFETEST ALPHA=.05;
TIME DAYS*CENSOR(1);
SURVIVAL OUT=SURV CONFTYPE=LOGLOG;
STRATA TREATMENT GROUP;
```

3.10.2.2 Mean Per-Subject Percent Wart Cleared

Mean per-subject percent of treated warts that are Clear (PWA=0) at each analysis visit will be summarized descriptively by treatment group and treatment cycle. Subjects with non-missing PWA values are only included. For each subject, percent of cleared warts are computed before summarizing across subjects in a treatment group. Data from subjects who begin treatment later in the study will be included once they start treatment. Treatment cycle start date can vary from subject to subject.

3.10.2.3 Complete Clearance in Subjects With a Single Wart at Baseline

Proportion of subjects with a single wart at baseline whose wart is Clear (PWA=0) will be summarized descriptively by treatment cycle, analysis visit, and treatment group. Treatment cycle start date can vary from subject to subject. Subjects with a single Wart in the beginning of treatment cycle and without a Wart assessment at the timepoint analyzed are assigned non-clearance.

3.10.2.4 Time to Clearance of All Warts

The last secondary endpoint analyzed, the difference in time to clearance of all warts from start of a treatment cycle between treatment groups, is summarized using Kaplan Meier analysis. Confidence intervals for clearance times are based upon the methods of Brookmeyer and Crowley[1]. This analysis will be performed on a subject level by treatment cycle. Treatment cycle start date can vary from subject to subject. Subjects whose warts are not cleared at the end of a treatment cycle are censored.

Kaplan-Meier estimates and associated confidence intervals are obtained using SAS statements as shown in Section 3.10.2.1.

3.11 Safety Analyses

Safety summaries will be conducted on the Safety Population.

The following sections detail the summaries performed on the safety data. Additional data handling rules including those for imputation of partially missing dates are provided in a separate SAP document pertaining to data handling and programming specifications.

The baseline scores for laboratory assessments and local skin reactions will be the last non-missing value collected before first application of A-101 45% in this study. For most subjects, Visit 1 laboratory measurements in this study are done on Visit 13 of parent double-blind study (A-101-WART-301 or A-101-WART-302).

3.11.1 Extent of Exposure

The duration of treatment, the number of application days (i.e. the actual count of days where an application occurred), the mean applications per wart (for each subject the sum of all applications across all treated warts and all application days divided by the total number of treatments for all treated warts), and the total applications will be summarized using descriptive statistics (n, mean, SD, median, minimum and maximum). The percentage of total wart treatments that were performed in 1, 2 or 3 applications is also provided.

Overall compliance is calculated as the total number of wart treatments performed during the treatment period (through date of last application to any wart) divided by the total number of wart treatments expected to be performed. The total number of warts treated is the sum of the retreatment and home application diary records completed times the number of warts assessed at baseline minus the number of warts scored as PWA=0 or having an LSR grade 3 at the most recent assessment (<= the date of the application).

3.11.2 Adverse Events

Adverse events are coded using the MedDRA (Version 22) and are categorized by system organ class (SOC) and preferred term (PT). Only treatment emergent adverse events are included in summary tabulations (i.e. adverse events occurring within 30 days of each application of study medication). All adverse events are included in the data listings including those that are not considered treatment emergent.

To allow differentiation as to which study period an Adverse Event occurred, three categories are defined based upon onset date. Adverse Events that had onset dates prior to the first application of study medication are considered "prior". Adverse events with onset dates on or within 30 days of an application of study medication are considered "treatment emergent". Events with onset dates more than 30 days after the most recent application of study medication are considered as "post-therapy." In this study, subjects can possibly receive medication up to three cycles and multiple doses of medication within a treatment cycle. The above rule will be applied to all known doses of medication while determining study period.

Frequency tabulations are presented by MedDRA SOC and preferred term, for all adverse events; study treatment-related adverse events, adverse events resulting in discontinuation of study treatment, serious adverse events and adverse events by maximum severity. Adverse events resulting in discontinuation are those with 'action taken' recorded as 'drug withdrawn'.

3.11.3 Local Skin Reactions

The number of subjects with local skin reaction signs or symptoms that worsened by at least 1 grade from baseline any time after the first application of study medication will be tabulated by treatment group for each LSR as well any LSR. A separate summary limited to LSRs that worsen and which occur within 30 days of the last application of study medication will be provided. Additionally, to assess effect of number of cycles of applications of study medication on LSR, this summary will be presented by treatment cycle also.

3.11.4 Laboratory Evaluations

Shift tables showing changes in relationship to the normal reference range grade from baseline to the "worst" relationship recorded post-baseline are tabulated. In the event a subject had both "low" and "high" post-baseline values the subject will be counted under both "low" and "high". As such, the percentages of the cells in the shift table may add to more than 100%.

Chemistry and hematology parameters will be summarized using descriptive statistics for each visit. Both actual values and changes from baseline will be summarized.

The number and percentage of subjects meeting criteria for hepatobiliary abnormalities will be provided.

3.12 Interim Analyses

No interim analyses are planned for this study.

3.13 Sample Size

The sample size is based on an estimate of how many subjects will be required to provide at least 100 subjects requiring repeated treatment for a wart over the course of the study.

- By recruiting 400 subjects, we estimate 200 subjects will have received active treatment in the A101-WART 301/302 studies.
- We expected approximately 26% of warts treated in A-101-WART-301/302 studies to be clear at the end of the A-101-WART-301/302 studies.
- Based on the assumption that 26% of warts will be clear, at least 148 subjects will require exposure to active treatment.
- We anticipate that some subjects originally randomized to vehicle (in double-blind studies) will be exposed to active treatment.

As a result, the study should exceed the target of exposing more than 100 subjects to repeated treatments over the course of the study.

3.14 Changes in/ Clarifications to the Conduct of the Study or Planned Analysis

Originally, both efficacy (primary and secondary endpoints) and safety analyses were planned on intent to treat (ITT) population. The primary objective of the study is to evaluate long-term safety of A-101 45% when applied twice weekly to common warts. Considering this and the fact that all treated subjects will administer the same medication (A-101 45%), it was deemed more appropriate to conduct both efficacy and safety analyses on the Safety Population. For that reason, all analyses will be conducted on the Safety Population. Data collected for subjects who did not receive treatment will be listed.

4. STATISTICAL SOFTWARE

All data summaries and listings will be performed using SAS® Version 9.4 or higher, under Windows operating system.

5. REFERENCES

1. Brookmeyer and Crowley, A Confidence Interval for the Median Survival Time, Biometrics 38, 29-41, March 1982.

APPENDIX A: ASSIGNMENT TO ANALYSIS VISIT

Due to the possibility of deviation from the protocol schedule as well as to incorporate data from unscheduled and/or early termination visits, analysis visits are defined below based on Treatment Period Study Day for each treatment cycle. These analysis visits are based on the nominal, scheduled visits in the protocol and treatment cycle. Analysis visit will be used in analyses performed by or on specific visit as well as for the identifiers on data listings. Both nominal visits as collected on the CRF and analysis visits will be retained in the SAS ADaM datasets.

Analysis Visits Within Each Treatment Cycle:

Analysis Visit	Treatment Period Study Day Range	Target Treatment Period Study Day
Px V1	1	1
Px V2	2 - 22	15
Px V3	23 - 36	29
Px V4	37 – 51	43
Px V5	52 – 81	60
Px V6	82 – 127	102
Px V7	128 – 163	144
EOS (End of Study) Visit	>= 164	182

Note: P indicates Treatment Period (Treatment Cycle), x indicates Treatment Period Number (Either 1 or 2 or 3), and V indicates Visit. There is only one EOS visit for all subjects.

In the event that more than one observation falls into the same study day range, the value closest to the "target day" is selected. If there's a tie in the absolute distance from the target day, the observation with the greater cycle day is selected.