GALDERMA LABORATORIES, L.P.

STATISTICAL ANALYSIS PLAN

Investigational Product:	*Sculptra® Aesthetic (injectable poly-L-lactic acid)*
Protocol No.:	GLI.04.SPR.US10321
Protocol Title:	*A Prospective, Open-Label, Multicenter Study to Evaluate the Long-Term Safety of Sculptra®Aesthetic in Immuno-Competent Subjects Stratified by Fitzpatrick Skin Type I-VI*
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Galderma Laboratories, L.P.
Protocol GLI.04.SPR.US10321

A Prospective, Open-Label, Multicenter Study to Evaluate the Long-Term Safety of Sculptra® Aesthetic in Immuno-Competent Subjects Stratified by Fitzpatrick Skin Type I-VI

SIGNATURE PAGE

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DOCUMENT HISTORY

Rev No	Date	Description
1.0	29-Mar-2018	Original document
2.0	17-Aug-2018	The following revisions were made to the statistical analysis plan: Section 4.3: Broaden the definition of completer2 population to capture subjects who missed Year 2 visit but remained in the study beyond Day 703. Section 4.4.4: Update for bullet 3 in Sensitivity Analyses, multiple imputation will be done separately for each of the following: injection site nodule and/or papule, and all other AEIs (excluding injection site nodules/papules). Section 5.1: Add that unscheduled visit will not be used for analysis purposes in this study. Section 5.2.1: 1. Clarify that when deciding on baseline characteristics to be used in multiple imputation models, two groups will be compared separately with subjects who remain in the study or have had an event of interest. One of these groups is subjects who discontinued without any injection site nodules and/or papules, and the other is subjects who discontinued without any AEI other than injection site nodules and/or papules. 2. Update that when conducting multiple imputations, AEIs will be divided into 2 distinct groups. One is injection site nodules and/or papules, and the other is any AEI other than injection site nodules and/or papules. 3. Continuous factor, number of injection sessions, will be tested using wilcoxon rank sum test, as the data is highly discrete. 4. Update the number of sets that will be imputed. 5. Update the algorithm used for multiple imputation. 6. Remove standard errors or CI from imputation estimates.

		Section 5.4: Add section to clarify how duration and time to onset are calculated. Section 6.0: Add a deviation for the MI modeling.

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1.0 Introduction

The safety and effectiveness of Sculptra® Aesthetic for the treatment of nasolabial fold (NLF) wrinkles was evaluated in a randomized, evaluator blinded, parallel group, multicenter clinical trial in the US (Study DL6049-0301). Immuno-competent subjects with previously untreated NLF wrinkles with wrinkle assessment score (WAS) of 2 (shallow) to 4 (deep) participated in the study.

The experience with Sculptra® Aesthetic in immune-competent subjects with darker skin types (ie, Fitzpatrick types IV-VI, see Appendix I in the clinical study protocol), was limited in the above study (ie, 22 out of 116 subjects treated with Sculptra® Aesthetic had skin type IV-VI). Thus, the Sponsor has committed to perform this postapproval study (PAS) to assess the safety of Sculptra® Aesthetic on at least 100 evaluable subjects with Fitzpatrick skin type IV-VI (including at least 15 with Fitzpatrick skin type IV and 85 with Fitzpatrick skin type types V or VI) up to 5 years (ie, completion of the follow-up phase). This PAS, in conjunction with the above pivotal study, would provide significant information to confirm the safety of Sculptra® Aesthetic in darker skin types over a longer period of observation and to assess device-related long-term incidence of chronic inflammation.

2.0 Study Design

2.1 Description of the Protocol

This is prospective, open-label, multicenter US study to evaluate the long-term safety of Sculptra® Aesthetic in immuno-competent subjects stratified by Fitzpatrick skin types I-III, IV, and V-VI.

This clinical study will be conducted in the US with approximately 863 subjects at a minimum of 20 sites, with a planned minimum of 15 subjects per site.

2.2 Duration of Study

The study participation for each subject will be approximately 5 years in duration. Subjects will receive open-label treatment at the screening/initial treatment visit (Visit 1, Day 1 – 1st injection session). Subjects will continue to receive open-label treatment for up to 9 weeks (Visit 2, Week 3 [2nd injection session]; Visit 3, Week 6 [3rd injection session]; and Visit 4, Week 9 [4th injection session]) if needed and determined by the clinical study Investigator. Subjects will continue with follow-up visits at Months 3, 6, 9, and 13, and Years 2, 3, 4, and 5.

2.3 Interim Analyses

Interim analyses are planned following completion of all subjects' Month 13, Year 2, 3, and 4 follow-up visits. All safety and efficacy data up to the interim cut-off date will be cleaned, interim locked, analyzed and reported. CCI [redacted]

3.0 Study Objectives

3.1 Primary

The primary objective of the study is to assess the long-term safety of Sculptra® Aesthetic in immune-competent subjects as a single regimen for correction of WAS 2 to 4 NLF contour deficiencies and other facial wrinkles in which deep dermal grid pattern (cross-hatch) injection technique is appropriate, for the following variables:

- The incidence of nodule and papules in subjects with Fitzpatrick skin type I-VI.
- The incidence of other adverse events of interest (hypertrophic scarring, keloid formation, change in skin pigmentation at the site of injection compared to adjacent skin, granulomas, skin necrosis, hypersensitivity reactions, and unexpected changes in wrinkle contour) in subjects with Fitzpatrick skin type I-VI.

3.2 Secondary

Secondary objectives include the following:

- To evaluate the time to onset, duration, severity, relationship to Sculptra® Aesthetic and/or injection procedure, and outcome of all adverse events, including adverse events mentioned under the primary objectives, during the course of the study, by Fitzpatrick skin type.
- To evaluate the change in the WAS from baseline to post-treatment follow-up time points at Months 6, 13, and Years 2, 3, 4, and 5 in NLFs and other facial wrinkles.
- To evaluate Investigator/subject global evaluations at Months 6, 13, and Years 2, 3, 4, and 5.

4.0 Statistical Analysis

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4.2 Analysis Variables

4.2.1 Demographic and baseline characteristics

Demographic and baseline characteristics will include subjects' sex, race/ethnicity, age, height, weight, Fitzpatrick classification skin type, medical history, prior and concomitant medications, wrinkle assessment and measurement at initial treatment for NLFs and other anatomic areas, and vital signs (sitting heart rate and blood pressure).

4.2.2 Safety variables

4.2.2.1 Adverse events

Adverse events (AEs) are defined as adverse events that develop or worsen during the on-treatment period (time from first dose of Sculptra® Aesthetic to the end of the study). All adverse events will be coded using the current version of MedDRA.

The injection site adverse events listed below are defined as **Adverse Events of Interest (AEI)** in this study.

- Injection Site Nodule
- Injection Site Papule
- Hypertrophic scarring
- Keloid formation
- Changes in the skin pigmentation at the site of injection compared to adjacent skin
- Granuloma (confirmed by a biopsy)
- Skin necrosis
- Hypersensitivity reactions
- Unexpected change in wrinkle contour

The co-primary safety endpoints are:

1. The percentage (incidence rate) of subjects with any injection site nodule and/or papule over 5 years.

2. The percentage (incidence rate) of subjects with any of the following injection site events over 5 years, and they are termed as AEI other than injection site nodule and/or papule:
    - Hypertrophic scarring
    - Keloid formation
    - Changes in the skin pigmentation at the site of injection compared to adjacent skin
    - Granuloma (confirmed by a biopsy)
    - Skin necrosis
    - Hypersensitivity reactions
    - Unexpected change in wrinkle contour

The secondary safety endpoints are:

- the percentages (incidence rate) of subjects with any injection site nodule and/or papule over 2 years
- the percentages (incidence rate) of subjects who experienced any AEI other than injection site nodule or papule over 2 years

Summaries on Adverse Events and Adverse Events of Interest only take into consideration of those events that are treatment emergent.

4.2.2.2 Laboratory safety variables

A urine pregnancy test for women of childbearing potential will be collected at Visit 1.

4.2.2.3 Vital signs and physical exam

Vitals signs (sitting heart rate and blood pressure) and physical examination (overall subject assessment and facial assessment) will only be collected at Visit 1 and considered as the baseline characteristics for each subject (see Section 4.4.1).

4.2.2.4 Other safety variables

Injection related events will be collected in the diary card through the study.

4.2.3 Efficacy variables

4.2.3.1 Primary efficacy variables

None

4.2.3.2 Secondary efficacy variables

The secondary efficacy endpoints are:

- Change from baseline to post-treatment follow-up time points in the WAS at Month 6, Month 13, and Years 2, 3, 4, and 5.
- Investigator/Subject Global Evaluations at Month 6, Month 13, and Years 2, 3, 4, and 5.

4.3 Analysis Populations

The intent-to-treat (ITT) population, per protocol (PP) population, and Completer2 and Completer5 populations are defined as follows:

ITT Population: All subjects who receive at least one Sculptra® Aesthetic injection

PP Population: All subjects who receive at least one Sculptra® Aesthetic injection and are without any major protocol deviation. Protocol deviations will be reviewed by the Sponsor/CRO to determine which subjects will be included in the PP population.

PP population based analysis will only be done if the number of subjects from PP population is at least 5% different from the ITT population.

Completer2 Population: All subjects who receive at least one Sculptra® Aesthetic injection and finish the second year visit. Subjects who finish the second year visit are those who did not discontinue before Day 703 (Day 731 - 4 weeks).

Completer5 Population: All subjects who receive at least one Sculptra® Aesthetic injection and completed the study.

4.3.1 Efficacy populations

The analysis population for efficacy will be the ITT population and the PP population. The ITT population is the primary population for hypothesis testing.

4.3.2 Safety populations

The analysis population for safety will include the ITT population and the PP population. The ITT population is the primary population for hypothesis testing. The Completer2 and Completer5 populations will be used for sensitivity analyses of the primary and secondary hypotheses.

4.3.4 Disposition of subjects

The general disposition of subjects during the study will be defined as follows: (a) **screened** subjects are those who have a written informed consent document; (b) **treated** subjects are those screened subjects who received at least 1 dose of Sculptra® Aesthetic; and (c) **completed** subjects are those treated subjects who complete all clinical trial protocol required visits.

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4.4.1 Demographics and baseline characteristics

Demographics and baseline characteristics will be summarized by descriptive statistics, which consist of mean, standard deviation, median, minimum and maximum for continuous variables, and frequency count and percentage for categorical variables.

A listing of concomitant medication that were used for injection site nodule and/or papule will be provided. These medications will be determined from a manual review of the indications reported for all medications that were used for treatment of an AE.

4.4.2 Extent of study treatment exposure and compliance

Extent of treatment exposure and compliance will be determined by the number of injection sessions, the total amount of Sculptra® Aesthetic (mL) used, the total amount of Sculptra® Aesthetic used per anatomic area and per injection session, and the amount of Sculptra® Aesthetic used per surface area (mL/cm^2) per WAS.

Volume per surface area will be calculated by taking the amount volume injected at a given injection area and in a given injection session. In the case where a given area has multiple injections, volume per surface area for this area will be calculated by obtaining volume per surface area for each session independently, and then averaging across all injections the area receives.

The treatment exposure and compliance will also be summarized by whether the area treated developed any injection site nodules and/or papules. Specifically, number of injections, total treatment volume (mL), volume per surface area (mL/cm^2), and volume per surface area by study center will be summarized in subgroups that are defined by whether the injection site had an injection site nodule and/or papule. These summaries will be done overall and by anatomic area.

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4.4.4 Analysis of safety data

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4.4.4.2 Other analyses of adverse events

All adverse events will be collected and summarized with the number of subjects reporting adverse events by number of injections, system organ class, preferred term, severity, relationship to the Sculptra® Aesthetic, and relationship to injection procedure.

For injection site nodules and/or papules and any other AEI, summaries will also include incidence rates by location and intervention, duration (<=30 days versus >30 days), and time to onset (<=30 versus >30 days for nodules and/or papules, and <=120 versus >120 days for any other AEI). Duration and time to onset of all events will also be summarized with descriptive statistics. Kaplan Meier estimates and plots will also be provided to estimate the maximum duration and time to the first occurrence within a subject. Time to onset is defined as the time from first injection to the start of the event.

To obtain duration of injection site nodules and/or papules and any other AEI, events that are ongoing will be handled in two ways: 1) excluding events that are ongoing at the time of data cutoff; and 2) assigning data cutoff date as the event end date.

The following frequency distributions of adverse events (incidence tables) will be provided:

- Overview of adverse events
- All AEs by number of injection sessions
- All AEs by system organ class and preferred term by decreasing frequency
- All AEs by system organ class, preferred term and intensity
- All AEs by system organ class, preferred term and relationship to treatment
- All AEs by system organ class, preferred term and relationship to procedure

The following listings will be provided:

- All adverse events
- Serious adverse events
- Adverse events that lead to discontinuation of Sculptra® Aesthetic
- Adverse events that lead to discontinuation of study
- Injection site nodules and papules
- AEI, other than injection site nodule and papule

The incidence rate of injection site nodule and/or papule will also be summarized by study site and baseline wrinkle assessment.

Subject reported injection related events collected in the diary card will be summarized by frequencies and percentages. Severity of subject reported injection related events after initial treatment session will be summarized by anatomic areas and Fitzpatrick skin type groups.

4.4.4.3 Laboratory variables analysis

Not applicable.

4.4.4.4 Analysis of vital sign variables

Not applicable.

4.4.4.5 Analysis of other safety variables

Not applicable.

4.4.4.6 Analysis of pharmacokinetic and pharmacodynamic variables

Not applicable.

4.4.4.7 Analysis of health economics variables

Not applicable.

4.4.5 Discontinuation Tracking

A listing for subject disposition and a table with summary of disposition will be provided. In the disposition summary table, early withdrawal at time points that are defined by each interim analysis will also be summarized. The programmatic thresholds for these time point are defined as below, and the target dates for these interim time points are defined in Table 1:

- Early withdrawal < Month 13: it includes subjects who discontinued before Month 13 (- 2 weeks);
- Early withdrawal < Year 2: it includes subjects who discontinued before Year 2 (- 4 weeks);
- Early withdrawal < Year 3: it includes subjects who discontinued before Year 3 (- 4 weeks);
- Early withdrawal < Year 4: it includes subjects who discontinued before Year 4 (- 4 weeks).

A subcategorization of CRF-defined discontinuation reasons will be further classified based on comments provided at a subject's exit. A listing and a summary table will be provided.

4.4.6 Interim analyses

Interim analyses will be conducted on all study variables at 4 time points:

- Following completion of all subjects Month 13 follow-up visits;
- Following completion of all subjects Year 2 follow-up visits;
- Following completion of all subjects Year 3 follow-up visits; and
- Following completion of all subjects Year 4 follow-up visits.

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For these interim analyses, AEs and concomitant medications that started on or before the study visit will be included. If the study visit was not conducted, events/medications that started on or before the scheduled study day + 4 weeks (2 weeks for Month 13) will be included.

5.0 Data Handling Conventions

5.1 Baseline and Follow-Up Visits

Visits and time points for all analyses will be as recorded on the eCRFs. Baseline will be the last non-missing values from the Visit 1 (Day 1)/Baseline visit scheduled to occur prior to receiving study treatment. Unscheduled visit will not be used for analysis purposes in this study.

5.2 Missing Data

5.2.1 Missing AEI data due to subject discontinuation

If a subject discontinues the study before 2 or 5 years without an adverse event of interest, the subject will be assumed to have no adverse events of interest between the date of discontinuation and the 2 or 5-year time point when conducting the formal hypothesis testing. A sensitivity analysis will be conducted using the multiple imputation method to impute an outcome for these subjects.

To better determine covariates that will be used to conduct multiple imputation for missing event, the subjects who remain in the study or have had an event of interest will be compared to those who drop out without any injection site nodules and/or papules (or any AEI other than injection site nodules and/or papules), with respect to baseline characteristics and number of injection sessions to assess if missing appears to be missing at random or missing completely at random. Baseline characteristics include demographics (age, gender, ethnicity and race), Fitzpatrick skin type and medical history. Continuous factors include age and number of injection sessions. Age will be compared using a two sample t-test. Number of injection sessions will be compared using a wilcoxon rank sum test, as the data is highly discrete. Categorical factors will be compared using Pearson's Chi-square test, with Fisher's exact test as an alternative when the cell counts are less than 5.

A listing of discontinuation reasons for subjects who discontinued without an injection site nodule and/or papule or any AEI other than injection site nodule and/or papule will be provided, to detail the reason for missing.

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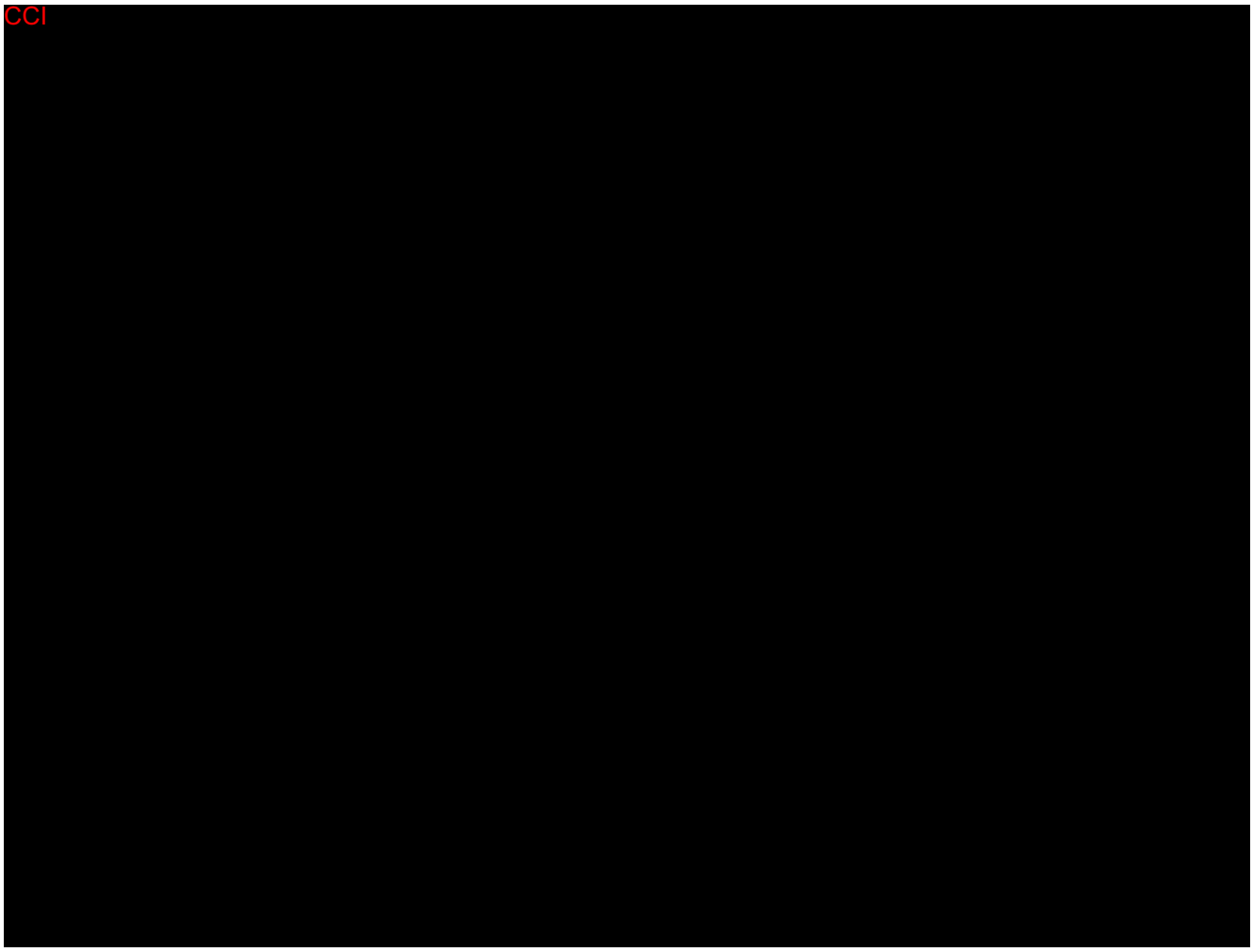

5.2.2 Rules for imputing stop dates for adverse event, subject reported event, and prior/concomitant therapy

The imputed stop date will be derived from the CRF event/therapy stop date. If the CRF stop date day, month, and year are not missing then the imputed stop date will equal the CRF stop date. If any part of the CRF stop date is missing, the following rules will be utilized to impute the stop date.

- If the event/therapy is ongoing, the stop date will be set to missing.
- Otherwise, if the year is missing, a) if the subject is still in the study and the study is ongoing, the event will be assumed to be ongoing, and stop date will be set to missing; b) if the subject has left the study, the stop date will be set to the subject's final study date.
- If the year is present and the month is missing, the stop date will be set to the minimum of the last day of the given year and the subject's final study date if the subject has left the study, and it will be set to the last day of the given year otherwise.

- If the year and month are both present, the stop date will be set to the minimum of the last day of the given month for the given year and the subject's final study date if the subject has left the study, and it will be set to the last day of the given month otherwise.

If the imputed stop date is non-missing and prior to the imputed start date, the imputed stop date will be set to the imputed start date.

5.2.3 Rules for imputing start dates for adverse event, subject reported event, and prior/concomitant therapy

The imputed start date will be derived from the CRF event/therapy start date. If the CRF start date day, month, and year are not missing then the imputed start date will equal the CRF start date. If any part of the CRF start date is missing, the following rules will be utilized to impute the start date.

- If the year is missing, the start date will be imputed as the minimum of the Study First Treatment Date and the imputed stop date.
- If the year and month are both present and are not the same as the year and month of the Study First Treatment Date, the start date will be set to the first day of the given month for the given year.
- If the year and month are both present and are the same as the year and month for both the Study First Treatment Date and the imputed stop date, the start date will be set to the minimum of the Study First Treatment Date and the imputed stop date.
- If the year and month are both present and are the same as the year and month of the Study First Treatment Date but not that of the stop date, the start date will be set to the date of Study First Treatment.
- If the month is missing but the year is present and is not the same as the year of the Study First Treatment, the start date will be set to January 1st of the given year.
- If the month is missing but the year is present and is the same as the year for both the Study First Treatment Date and the imputed stop date, the start date will be set to the minimum of the Study First Treatment Date and the imputed stop date.
- If the month is missing but the year is present and is the same as the year of the Study First Treatment Date but not that of the stop date, the start date will be set to the date of first treatment.

5.2.5 Rules for imputing other adverse event data

If the assessment of the intensity is missing, the most severe case will be assumed in the frequency tables of adverse event intensity.

If the assessment of the relationship to the Sculptra® Aesthetic or injection procedure is missing, a possible relationship to the Sculptra® Aesthetic will be assumed in the frequency tables of possibly related adverse events.

5.3 Relative Day Ranges and Visit Windows

If a subject discontinues early, the efficacy data (wrinkle assessments and investigator/subject global evaluations) from Visit 12 (Year 5) will be reassigned to a scheduled visit based on the relative ranges in the following table. If a result already exists for the calculated visit or the calculated visit was not a scheduled visit, the next scheduled visit will be assigned.

Relative day calculations will be the parameter visit date of interest minus the Study First Treatment Date plus one.

Table 1: Visit Collection Time and Relative Day Ranges

Collection Time (Target Day ± Visit Window)	Relative Day Ranges
Baseline (Day 1)	≤ Day 1
Week 3 (Day 22 ± 3 days)	Day 2 to Day 32
Week 6 (Day 43 ± 3 days)	Day 33 to Day 53
Week 9 (Day 64 ± 3 days)	Day 54 to Day 124
Month 6 (Day 184 ± 2 weeks)	Day 125 to Day 290
Month 13 (Day 397 ± 2 weeks)	Day 291 to Day 564
Year 2 (Day 731 ± 4 weeks)	Day 565 to Day 913
Year 3 (Day 1096 ± 4 weeks)	Day 914 to Day 1278
Year 4 (Day 1461 ± 4 weeks)	Day 1279 to Day 1643
Year 5 (Day 1826 ± 4 weeks)	≥ Day 1644

5.4 Calculation of Duration and Time to Onset:

Below are the rules on how duration and time to onset are calculated:

1. Duration = Event End Date - Event Start Date + 1

   For events that are ongoing, the formula will be updated per following scenarios:

   a. If the subject had XXX visit, duration will be XXX visit date minus start date plus 1;

   b. If the subject discontinued the study, duration will be discontinuation date minus event start date plus 1;

c. If none of the above, the event's duration will be time of visit minus study day of event start date plus 1, where time of visit is defined as scheduled study day + 4 weeks (2 weeks for Month 13).

2. Time to Onset (from treatment) = Event Start Date - Date of First Treatment.

6.0 Deviations from protocol

The following changes were made to the analyses planned in the protocol.

- Study primary objectives in this SAP were revised compared to those stated in Protocol Section 5.1 to be consistent with the primary endpoints as stated in the co-primary safety endpoints (Protocol Section 13.3.2.1) and primary hypotheses (Protocol Section 13.5.4.1).
- Analysis of duration and time to onset were only provided for the AEIs. These changes were made to clarify inconsistencies in the protocol between section 13.3.2.1 and 13.5.4.2. The SAP follows what is in the protocol section 13.5.4.2.
- PP population based analysis will only be conducted if it is at least 5% different than the ITT population.
- Clarification was made to the description of the groups being compared for determining covariates in the MI model (SAP Section 5.2.1) from what was stated in the protocol Section 13.5.4.1.