Statistical Analysis Plan

Clinical Trial Number: 43USSA2112

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Abbreviations and Definitions of Terms

AE	Adverse Event
CCI	[redacted]
ATC	Anatomical Therapeutic Chemical
BOCF	Baseline Observation Carried Forward
CIPR	Central independent photographic reviewer
CIs	Confidence intervals
CSR	Clinical Study Report
eCRF	Electronic case report form
FDA	Food and Drug Administration
FST	Fitzpatrick skin type
GAIS	Global Aesthetic Improvement Scale
GDS	Galderma Décolletage Scale
HCL	Hydrochloride
ICH	International Conference on Harmonisation
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
PP	Per protocol
PT	Preferred term
SAP	Statistical Analysis Plan
SOC	System organ class
CCI	[redacted]
SWFI	Sterile Water For Injection
WHODD	World Health Organization Drug Dictionary

1 Study Information

1.1 Background

This statistical analysis plan (SAP) describes the analysis variables and statistical procedures that will be used to analyze and report the results from Protocol 43USSA2112 (v2.0), dated 31 May 2022. No subjects were enrolled prior to Protocol v2.0.

The SAP was written in accordance with the recommendations outlined in the International Conference on Harmonisation (ICH) E9 Guideline entitled "Guidance for Industry: Statistical Principles for Clinical Trials" and the ICH-E3 Guideline entitled "Guidance for Industry: Structure and Content of Clinical Study Reports".

1.1.1 Study Design

This is a prospective open-label study to evaluate the safety and effectiveness of *Sculptra* for correction of wrinkles in the décolletage area.

Approximately 30 subjects will be enrolled in the study and randomized 1:1 to receive either *Sculptra* reconstituted with 8 mL Sterile Water For Injection (SWFI) with the addition of 1 mL 2% lidocaine hydrochloride (HCl) or *Sculptra* reconstituted with 17 mL SWFI with the addition of 1 mL 2% lidocaine HCl. Subjects will be stratified by Galderma Décolletage Scale (GDS) severity score (moderate or severe) and study center.

Eligible subjects will perform a screening visit and baseline visit; these visits may be combined, if appropriate. Eligible subjects will be offered treatment with *Sculptra* in four sessions spaced one month (+2 weeks) apart.

Subjects will be injected with *Sculptra* by the Treating Investigator at Baseline. Sufficient amount of product, as determined by the Treating Investigator, should be injected to achieve optimal correction, which is defined as at least a one grade improvement on the GDS and best correction that could be achieved as agreed upon by the Treating Investigator and the subject. Three additional treatment sessions may be performed if needed to achieve optimal correction, as determined by the Treating Investigator and subject. Treatment will stop when optimal correction has been achieved and subsequent visits will be follow-up visits.

CCI [redacted] Safety follow-up assessments will also be conducted one month after each treatment (Visits 3a, 4a, 5a and 6). Safety and effectiveness data will be collected for up to 9 months following the initial treatment.

1.1.2 Number of Subjects and Randomization

Approximately 30 adult female subjects will be randomized 1:1 to receive either *Sculptra* reconstituted with 8 mL SWFI with the addition of 1 mL 2% lidocaine HCl or *Sculptra* reconstituted with 17 mL SWFI with the addition of 1 mL 2% lidocaine HCl. Subjects will be stratified by GDS severity score and study center. Randomization numbers will be allocated in ascending sequential order to each subject.

1.2 Study Objectives and Endpoints

1.2.1 Primary Effectiveness Objective and Endpoint

The primary objective of the study is to evaluate the effectiveness of *Sculptra* for correction of wrinkles in the décolletage area. The primary endpoint is the percentage of responders, defined by at least one grade improvement from baseline, on the GDS, as assessed live by the Treating Investigator, at Month 9 for each treatment group.

1.2.2 Secondary Effectiveness Objectives and Endpoints

To evaluate the effectiveness of *Sculptra* for correction of wrinkles in the décolletage area the following endpoints will be used:

1. Percentage of responders, defined by at least one grade improvement from baseline, on the GDS, as assessed live by the Treating Investigator, at Month 6.
2. Percentage of responders, defined by having at least "Improved" (improved, much improved or very much improved) according to the Global Aesthetic Improvement Scale (GAIS), as assessed by the subject and the Treating Investigator separately, at Month 6 and 9.

1.2.4 Safety Objectives and Endpoints

The safety objectives and endpoints are as follows:

- To evaluate the incidence, intensity, time to onset, and duration of adverse events (AEs) collected throughout the study period.
- Incidence, intensity, time to onset and number of days of pre-defined expected post-treatment events collected using subject diaries for 28 days from each treatment.

1.3 Effectiveness Assessments

For all assessments, baseline will be defined as the observation that is closest to but prior to study treatment on Day 1. Change from baseline will be calculated as the value at a given time point minus the baseline value.

1.3.1 Galderma Décolletage Scale (GDS)

The GDS is a 5-point validated scale used to assess lines and wrinkles. The scale assessment will be performed live by the Treatment Investigator at all visits.

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1.3.2 Global Aesthetic Improvement Scale (GAIS)

The 7-grade GAIS will be used to assess the aesthetic improvement of the décolletage live by the Treating Investigator and the subject, independently of each other, by comparison to a photograph taken at the baseline visit before the first treatment. The GAIS will be assessed at 1 month following each treatment, 6 and 9 months after baseline.

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[redacted]	[redacted]

CCI [redacted]

1.4 Safety Assessments

The methods for collecting safety data are described in Section 7 of the protocol. Data to be collected include the following:

- Adverse events.
- Subject diaries to be completed daily for 28 days following each treatment session with direct questioning for the following pre-identified symptoms: pain, tenderness, redness, bruising, swelling, itching, and other.
- Urine pregnancy test for women of childbearing potential performed at screening and all treatment visits (prior to treatment).
- CCI [redacted]
- CCI [redacted]
- Device deficiencies assessed at all treatment visits.

2 Statistical Methods

2.1 General Methods

Any change made to the finalized SAP before database lock will result in an SAP amendment. Otherwise, changes will be documented in the Clinical Study Report (CSR). However, if additional supportive or exploratory analyses are requested after SAP approval, this will not require amendment of the SAP, but these additional analyses will be described in the CSR.

Some of the analyses detailed here may be more explicit or in some respects different from those stated in the protocol. In case of differences, this SAP supersedes the statistical sections in the protocol.

2.1.1 Programming Conventions

CCI [redacted] will have responsibility for performing analyses. All computations for statistical analyses will be performed using SAS® software, Version 9.4 or later. All SAS programs used in the production of statistical summary outputs will be validated with independent programming prior to finalization. In addition, all program outputs will be independently reviewed. The validation process will be used to confirm that all data manipulations and calculations were accurately done. Once validation is complete, a senior statistical reviewer will perform a final review of the documents to ensure the accuracy and consistency with this plan and consistency within tables. Upon completion of validation and quality review procedures, all documentation will be collected and filed by the project statistician or designee.

The electronic case report form (eCRF) data for all subjects will be included in the analysis datasets that are prepared for use in table and figure production.

2.1.2 Reporting Conventions

The formats for the tables, listings, and figures described in this SAP will be provided in a companion document. Changes to the formats of these reports that are decided after the finalization of the SAP will not require an amendment. In addition, any additional supportive or exploratory analyses requested after SAP approval will not require amendment of the SAP. These additional analyses will be described in the CSR.

Study data from the eCRFs as well as derived variables will be provided in subject data listings. An indication of specific listings for each data type will not be indicated in the text of subsequent SAP sections. Data listings supplied as part of the CSR will be sorted by study site number concatenated with subject number, treatment group, assessment dates, and/or time point.

The following conventions will be applied to all data presentations and analyses:

- Confidence intervals (CIs) will be two-tailed and constructed at a confidence level of 95%. Statistical tests will be performed at a significance level of 5%, and p-values will be two-sided, unless otherwise specified.
- Quantitative variables will generally be summarized by the number of subjects, mean, standard deviation, median, minimum, and maximum. Unless otherwise specified, the minimum and maximum values will be displayed to the same number of decimal places as the raw data, the mean and median will be presented to one extra decimal place compared to the raw data, and the standard deviation will be displayed to two extra decimal places compared to the raw data.
- Categorical variables will be summarized by the number and percentage of subjects (and number of events where appropriate) within each category. Unless otherwise specified, the percentage will be presented in parentheses to one decimal place. Frequency and percentage values of 0 will be presented as ‘0’ rather than ‘0 (0)’.
- All summary tables will include the analysis population sample size (i.e., number of subjects) in each treatment group.
- Date variables will be formatted as DDMMMYYYY for presentation.

2.2 Analysis Populations

The statistical analyses will be performed based on the following subject populations.

2.2.1 Safety Population

The Safety population includes all subjects who were treated with *Sculptra*. Subjects are analyzed according to the treatment received.

2.2.2 Intent-to-Treat (ITT) Population

The ITT population includes all subjects who were randomized, and will be analyzed according to the randomization scheme. All effectiveness variables will be analyzed based on the ITT population.

2.2.3 Per-Protocol (PP) Population

The PP population includes all ITT subjects who complete the visit 9 months after baseline, and are without any deviations considered to have substantial impact on the primary effectiveness outcome. If the PP population contains less than 90% of the subjects in the ITT, a sensitivity analysis of the primary effectiveness endpoint will be performed based on the PP population.

2.3 Study Subjects

Demographic endpoints and subject characteristics will be summarized using descriptive statistics by treatment group and overall based on the ITT population using observed cases. There are no planned inferential statistical analyses of demographic endpoints or subject characteristics.

2.3.1 Subject Disposition

The number of subjects screened will be shown in total and by study site.

The number of subjects in each study population (i.e., ITT, PP, and Safety) will be summarized by study site and in total (by treatment group and overall).

The disposition of subjects will be presented by treatment group, and in total, including numbers of subjects who were completed and withdrawn (including primary reason for withdrawal). These numbers will also be presented by study site.

The number of subjects expected, completed, withdrawn, and missed will be summarized by scheduled visit, using the following definitions:

- Expected = all subjects at screening minus subjects who have withdrawn up to that visit.
- Completed = subjects who showed up at that visit.
- Withdrawn = all subjects who have withdrawn up to that visit (cumulative).
- Missed = expected subjects minus completed subjects.

The end of study status will be listed for all subjects (both completed and withdrawn) individually, including at least subject number, end of study date, and last visit performed. In addition, reason for withdrawal will be provided for withdrawn subjects.

2.3.2 Protocol Deviations

Subjects with any protocol deviations will be summarized by treatment group, overall, by site, and by type. Subjects with out-of-window visit protocol deviations will be presented by visit and number of days out of window for each treatment group and overall.

Depending on the seriousness of a protocol deviation, a subject might be excluded from the PP population, which shall be documented prior to database lock. Since the PP population includes subjects who complete the visit 9 months after baseline, the focus will be on major deviations occurring before and at the Month 9 visit which are considered to have a substantial impact on the primary effectiveness outcome, see Table 3 below for list. Reasons for exclusion from the PP population also will be summarized.

Table 3. Major Protocol Deviations Causing Exclusion from Per-Protocol Population

Major Deviation
Month 9 visit out of window by greater than 21 days or earlier than 7 days
Subject did not receive treatment as randomized
GDS live assessment by Treating Investigator not done at Month 9 (primary endpoint)
GDS live assessment by Treating Investigator not done at screening or baseline
GDS live assessment by Treating Investigator at baseline is not grade 2 or 3 (moderate or severe)
Prohibited concomitant treatments/procedures prior to Month 9 visit considered to have substantial impact on primary effectiveness outcome
Prohibited medical history, unstable medical history condition, or medical history condition that worsens prior to Month 9 visit considered to have substantial impact on primary effectiveness outcome

2.3.3 Demographic Characteristics

Age and body mass index will be summarized as continuous variables.

Gender, race (including Asian subgroups), ethnicity, Fitzpatrick Skin Type (FST) score, childbearing potential, cup size, and baseline GDS (Treating Investigator) will be summarized as categorical variables.

2.3.4 Medical History, Medications, and Procedures

Prior and concomitant medications, vaccines, and procedural anesthetics will be coded using the World Health Organization Drug Dictionary (WHODD). Medical history, prior cosmetic treatments/procedures, and concomitant procedures/treatments will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

Prior medications/procedures are the medications/procedures with stop dates prior to first study treatment session. Medications/procedures after the first study treatment session will be considered concomitant.

Subjects reporting medical history, prior cosmetic treatments/procedures, and concomitant procedures/treatments will be summarized by System Organ Class (SOC) and Preferred Term (PT). Procedural anesthetics will only be listed.

Subjects reporting concomitant medications and vaccines will be summarized separately, by WHODD Anatomical Therapeutic Chemical (ATC) Class Level 3 (if Level 3 is not available, the highest class available will be used) and WHODD preferred name. Prior medications will only be listed.

2.4 Effectiveness Analysis

2.4.1 Datasets Analyzed

The ITT population is primary for all effectiveness analyses. The primary effectiveness analysis will be repeated using the PP analysis population if there is at least a 10% difference in the number of subjects between the PP and ITT populations.

2.4.2 Handling of Missing Data

Number of missing values will be summarized and reported as appropriate.

For the ITT analysis of the Treating Investigator GDS Responder rate at Month 9 after baseline (primary endpoint), missing values will be assumed to be missing due to lack of effect. Therefore, the primary method of imputation will use the baseline observation carried forward (BOCF) method. Impact of missing data on the primary endpoint will be evaluated by performing sensitivity analysis based on the observed cases, as well as worst-case and best-case imputation in the ITT set.

All other effectiveness endpoints will be evaluated based on the observed cases in ITT.

Descriptive statistics of all safety data will be performed on observed cases in the Safety population.

2.4.3 Primary Effectiveness Analysis

Responder rate for each treatment based on the GDS, as assessed live by the Treating Investigator at 9 months after baseline, will be the primary effectiveness endpoint. A responder will be defined as a subject with at least 1 grade improvement from baseline. The response rate will be calculated and presented with the 95% confidence intervals (calculated via Clopper-Pearson) for each treatment group and overall.

2.4.4 Secondary Effectiveness Analysis

(i) To evaluate the effectiveness of *Sculptra* for correction of wrinkles in the décolletage area, the following will be presented.

The percentage of responders on the GDS as assessed live by the Treating Investigator at 6 months after baseline will be presented along with the 95% confidence intervals (calculated via Clopper-Pearson) for each treatment group and overall.

The response rates based on the GAIS as assessed by the investigator and the subject, respectively, at each visit will be calculated and presented along with their 95% confidence intervals (calculated via Clopper-Pearson) for each treatment group and overall. A bar plot of the percentage of responders (at least “Improved”) by visit also will be produced for each evaluator type (investigator and subject) and presented by treatment group and overall. For the GAIS, response rate is defined as a subject with a rating of at least “improved”.

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2.4.6 Subgroup Analyses

All data will be summarized by treatment group injection volume: 8 vs 17 mL.

2.5 Safety Analysis

Safety endpoints will be summarized using descriptive statistics by treatment group based on the Safety population using observed cases. There are no planned inferential statistical analyses of safety endpoints.

2.5.1 Treatment Administration, Post-injection Care, and Procedural Anesthetics

Treatment administration endpoints will be summarized for each treatment session by treatment group and overall, including injection technique, depth of injection, needle size, needle brand, and number of needles, vials, and syringes.

The number of subjects with any post-injection care and procedural anesthetics will be summarized by type.

Injection volume will be summarized for each treatment session and overall.

2.5.2 Adverse Events (AEs)

All AEs will be coded according to MedDRA and summarized by System Organ Class (SOC), Preferred Term (PT), and treatment. The number of subjects with at least one event, associated percentage, and number of events will be provided.

For subject counts, a subject will only be counted once per SOC and once per PT in cases where multiple events are reported for a subject within SOC or PT. For event counts, subjects with multiple events in a category will be counted for each event.

The number of subjects with AEs related to study product or study product injection procedure and unrelated AEs will be presented by SOC, PT, and maximum intensity. Action taken for related AEs will also be summarized by SOC and PT using number of events. AEs related to study product or injection procedure with late onset (> 21 days after most recent treatment session) will be listed.

Serious AEs and AEs of special interest (AESIs) will be listed. CCI [redacted]

For AEs related to study product or study product injection procedure, the number of days to onset and the duration of event will be summarized by SOC and PT using mean, standard deviation, median, minimum, and maximum. Days to onset of an AE will be derived as the start date minus the date of most recent treatment session. Duration of an AE will be derived as the stop date minus the start date + 1. Missing stop date will not be imputed, and therefore no duration will be calculated in these cases.

In addition, a summary of all AEs will be provided, which will include (but is not limited to):

- number of subjects with at least one AE and number of events (in total as well as serious AEs),
- number of subjects with at least one related AE and number of events (in total as well as serious AEs),
- number of subjects with at least one AESI and number of events,
- number of subjects with at least one unrelated AE and number of events (in total as well as serious AEs),
- number of subjects who did not have an AE.

2.5.3 Pre-defined, Expected, Post-treatment Events

The number and percentage of subjects reporting each pre-defined, expected, post-treatment symptom, as collected in the 28-day diary, will be presented in total and by maximum intensity for each treatment session and overall. The number of days with the event for each treatment session will be similarly presented by day category (1, 2-7, 8-14 and 15-28 days). The percentage of subjects with each event also will be plotted for each treatment session by day.

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CCI [redacted]

2.7 Determination of Sample Size

2.7.1 Sample Size

The sample size of approximately 30 subjects is not based on a statistical calculation. CCI [redacted]

2.8 Changes in the Analysis Planned in the Protocol

There are no changes to the analysis planned in the protocol.

3 Reference List

There are no other references beyond those that are included in the protocol.

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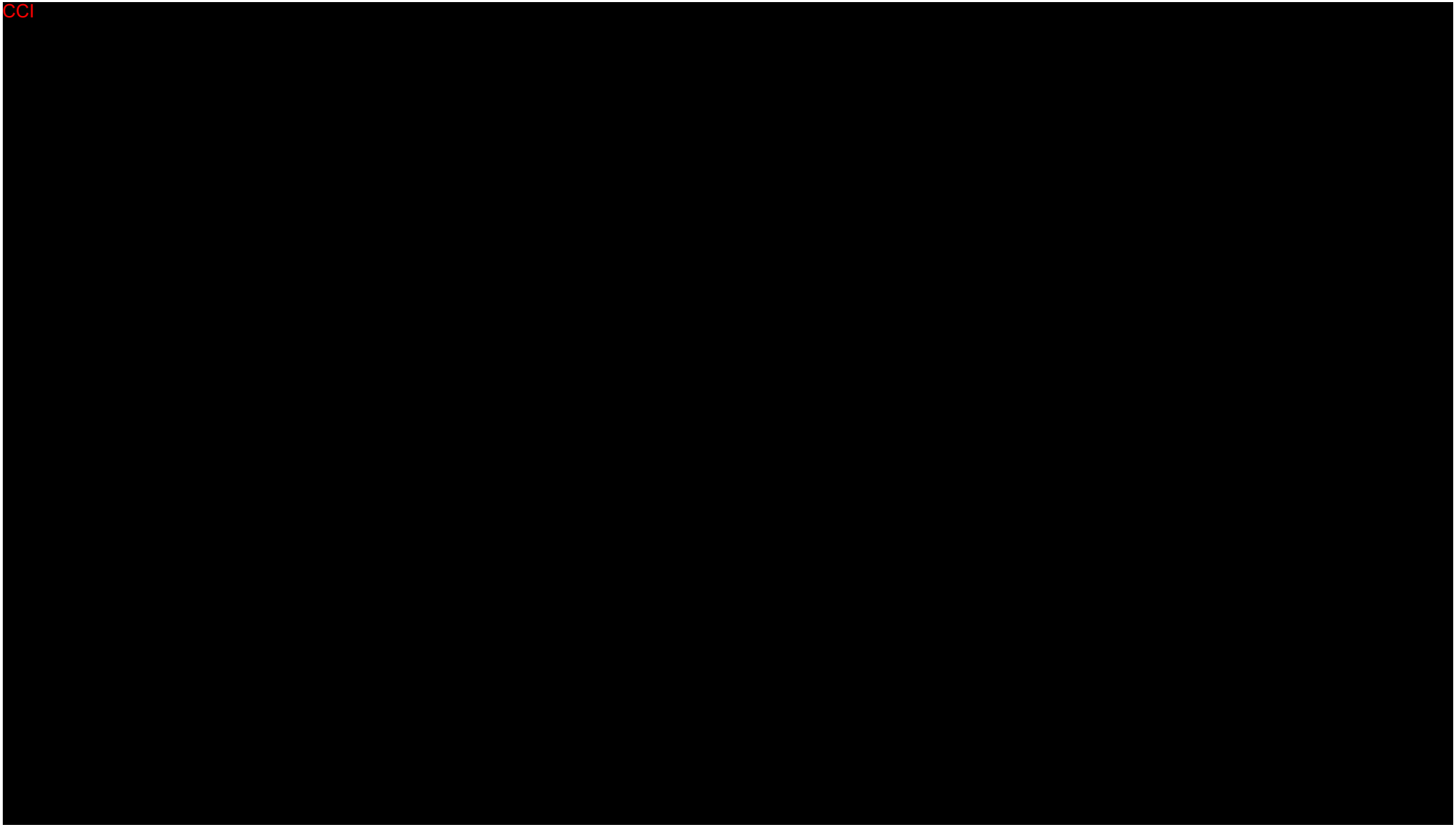

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SIGNATURES PAGE

Date	Signed by
PPD	
Justification	Approved by Owner

PPD	
Justification	Approved by Technical Expert

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Justification	Approved by Project Manager