STATISTICAL ANALYSIS PLAN

DOCUMENT NO. ANG-SAP-007

Protocol Title:	A Multicenter, Prospective, *R*andomized, Subject and *E*valuator Blinded *C*omparative Study of Nerve Cuffs and Avance® Nerve Graft Evaluating Recovery *O*utcomes for the Repair of *N*erve Discontinuities (RECON)
Phase:	Pivotal
Protocol No.(s):	ANG-CP-007
Protocol Date(s)	Version 4.0 – 12 May2021 Version 3.0 – 22 February 2019 Version 2.0 – 09 June 2017 Version 1.1 – 13 April 2015
Analysis Plan Version and Date	Version 3.0 : 04 March 2022
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[redacted]

STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

This Statistical Analysis Plan has been prepared in accordance with team reviewers' specifications.

Prepared by:

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Mar 7, 2022

Date

Reviewed and Approved by:

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Mar 7, 2022

Date

Mar 8, 2022

Date

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1. INTRODUCTION

This document describes the statistical methods and data presentations to be used in the summary and analysis of data from Protocol ANG-CP-007. Background information is provided for the overall study design and objectives. The reader is referred to the study protocol and case report forms (CRFs) for details of study conduct and data collection.

1.1. STUDY OVERVIEW

ANG-CP-007 is a multi-center prospective, randomized, controlled, evaluator and subject blinded study in subjects requiring nerve reconstruction in the hand distal to the superficial palmar arch. The study was planned to enroll at least 150 subjects in up to 20 sites at a target site enrollment range of 8-14 subjects (capped at 170 subjects) to control for site effects while maintaining [redacted]% attrition. Following completion of a pre-planned interim analysis, the enrollment was increased to 220 subjects.

Subjects meeting the inclusion and exclusion criteria will be centrally randomized in a 1:1 ratio [redacted] to receive either the Avance® Nerve Graft or the control (Nerve Cuff) in the primary target repair. If a subject has multiple repairs, all qualifying repairs should be made according to the assigned repair type for the primary target repair. The primary target repair must be identified prior to randomization as the repair with the longest qualifying injury. Should more than one injury measure as the longest qualifying injury, the investigator will assign the repair to be followed as the primary target repair.

Placement of Nerve Cuff or Avance® Nerve Graft will follow product instructions for use. Direct suture and autograft may be utilized for nerve gaps <5 mm or > 25 mm. Photographs of the surgical site and surgical implant should be taken if possible. Wound closure and immobilization will be based on the institution's standard of care. Subjects will be followed for a total of 12 months post successful implantation of Avance® Nerve Graft or Nerve Cuff. This study will consist of a screening visit, an operative visit, and 5 post-operative follow-up visits at 1, 3, 6, 9, and 12 months.

Adverse events will be collected to monitor subject safety, while the static two-point Discrimination (s2PD), [redacted], Medical Research Council Evaluation of Sensory Function (MRCC) Rating for Recovery of Sensory Function, [redacted] and Pain Assessment- Visual Analog Scale (VAS) will be measured to determine efficacy. The primary efficacy endpoint will be the s2PD at Month 12 (Visit 7).

2. SCHEDULE OF ASSESSMENTS

Assessments	Visit 1[1] Screening	Visit 2[1] Operative Day 0	Visit 3 Month 1	Visit 4 Month 3	Visit 5 Month 6	Visit 6 Month 9	Visit 7 Month 12
Informed Consent	X						
Inclusion/Exclusion Criteria	X	X					
Relevant Medical History	X						
Demographics	X						
Traumatic Injury History		X					
Operative Information		X					
Randomization		X					
Sensory Assessments[2]	X[3]		X	X	X	X	X
Pain Assessments - VAS	X[3]		X	X	X	X	X
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							
Rehabilitation Regime Type/Compliance			X	X	X	X	X
[redacted]							
Adverse Events		X	X	X	X	X	X

1. Screening and Operative Day 0 assessments may be performed on the same day.
2. Sensory Assessments should include:
   a. s2PD [redacted]
   [redacted]
   c. MRCC Rating for Recovery of Sensory Function.
3. [redacted]

2.1. GLOSSARY OF ABBREVIATIONS

Δ	difference in means
[redacted]	[redacted]
μ	population mean
AE	adverse event
ANCOVA	analysis of covariance
CI	confidence interval
[redacted]	[redacted]
CRF	case report form
CV	coefficient of variation
[redacted]	[redacted]
EDC	electronic data capture
H_0	null hypothesis
H_1	alternative hypothesis
LSMeans	least-squares means
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
ITT	intent-to-treat
MRCC	Medical Research Council Evaluation of Sensory Function
N	number of observations
[redacted]	[redacted]
PP	per-protocol population
RECON	A Multicenter, Prospective, *R*andomized, Patient and *E*valuator Blinded *C*omparative Study of Nerve Cuffs and Avance® Nerve Graft Evaluating Recovery *O*utcomes for the Repair of *N*erve Discontinuities
s2PD	static two-point discrimination
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
[redacted]	[redacted]
TEAE	treatment emergent adverse event
VAS	visual analog scale
WHO	World Health Organization

3. OBJECTIVES

The primary objective of the study is to evaluate the safety and effectiveness of the Avance® Nerve Graft for non-inferiority and if met, superiority, of static two-point discrimination at twelve months as compared to Nerve Cuffs [redacted]

The secondary objectives of this study are to [redacted], compare functional recovery outcomes and rates; time to recovery; degree of recovery over time; [redacted] for each treatment group.

4. GENERAL STATISTICAL CONSIDERATIONS

4.1. SAMPLE SIZE AND POWER

The study was initially sized under the following conditions:

The study was planned to enroll at least 150 subjects at 20 sites. Following a pre-planned blinded interim analysis, the sample size was increased to a maximum of 220 subjects at up to 25 sites.

[redacted]

4.2. RANDOMIZATION AND MASKING

Up to 220 subjects at up to 25 sites at a target site enrollment range of 8-14 subjects may be enrolled to control for site effects while maintaining an acceptable level of attrition. Subjects will be centrally randomized 1:1 to one of two treatment groups—Avance® Nerve Graft or control (Nerve Cuff)—in accordance with a computer-generated randomization schedule created by non-study personnel. Randomization will be stratified [redacted] The randomization will occur intraoperatively, after confirmation that all inclusion and no exclusion criteria have been met for an individual subject and the gap length has been determined.

For single nerve injuries in the hand, the innervating digit will be considered the "target digit" upon which all follow up sensory assessments will be conducted upon.

For subjects presenting with multiple nerve injuries during randomization to treatment, multiple repairs may be included in the study. A primary target repair will be identified prior to randomization. This repair will be utilized for all analyses. The primary target repair will be the repair with the longest qualifying injury. Should multiple qualifying injuries have the same "longest qualifying gap length", then the investigator will assign one of the repairs as the primary target repair.

Each individual injured nerve must meet study inclusion exclusion criteria and receive the same treatment group (Avance® Nerve Graft or Nerve Cuff) for a repair to be performed. Whether repairing one or multiple nerves with Avance® Nerve Graft or Nerve Cuff, the acceptability of treating the repair with either treatment needs to be decided prior to the randomization of a subject.

While blinding the surgeon to treatment is not possible, blinding the patient and the assessor is possible and all efforts should be taken to preserve this blind. Randomization will be used to assign the subject to a study group intra-operatively therefore the subject will be blinded to the treatment used. Direct verbal or written communication regarding treatment identification beyond what is required at an institution for the recording of the surgical procedures is prohibited. The assessments for the efficacy endpoints will be conducted by a qualified evaluator who has been blinded to the subject's study group assignment. [redacted] A subject satisfaction assessment will be collected from each subject during Month 1, 3, 6, and 9and during the last follow-up visit, Month 12. Questions surrounding randomization to treatment will be completed at Month 12. The study coordinator will then review source documentation for entry into subject CRFs. The sponsor and representatives utilized by the sponsor to handle data management and analysis will remain blinded to treatment during query resolution and database lock. Unblinding of treatment group assignments will occur after the database has been cleaned, quality checked, and locked and the protocol violations have been determined.

4.3. HANDLING OF DATA

4.3.1. Strata and Covariates

All primary and secondary efficacy analyses will be adjusted for the stratification factor: [redacted]

4.3.2. Examination of Subject Subsets

The primary efficacy endpoint and selected secondary endpoints may be summarized separately by investigative site, gap length [redacted] using descriptive statistics by treatment group and study day, where appropriate. Statistical testing of treatment differences within subgroups may be performed. Summaries by treatment group, separately for each subgroup, will use the number of subjects (N), mean, median, SD, standard error (SE), coefficient of variation (CV), minimum, and maximum.

4.3.3. Multiple Testing and Comparisons

As the interim analysis was conducted using group blinded data, no adjustment for type I error was necessary for this additional analysis.

As the tests of non-inferiority and superiority are being performed in a closed testing procedure for the primary endpoint, no adjustment for multiple testing is required. To control type I error inflation associated with testing of multiple secondary endpoints, a step-down procedure will be utilized in the assessment of the secondary efficacy endpoints:

1. Response rate for recovery for s2PD at Month 12
2. Percent recovery to pre-injury baseline in s2PD at Month 12
3. Time to recovery of s2PD
4. MRCC at Month 12
5. Reduction in pain as measured with the VAS pain assessment at Month 12

For this procedure, the hypotheses will be tested sequentially based on the specified ordering. Statistical testing will continue at the α=0.05 level until a p-value greater than 0.05 is observed. [redacted]

4.3.4. Missing Data and Outliers

Every effort will be made to obtain required data at each scheduled evaluation from all subjects who have been randomized. In situations where it is not possible to obtain all data, it may be necessary to impute missing data. For the primary and secondary endpoints that are not based on subject reported outcomes, observed data will be modelled using repeated measures mixed modelling techniques. [redacted]

All sensory assessments (s2PD, [redacted] MRCC, [redacted] VAS, [redacted] will be repeated using an imputation method, missing values of which could be due to the COVID-19 pandemic. For all Month 12 results missing due to COVID-19, [redacted] If the repair has missing Month 12 s2PD [redacted] unrelated to COVID-19, [redacted] If the repair has missing Month 12 for any other sensory assessment unrelated to COVID-19, then the analysis value will not be imputed and will be considered not done.

4.3.5. By Study Visit Displays

When data are collected serially over time, individual data presentations may include by-visit displays. For these presentations, visits will be mapped according to the following sponsor defined visit windows:

Visit per EDC or Lab Vendor Data or Study Day	Analysis Visit
V1 - Pre-Op Screening	Screening
Visit 1	Operative Day
[redacted]	Month 1
[redacted]	Month 3
[redacted]	Month 6
[redacted]	Month 9
[redacted]	Month 12

If assessments are collected multiple dates or times within a given visit, the result closest to the scheduled visit date will be used for summary presentations. If two measurements have the same distance to the expected date, the earlier value will be used. If a subject has multiple non-missing values on the same date, then the last one is used, as determined by the time collected, if available.

4.3.6. Derived and Transformed Data

Transformations for variables with skewed distributions may be performed as appropriate.

4.3.7. Definitions and Terminology

Baseline Value
For purposes of analysis, the baseline value is defined as the value captured at the baseline assessment. If this value is not available, the most recent value obtained prior to the repair will be used for the baseline value.

Day 0 (Baseline)
Day 0 is the day/time of the repair.

Pre-Injury Baseline
Pre-injury baseline is defined as contralateral digit associated to the target digit.

Study Day
Study Day is defined relative to Baseline (Day 0). Thus, the study day of an event is calculated as: Study Day = event date – date of Day 0 + 1.

Days on Study
Days on Study is the number of days from Day 0 to the date of study completion or early termination as recorded on the STUDY TERMINATION CRF.

Age
The age of a subject is defined as (Date of Day 0 – Date of Birth + 1) / 365.25.

Target Repair
Repair identified prior to randomization as the repair with the longest qualifying gap length. This repair will be utilized for all analyses of efficacy.

Static two-point Discrimination (s2PD)
s2PD is a tool that measures nerve innervation density (the number of nerve endings present in the area tested) by determining the ability to discern the difference between one and two-points at set distance. It relates to a patient's ability to determine not only that they can feel but "what" they are feeling. The Mackinnon-Dellon Modification to the Medical Research Council Classification of Sensory Recovery rates 2PD of 7 to 15 mm as S3+ recovery and less than 7 mm as S4 or "near normal" levels of sensation. If two-point discrimination is absent, the subject will be assigned a score of 16 mm.

s2PD Responder
A responder is defined as subjects with s2PD score of 2 mm – 15 mm.

Time to Recovery of s2PD
Time to recovery of s2PD is defined as the number of months from Operative day to the initiation of S3+ or greater at Visit 4, Visit 5, Visit 6, or Visit 7.

[redacted]

[redacted]

[redacted]

MRCC Classification of Sensory Recovery

The MRCC scale serves to determine the level of sensory function of a target area in the hand.

MRCC Classification of Sensory Function	
Rating	**Medical Research Council Classification of Sensory Recovery as modified by Mackinnon**
S0	Absence of sensibility in the autonomous area
S1	Recovery of deep cutaneous pain sensibility within the autonomous area of the nerve
S2	Return of some degree of superficial cutaneous pain and tactile sensibility within the autonomous area of the nerve
S3	Return of superficial cutaneous pain and tactile sensibility throughout the autonomous area, with disappearance of any previous over response
S3+	Return of sensibility as in S3; in addition, there is some recovery of two-point discrimination within the autonomous area (7-15 mm)
S4	Complete recovery (two-point discrimination, 2-6 mm)

[redacted]

The Visual Analog or Analogue Scale (VAS) for Pain

This pain scale is designed to present to the respondent a rating scale with minimum constraints. Respondents will mark the location on the 10-centimeter line corresponding to the amount of pain they experienced. VAS data are recorded as the number of millimeters from the left of the line with the range 0-100.

[redacted]

[redacted]

4.3.8. Imputation of Incomplete Dates

An incomplete date is any date for which either the day, month or year is unknown, but all three fields are not unknown. An incomplete date occurs when the exact date an event occurred or ended cannot be obtained from a subject. For many of the analyses, a complete date is necessary to determine if the event should be included in the analysis (i.e., if the event is treatment emergent) or to establish the duration of an event. In such cases, incomplete dates will be imputed.

For purposes of imputation, all resolved events with an incomplete end date are assumed to have ended on or before the day the final report of the case report form was completed. To minimize bias, the project statistician will impute incomplete start dates in a systematic, but reasonable manner. If the month/year is the same as the Day 0 month/year, then the date will be set to the date of Day 0. In other cases, missing days will be imputed as the day component of Day 0; missing months/years will be imputed as the month/year of Day 0. A list of incomplete and imputed dates will be prepared by the project statistician or statistical programmer(s) and will be submitted for review by the clinical project manager and sponsor.

4.4. TIMING OF ANALYSES

The study team will review study conduct and emerging safety information on an ongoing basis to ensure the protection of subject welfare.

[redacted]

A final analysis is planned after the last subject completes or discontinues the study, and the resulting clinical database has been cleaned, quality checked, and locked.

5. ANALYSIS POPULATIONS

The populations for analysis will include the Intent-to-Treat (ITT), Per-Protocol (PP), and safety populations.

5.1. INTENT-TO-TREAT POPULATION

The ITT population will include all subjects who are randomized. Subjects will be analyzed in the repair group to which they were randomized. All screen failures and randomization failures will not be included in the ITT population. The ITT population will be used for analyses of accountability, demographics, efficacy (superiority testing) and the calculation of the 95% confidence interval about the mean s2PD in the Avance® Nerve Graft group.

5.2. PER-PROTOCOL POPULATION

The PP population will include all subjects in the ITT population who have completed a minimum of 6 months follow-up and have no major protocol violations. This population will be the primary analysis population for the test of non-inferiority.

5.3. SAFETY POPULATION

The safety population will include all subjects who received a nerve repair. Subjects will be analyzed according to the repair received. This population will be used for all safety analyses.

6. STATISTICAL METHODS

Descriptive statistical methods will be used to summarize the data from this study, with hypothesis testing performed for the primary and other selected efficacy endpoints. Unless stated otherwise, the term "descriptive statistics" refers to number of subjects (N), mean, median, SD, SE, CV, minimum, and maximum for continuous data and frequencies and percentages for categorical data. The term "treatment group" refers to randomized treatment assignment: Avance® Nerve Graft or Nerve Cuff. All data collected during the study will be included in data listings. Unless otherwise noted, the data will be sorted first by treatment assignment, subject number, and then by date within each repair number.

Unless specified otherwise, all statistical testing will be two-sided and will be performed using a significance (alpha) level of 0.05.

The statistical analyses will be conducted with the SAS® software package 9.4. All analyses will be subject to formal verification procedures. Specifically, results will be verified utilizing independent programming prior to issuance of the draft statistical report. All documents will be verified by the lead statistician to ensure accuracy and consistency of analyses.

6.1. SUBJECT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS, VISIT COMPLETION

Subject disposition (enrollment by site, eligibility, treatment information, and populations for analysis) will be presented for all subjects. The number of subjects who completed the study and discontinued from the study will be provided. The reasons for early discontinuation also will be presented. Additionally, the number of days on study will be summarized by treatment group.

A summary of the number and percentage of subjects completing each study visit will be provided.

Demographic and baseline characteristics including age, sex, race, type of traumatic injury sustained, number of nerves that are injured, assessment of functional loss due to injury, sensory assessments, pain assessment [redacted] for each subject will be summarized descriptively by repair type.

6.2. EFFICACY ANALYSIS

6.2.1. Primary Efficacy Endpoint

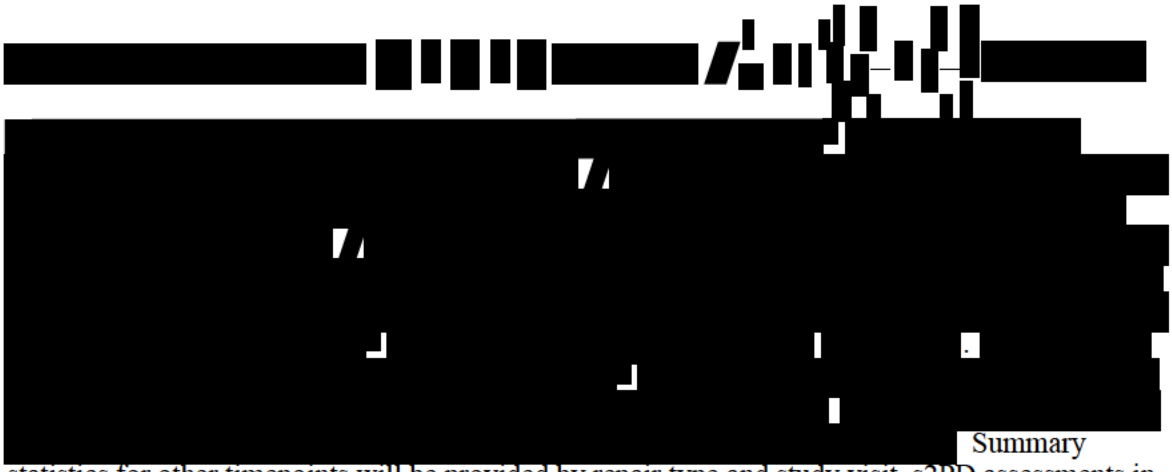
The primary efficacy endpoint will be the s2PD in the target repair at Month 12.

6.2.2. Primary Efficacy Analysis

Test of non-inferiority and superiority of Avance® Nerve Graft to Nerve Cuffs with respect to s2PD will be conducted using closed testing procedures. [redacted]

[redacted] Differences among the treatment groups will be evaluated using the difference at Month 12, [redacted]

[redacted]



Summary statistics for other timepoints will be provided by repair type and study visit. s2PD assessments in the contralateral digit will be summarized descriptively by repair type and study visit. Graphical presentations of these data will be provided.

6.2.2.1. Sensitivity Analysis and Remedial Measures

Assessment of the Effect of Population Definitions

Should a discrepancy be noted in the final database for any repair such that the repair type received differs from the randomized repair assignment, secondary analyses of the primary efficacy endpoint will be repeated with the subjects analyzed according to the repair received.

Supportive Non-inferiority Analysis

A supportive non-inferiority analysis will be conducted utilizing the ITT population. For this analysis, non-inferiority will be supported if the lower limit of the 95% CI about the between the mean s2PD of the target repairs for the Avance® Nerve Graft and the mean s2PD of the target repairs for the Nerve Cuff at Month 12 in the ITT population is > -2 **and** the upper limit of the 95% CI about the s2PD for the Avance® Nerve Graft in the ITT population is less than 13.

Assessment of Normality

The assumption of normality of the primary efficacy endpoint will be assessed with the Shapiro-Wilk statistic of model residuals. Residuals will be visually examined for heterogeneity via scatter plots. If either assumption is violated, overall treatment differences will be assessed using the analysis, as specified in section 6.2.2, on the ranked dependent data.

Investigation of Site Effect

For the primary efficacy endpoint, a preliminary test of the interaction of repair type and investigational site will be conducted using the analysis specified in section 6.2.2 with additional fixed effects that include site and repair type by site interaction. If the interaction test is not significant at the 0.10 level, then this term and the first order term (site) will not be included in the model used to construct treatment comparisons. It is anticipated that there will not be a clinically relevant, qualitative interaction in the study. Regardless of whether or not a repair type-by-site interaction is statistically significant at the 0.10 level, further exploratory analyses will be performed. Specifically, these analyses will include examination of the treatment differences within each site utilizing graphical techniques, descriptive statistics, and confidence intervals.

These examinations will be utilized to determine the nature of the interaction (i.e., identify whether it is a "qualitative interaction") and to identify any extreme sites. Should extreme sites be identified, a supplemental statistical analysis of primary and secondary endpoints will be prepared excluding those sites.

If there are a large number of low-enrolling investigational sites, examination of the site effect by the method above may not be possible. As such, sites may be combined utilizing a pooling algorithm defined prior to breaking the study blind. The goal of pooling low-enrolling sites will be to have a sufficient number of subjects per treatment group within site for the analysis of variance and for the evaluation of treatment-by-site interaction. The pooling rule is described below:

- Low-enrolling sites will be defined as those that have fewer than 4 target repairs with Month 12 s2PD in any treatment group.
- Within these low-enrolling sites, sites will be pooled with respect to type of site and the total number of target repairs with Month 12 data.
- Low-enrolling sites of similar type will be ordered from largest to smallest based on the total number of target repairs with Month 12 data. Sites will be pooled together until the derived pooled site has at least 4 repairs with s2PD in each treatment group.
- Any remaining sites from this procedure that do not have a sufficient number of subjects to form another derived site will be pooled with the last pooled site.

Investigation of Gap Length by Repair Type Interaction

For the primary efficacy endpoint, a preliminary test of the interaction of gap length and repair type will be conducted using the analysis specified in section 6.2.2 with the additional fixed effect gap length (as a continuous variable) by repair type interaction. If the interaction test is not significant at the 0.10 level, then this term will not be included in the model used to construct treatment comparisons. It is anticipated that there will not be a clinically relevant, qualitative interaction in the study. Regardless of whether or not a repair type by gap length interaction is statistically significant at the 0.10 level, further exploratory analyses will be performed. Specifically, these analyses will include examination of the treatment differences according to gap length utilizing graphical techniques, descriptive statistics, and confidence intervals. These examinations will be utilized to determine the nature of the interaction (i.e., identify whether it is a "qualitative interaction").

Assessment of Impact of Single versus Multiple Repairs

The primary analysis will be conducted using the assumption that the response is not impacted by the number of repairs performed for a given subjects. To determine the impact, if any, of this assumption, a subgroup analysis will be conducted comparing the results of the primary efficacy analysis for those subjects who have a single repair to those subjects who have multiple repairs made. A secondary analysis of the primary efficacy endpoint may be conducted utilizing all repairs. This analysis will utilize a repeated measures ANCOVA model with fixed effects of repair type, visit, and gap length and a random effect for repair (subject).

Investigation of Subset/Covariate Effects

[redacted]

Assessment of the Effect of Imputation Methods

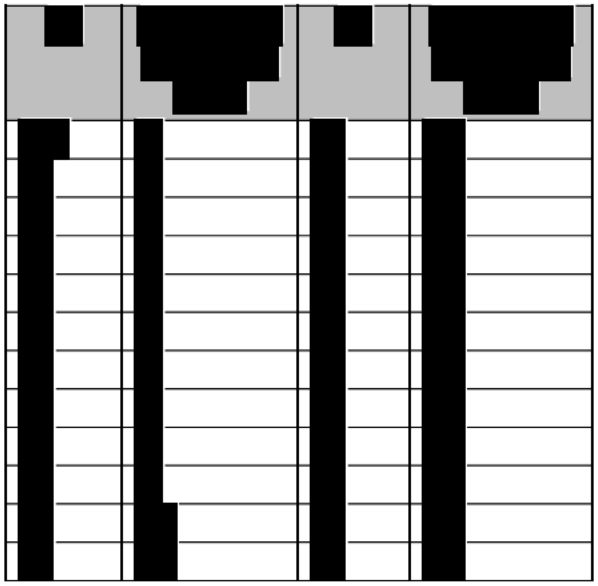
A sensitivity analysis may be conducted to ascertain the effect, if any, of the imputation methods for missing data. Secondary analyses of the primary efficacy endpoint may be conducted by the following:

- Missing Month 12 data will be imputed utilizing a Markov chain Monte Carlo multiple imputation procedure using repair type and [redacted] as covariates. For this method, 5 imputation datasets will be prepared utilizing PROC MI in SAS. These data will be analyzed by imputation using an ANCOVA model. This model will include fixed effects for [redacted] and repair type. The results will be combined using PROC MIANALYZE in SAS.
- If a repair has a missing Month 12 s2PD, then the value will be imputed as no response (i.e., 16) and conduct an ANCOVA analysis utilizing the Month 12 s2PD data. This model will include fixed effects for [redacted] and repair.
- If a repair has a missing Month 12 s2PD, then sensitivity will be assessed utilizing a pattern mixture model as described in the report from the National Academy of Sciences entitled "The Prevention and Treatment of Missing Data in Clinical Trials". Here, each treatment group will be analyzed separately, and models prepared for those that have missing data and those who do not using a range of values for the sensitivity parameter (α_o).

If it is found that the primary endpoint is sensitive to the analysis methods listed, supplemental analyses may be conducted for the other efficacy endpoints using the alternate analysis methods referenced above.

[redacted]

[redacted]



6.2.3. Secondary Efficacy Endpoints

The secondary efficacy endpoints for the study include the following:

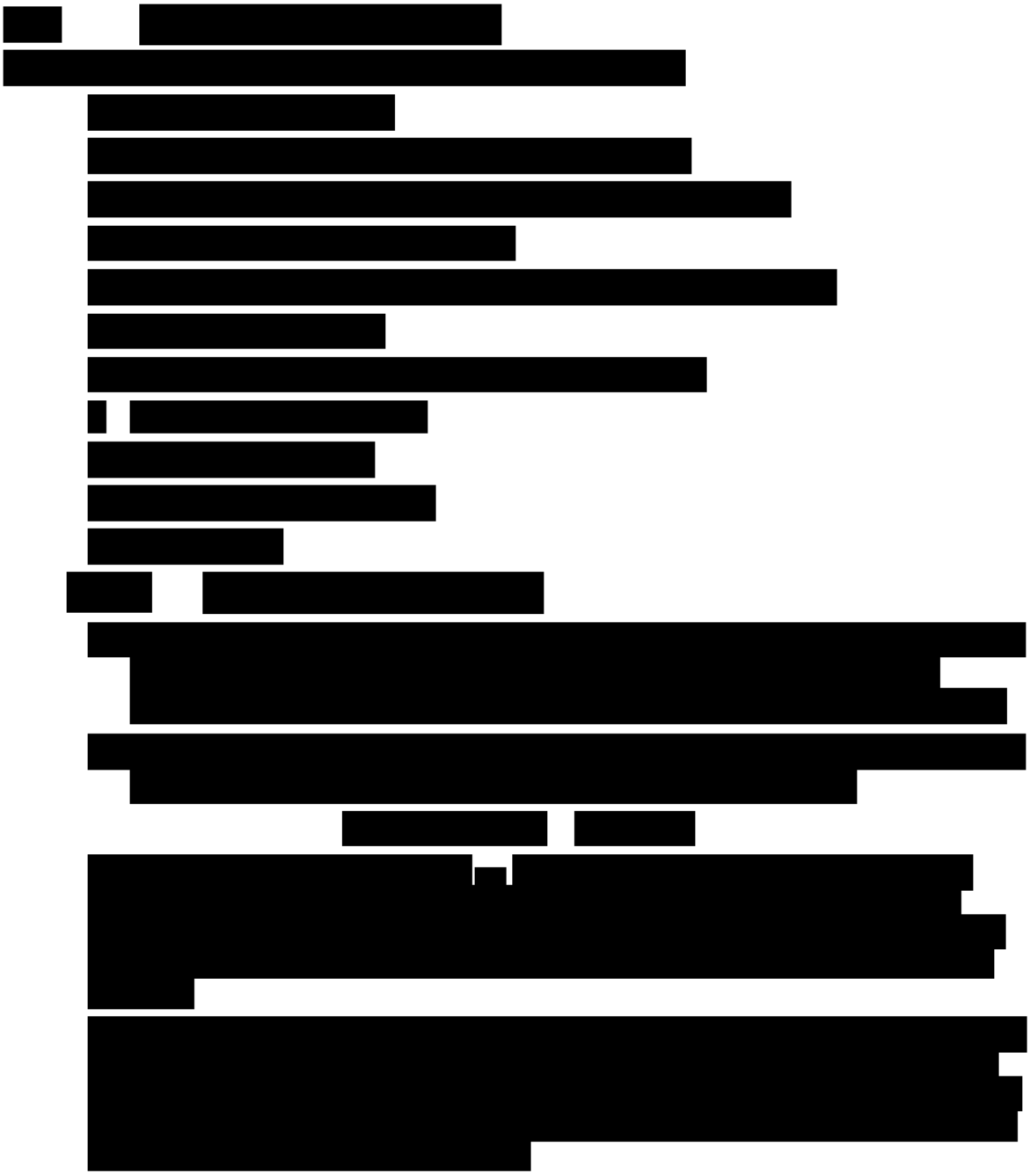
1. Response rate for recovery for s2PD at Month 12
2. Percent recovery to pre-injury baseline in s2PD at Month 12
3. Time to recovery of s2PD
4. MRCC at Month 12
5. Reduction in pain as measured with the VAS pain assessment at Month 12

6.2.3.1. Secondary Efficacy Analysis

All secondary endpoints will be summarized using descriptive statistics by repair type, and study day/time, if appropriate.

1. The number and response rate of subjects who recover s2PD (i.e., s2PD 2 mm - 15 mm) in the target repair at Month 12 will be summarized by repair type. Differences between the repair types will be assessed using a logistic regression analysis with effects for repair type and [redacted]. Responders will be presented graphically.
2. Percent recovery to pre-injury baseline in s2PD assessment in the target repair will be summarized for each repair type and study visit. A test of superiority of the Avance® Nerve Graft to the Nerve Cuff will be assessed using the LS Mean differences from a repeated measures ANCOVA model with fixed effects for [redacted]
3. Time to recovery of s2PD is defined as the number of months from Operative day to the initiation of S3+ or greater at Visit 4, Visit 5, Visit 6, or Visit 7. [redacted]
4. A two-tailed Wilcoxon rank sum test will be used to detect a distribution shift of the MRCC score between repairs with Avance® Nerve Graft and repairs with Nerve Cuff at Month 12. [redacted]

5. VAS pain assessment in the target repair will be summarized in the same fashion as percent recovery to baseline in s2PD. VAS pain assessment will be presented graphically.



[redacted]

graphically.

[redacted]

6.3. SAFETY

6.3.1. Adverse Events

AEs will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ classification. If a subject experiences multiple events that map to a single preferred term, the greatest intensity and/or strongest investigator assessment of relation to repair type will be assigned to the preferred term for the appropriate summaries. Should an event have a missing severity or relationship, it will be classified as having the worst intensity and/or strongest causal relationship to repair type as appropriate. Summaries of treatment emergent AEs will include any AEs reported beginning with the completion of the repair on Day 0. The occurrence of treatment emergent adverse events (TEAEs) will be summarized by repair type using preferred terms, system organ classifications, and severity. Separate summaries of treatment emergent serious adverse events, treatment emergent adverse events related to study drug, and treatment emergent adverse events related to repair type will be generated.

All adverse events reported will be listed for individual subjects showing both verbatim and preferred terms. All adverse events that occurred prior to the repair will be excluded from the tables but will be included in the listings.

Missing onset dates will be imputed as previously outlined in Section 4.3.8 as required to determine treatment emergent events.

[redacted]

7. PROTOCOL VIOLATIONS

Possible protocol deviations will be identified and displayed in a data listing and sorted by subject and study day (where applicable).

Prior to unblinding, the study team will review the deviations and determine whether any of these factors affect data integrity, validity, and interpretability. Based on this review, the study team will recommend subjects to be excluded from the per-protocol and modified intent-to-treat analysis populations that will be used for selected efficacy endpoints in the final analysis. The following deviations would be considered as major:

- Failed to meet inclusion and exclusion criteria.
- Had the incorrect repair performed relative to the randomized assignment.
- Experienced an AE that was deemed unrelated to the nerve repair that resulted in a revision of the nerve repair, removal of the randomized repair or resection of the soft tissue in the autonomous zone associated with the nerve repair.
- Was non-compliant with follow-up assessments.

8. CHANGES IN THE PLANNED ANALYSES

There were changes made to the analysis detailed in this version of the SAP that differ from what is detailed in latest version of the protocol (Version 4). The following are the changes in the planned analyses described in the protocol.

- The definition of the ITT Population was updated to clarify that screen failures and randomization failures would not be included in the ITT population.
- Per Axogen's decision, the secondary endpoints and tertiary endpoints were changed from what is described in the protocol. [redacted] was moved from a secondary to a tertiary endpoint and MRCC was moved from a tertiary to a secondary endpoint.
- [redacted]
- [redacted]
- An imputation method surrounding COVID-19 related missing data was added to the SAP.
- The definition of time to recovery and its analysis was updated in comparison to what was written in the protocol.
- [redacted]
- The protocol indicates that percent recovery from baseline in VAS pain scores would be assessed. Per the definition of percent recovery from baseline, data from the contralateral digit is required. Contralateral assessments for VAS were not captured therefore this analysis was not performed and the SAP was updated to reflect that.
- [redacted]
- MRCC as a secondary endpoint and therefore its [redacted] analysis as such was added to the SAP.

- [redacted]
- Section 6.2.5 details additional supplemental summaries to be created per Axogen's request.
- Section 6.3.2 details and additional summary of concomitant medications added per Axogen's request.

Should any additional changes to protocol specified analyses occur, these changes will be fully described in the Clinical and Statistical Report.

9. REFERENCES

National Research Council. (2010). *The Prevention and Treatment of Missing Data in Clinical Trials.* Panel on Handling Missing Data in Clinical Trials. Committee on National Statistics, Division of Behavioral and Social Sciences and Education. Washington, DC: The National Academies Press.

Campbell, Michael J., and Martin J. Gardner. "Calculating Confidence Intervals For Some Non-Parametric Analyses." *British Medical Journal (Clinical Research Edition)*, vol. 296, no. 6634, BMJ, 1988, pp. 1454–56, http://www.jstor.org/stable/29530803.

10. REVISION HISTORY

Date of Revision	Description of Revision
[redacted]	[redacted]
[redacted]	[redacted]

11. PROGRAMMING CONVENTIONS

- Page orientation, margins, and fonts: Summary tables, listings, and figures will appear in landscape orientation. There should be a minimum of a 1.25" boundary on the upper (bound) edge, and a minimum of a 1.0" boundary on the remaining three edges. Output should be printed in Courier New with a point size of 8. Titles may be printed using a larger font (e.g., Arial point size 10).
- Identification of analysis population: Every summary table and figure should clearly specify the analysis population being summarized. Listings will be prepared for all subjects/repairs randomized.
- Group headers: In the summary tables, the group headers will identify the treatment group and the within-group sample size for the indicated analysis population. Of note, the header's sample size does not necessarily equal the number of subjects/repairs actually summarized within any given summary module; some subjects/repairs in the analysis population may have missing values and thus may not be summarized.
- Suppression of percentages corresponding to null categories: When count data are presented as category frequencies and corresponding percentages, the percent should be suppressed when the count is zero in order to draw attention to the non-zero counts.
- Presentation of sample sizes: Summary modules should indicate, in one way or another, the number of subjects/repairs actually contributing to the summary statistics presented in any given summary module. As mentioned above, this may be less than the number of subjects/repairs in the analysis population.
    - ♦ In the quantitative modules describing continuous variables (and thus presenting sample size, means, and standard deviations), the sample size should be the number of non-missing observations
    - ♦ For categorical variables that are presented in frequency tables, the module should present the total count in addition to the count in each category. Percentages should be calculated using this total as the denominator, and the percentage corresponding to the sum itself (that is, 100%) should be presented so as to indicate clearly to a reviewer the method of calculation.
- Sorting: Listings will be sorted by treatment group, subject number, repair number and date, if applicable. If a listing is sorted in a different manner, a footnote will indicate as such.
- General formatting rules: Rounding for all variables will occur only as the last step, immediately prior to presentation in listings, tables, and figures. No intermediate rounding will be performed on derived variables. The standard rounding practice of rounding numbers ending in 0-4 down and numbers ending in 5-9 up will be employed.
- The presentation of numerical values will adhere to the following guidelines:
    - ♦ Raw measurements will be reported to the number of significant digits as captured in the CRFs.

- Standard deviations will be reported to one decimal place beyond the number of decimal places the original parameter is presented.
- Means will be reported to the same number of significant digits as the parameter.
- Calculated percentages will be reported with no decimals.

- Dates will be formatted as DDMONYYYY. Partial dates will be presented in data listings as recorded in CRFs.

Time will be presented according to the 24-hour clock (HH:MM)