

## Statistical Analysis Plan: NTx20201

**Study Title:** A Phase 2a, Multicenter, Randomized, Patient and Evaluator Blinded, Controlled Study Evaluating the Safety and Efficacy of NTX-001 Compared to Standard of Care in the Treatment of Acute Single Transected Peripheral Nerve Injury Occurring below the Distal Border of the Brachial Plexus Requiring Surgical Repair.

**Study Number:** NTx20201

**Study Phase:** 2a

**Sponsor:** Neuraptive Therapeutics, Inc.  
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**Version** Draft #2,

**NCT #:** NCT04572906

**Date:** 25JUL2022

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| Version History |                                                                                                                                                                                                                                                           |
|-----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Version: 1.0    | Initial version                                                                                                                                                                                                                                           |
| Version: 2.0    | Made formatting adjustments; added formatting and style instructions.<br>Added key secondary endpoint.<br>Added clarification on analysis details for most exploratory endpoints.                                                                         |
| Version 3.0     | Addition of grip strength exploratory analysis.<br>Addition of MHQ percent change from baseline threshold endpoint.<br>Addition of sensitivity analysis for primary endpoint.<br>Details for additional interim analysis added.<br>Updated MMS personnel. |

# 1 TABLE OF CONTENTS

|        |                                                                        |    |
|--------|------------------------------------------------------------------------|----|
| 1      | TABLE OF CONTENTS .....                                                | 3  |
|        | LIST OF TABLES .....                                                   | 4  |
|        | LIST OF APPENDICES .....                                               | 4  |
| 2      | SIGNATURE PAGE .....                                                   | 5  |
| 3      | LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS .....                   | 6  |
| 4      | INTRODUCTION .....                                                     | 8  |
| 5      | TRIAL OBJECTIVES .....                                                 | 8  |
| 5.1    | Primary Objectives .....                                               | 8  |
| 5.2    | Exploratory Secondary Objectives .....                                 | 8  |
| 6      | STUDY DESIGN CONSIDERATIONS .....                                      | 9  |
| 6.1    | Study Design .....                                                     | 9  |
| 6.2    | Sample Size Determination .....                                        | 11 |
| 6.3    | Efficacy Measures .....                                                | 11 |
| 6.4    | Safety Measures .....                                                  | 12 |
| 6.5    | Baseline and Other Subject Characteristics .....                       | 12 |
| 7      | STUDY POPULATIONS .....                                                | 13 |
| 7.1    | Analysis Populations .....                                             | 13 |
| 7.2    | Subgroups .....                                                        | 14 |
| 8      | CHANGES IN CONDUCT OR PLANNED ANALYSES FROM THE PROTOCOL .....         | 14 |
| 9      | OVERALL STATISTICAL CONSIDERATIONS .....                               | 14 |
| 9.1    | General Conventions .....                                              | 14 |
| 9.2    | Baseline definition .....                                              | 15 |
| 9.3    | Handling of Missing Data .....                                         | 15 |
| 9.4    | Interim Analysis .....                                                 | 16 |
| 9.5    | Pooling Strategy for Study Sites .....                                 | 18 |
| 10     | BASELINE AND OTHER SUBJECT CHARACTERISTICS EVALUATION<br>METHODS ..... | 18 |
| 10.1   | Subject Disposition .....                                              | 18 |
| 10.2   | Analysis Populations .....                                             | 18 |
| 10.3   | Protocol Deviations .....                                              | 18 |
| 10.4   | Demographics and Baseline Characteristics .....                        | 19 |
| 10.5   | Medical History .....                                                  | 20 |
| 10.6   | Prior and Concomitant Medications .....                                | 20 |
| 10.7   | Surgical Details and Treatment Characteristics .....                   | 20 |
| 10.8   | Post-Operative Product Evaluation .....                                | 21 |
| 10.9   | Nerve Injury Characteristics and Class .....                           | 21 |
| 11     | EFFICACY ENDPOINT EVALUATION METHODS .....                             | 22 |
| 11.1   | Primary Analysis .....                                                 | 22 |
| 11.1.1 | Sensitivity Analysis for Primary Endpoint .....                        | 23 |

|        |                                                                |    |
|--------|----------------------------------------------------------------|----|
| 11.2   | Secondary Analysis.....                                        | 23 |
| 11.2.1 | Sensitivity Analysis for Secondary Endpoint .....              | 24 |
| 11.3   | Exploratory Secondary Analysis.....                            | 24 |
| 11.3.1 | Sensitivity Analysis for Exploratory Secondary Endpoints ..... | 33 |
| 12     | SAFETY ASSESSMENT EVALUATION METHODS .....                     | 33 |
| 12.1   | Adverse Events .....                                           | 33 |
| 12.2   | Laboratory Tests .....                                         | 34 |
| 12.3   | Vital Signs.....                                               | 34 |
| 12.4   | Physical and Occupational Therapy.....                         | 35 |
| 12.5   | Splint Assessments.....                                        | 36 |
| 13     | REFERENCES .....                                               | 36 |
| 14     | APPENDICES .....                                               | 37 |

## LIST OF TABLES

|         |                                                        |     |
|---------|--------------------------------------------------------|-----|
| Table 1 | MRCC Sensoring Scoring .....                           | 26  |
| Table 2 | MRCC Motor Scoring .....                               | 27  |
| Table 3 | SWMT Filaments.....                                    | 28  |
| Table 4 | Cold Intolerance Symptom Severity (CISS) Scoring ..... | 31  |
| Table 5 | PGIC Responses .....                                   | 32  |
| Table 6 | Criteria for Abnormal Vital Signs .....                | 382 |
| Table 7 | Prospective Efficacy Analyses.....                     | 38  |
| Table 8 | MHQ Scoring Scales .....                               | 386 |

## LIST OF APPENDICES

|            |                                                                                                                  |    |
|------------|------------------------------------------------------------------------------------------------------------------|----|
| Appendix 1 | Schedule of Assessments and Procedures.....                                                                      | 37 |
| Appendix 2 | Summary of Prospective Efficacy Analyses .....                                                                   | 38 |
| Appendix 3 | Michigan Hand Questionnaire (MHQ) Scoring.....                                                                   | 38 |
| Appendix 4 | Imputation Rules for Missing or Partial Dates for AEs and Medical History .....                                  | 41 |
| Appendix 5 | Imputation Rules for Missing or Partial Dates for Prior and Concomitant Medications and Medical Procedures ..... | 42 |

## 2 SIGNATURE PAGE

**Study Title:** A Phase 2a, Multicenter, Randomized, Patient and Evaluator Blinded, Controlled Study Evaluating the Safety and Efficacy of NTX-001 Compared to Standard of Care in the Treatment of Acute Single Transected Peripheral Nerve Injury Occurring below the Distal Border of the Brachial Plexus Requiring Surgical Repair.

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### 3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

|           |                                                                                                                                                       |
|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------|
| AE        | Adverse Event                                                                                                                                         |
| ADL       | Activities of Daily Living                                                                                                                            |
| ATC       | Anatomical Therapeutic Chemical Classification                                                                                                        |
| CHW       | Cui-Hung-Wang                                                                                                                                         |
| CISS      | Cold Intolerance Symptom Severity                                                                                                                     |
| CL        | Contralateral                                                                                                                                         |
| CMAP      | Compound Muscle Action Potential                                                                                                                      |
| CRA       | Clinical Research Associate                                                                                                                           |
| CRF       | Case Report Form                                                                                                                                      |
| DC        | Discontinuation                                                                                                                                       |
| DPD       | Diastolic Blood Pressure                                                                                                                              |
| EP        | Electrophysiology                                                                                                                                     |
| IP        | Investigational Product                                                                                                                               |
| ITT       | Intent-to-Treat                                                                                                                                       |
| MAC       | Monitored Anesthesia Care                                                                                                                             |
| MedDRA    | Medical Dictionary for Regulatory Activities                                                                                                          |
| MHQ       | Michigan Hand Questionnaire                                                                                                                           |
| mITT      | Modified Intent-to-Treat                                                                                                                              |
| MMRM      | Mixed Model Repeated Measures                                                                                                                         |
| MRCC(s/m) | <British> Medical Research Council Classification (sensory/motor)                                                                                     |
| MTPD      | Moving Two Point Discrimination                                                                                                                       |
| NPRS      | Numeric Pain Rating Scale                                                                                                                             |
| NTX-001   | Investigational Product (IP) configured as surgical use product of several solutions (irrigation and fusion) and an isolation chamber medical device. |
| NVC       | Nerve Conduction Velocity                                                                                                                             |
| OT        | Occupational Therapy                                                                                                                                  |
| PGIC      | Patient Global Impression of Change                                                                                                                   |
| PP        | Per-Protocol                                                                                                                                          |
| PT        | Preferred Term, or Physical Therapy                                                                                                                   |

|       |                                           |
|-------|-------------------------------------------|
| SAE   | Serious Adverse Event                     |
| SBP   | Systolic Blood Pressure                   |
| SD    | Standard Deviation                        |
| SE    | Standard Error                            |
| SoA   | Schedule of Activities                    |
| SOC   | System Organ Class                        |
| SoC   | Standard of Care                          |
| STPD  | Static Two Point Discrimination           |
| SWMT  | Semmes Weinstein Monofilament Test        |
| TEAE  | Treatment-Emergent Adverse Event          |
| WHODD | World Health Organization Drug Dictionary |

## 4 INTRODUCTION

The purpose of this statistical analysis plan is to describe the framework for the reporting, summarization and statistical analysis methodology of the safety and efficacy parameters measured throughout the study. It is based on Protocol NTx20201 Version 3.0 dated 27APR2021.

## 5 TRIAL OBJECTIVES

### 5.1 Primary Objectives

- To assess the safety of NTX-001 across 48 weeks following the surgical repair of a peripheral nerve injury occurring below the distal border of the brachial plexus.
- To assess functionality using MHQ (Michigan Hand Questionnaire) Total Score at Week 12 following the surgical repair of a peripheral nerve injury occurring below the distal border of the brachial plexus.

### 5.2 Exploratory Secondary Objectives

- To assess electrophysiological (EP) continuity after NTX-001 treatment; stratified by injury location.
- To assess improvement from baseline in the following assessments when NTX-001 is used in conjunction with standard suture neurorrhaphy:
  - British Medical Research Council Classification (MRCC) sensory scale, and/or the MRCC motor scale (based on location of injury)
  - Semmes Weinstein Monofilament Test (SWMT)
  - Relative Grip/Pinch Strength
  - MHQ
  - Cold Intolerance Symptom Severity (CISS)
  - Patient Global Impression of Change (PGIC)
  - Numeric Pain Rating Scale (NPRS)

## 6 STUDY DESIGN CONSIDERATIONS

### 6.1 Study Design

The hypothesis of the study is that subjects that experience an acute single transected peripheral nerve injury (multiple transected digital nerves of the hand are allowed and with each digital repair following the randomization assignment) occurring below the distal border of the brachial plexus to the fingertip requiring surgical repair will have outcomes that reflect improved quality and time to restoration of motor function and sensation with the adjunct use of the NTX-001.

A total of 48 subjects will be randomized to meet the study goal of 40 evaluable subjects, assuming a 15% dropout rate. Subjects will be enrolled in a 1:1 randomization schema (24 subjects to NTX-001; 24 subjects to the Standard of Care (SoC)). Additional subjects may be enrolled to account for early withdrawal (protocol deviations, withdrawal of consent, noncompliance, etc.). Subjects will be stratified by two locations of injury:

- Distal border of brachial plexus to wrist crease;
- Distal border of wrist crease to fingertip.

The following are further descriptions of the study design and conduct:

- Phase 2a;
- The Investigational Product under study is called NTX-001;
- Patient and Evaluator Blinded, Randomized-Controlled, Multi-Center Study;
- Methods to reduce bias, the study will be executed in such a way as to minimize bias in the conduct of the postoperative evaluation of study subjects by the following methods:
  - Subjects will be randomized into one of two groups using a blinded method provided by an independent statistician;
  - Any records generated during the surgery will be maintained separate from the study files and will not be accessible by other study personnel;
  - Subjects will not be informed as to which study arm they have been assigned until after the study is completed;
  - Subjects will be blindfolded, or actual testing obscured to the subject during assessment for items 3 and 5 as noted below;
  - Postoperative evaluations such as functional motor and sensory assessments will be performed by the same qualified evaluator (if possible), blinded to treatment assignment;

- An unblinded site monitor (CRA) will review the surgical records and be responsible for NTX-001 accountability and application (IP Administration) compliance. Functional motor and sensory assessments will be done according to instructions for that assessment, in an attempt to prevent questionnaire fatigue, and if possible, standardize the assessment sequence as follows and conduct on contralateral (CL) side as noted:
  1. NPRS-Pain
  2. Vital Signs
  3. MRCC Sensory and/or Motor based on location of injury (CL)
  4. MHQ Patient Related Outcome
  5. Semmes Weinstein Monofilament Test (CL)
  6. Grip/Pinch Strength – (CL)
  7. CISS
  8. PGIC
  9. PT/OT/Splint Compliance
  10. EP - CMAP and NCV will be the last test conducted if all others are done on the same day or it can be done on another day within the allowable window before or after the scheduled visit.
- There will be two groups under study, subjects randomized to the NTX-001 Product and subjects to the SoC group. Subject follow-up will be at 4, 8, 12, 24, 36 and 48 weeks post repair.
- An interim analysis will be performed to re-assess the adequacy of the study sample size based on the primary efficacy endpoint of interest, the change from baseline in MHQ total score at week 12, after approximately 20 randomized subjects (about 10 subjects in NTX-001 group and about 10 subjects in SoC group) have completed 12 weeks of treatment.
- Subjects will be studied for 48 weeks after surgical repair of the affected peripheral nerve.
- The study will be conducted in up to 15 sites in the United States.

A subject is considered to have completed the study if they have completed all phases of the study including the last visit shown in the Schedule of Assessments (SoA) (Appendix 1). The end of the study is defined as completion of the last visit (Visit 8 or Week 48). Subjects will participate in the study for a total of approximately 48 weeks. Participation will consist of a screening visit, a treatment or surgical visit, Week 1 visit (Baseline Period) and follow-up visits that will occur at Weeks 4, 8, 12, 24, 36 and 48.

## 6.2 Sample Size Determination

Considering a one-sided significance level of 0.05, a sample size of 20 subjects per group can provide 90% power to detect a difference of 5.0 with a standard deviation of 5.3 in the primary efficacy endpoint of change from baseline of MHQ total score between NTX-001 and SoC at Week 12, assuming that the change from baseline MHQ total score is 7.0 and 2 for each of the NTX-001 and SoC groups, respectively.

Approximately 48 subjects will be enrolled to meet the goal of 40 evaluable subjects to complete the study with about 15% drop out rate. A subject is evaluable if the subject meets the modified intent to treat (mITT) population criteria (refer to Section 7.1).

Potential subjects who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

## 6.3 Efficacy Measures

### Primary Endpoints:

- Change from baseline of MHQ Total Score at Week 12.

### Secondary Endpoint:

- Percent of recovery of MHQ Total Score at Weeks 12 and 24.

### Exploratory Secondary Endpoints:

The following will be evaluated intraoperatively and percutaneously at Week 12. Week 12 is considered a critical visit and is to be conducted onsite. Facility and individual infection control policies will be followed during the visit.

- Electrophysiological parameters:
  - SNAP amplitude
  - Sensory NCV
  - CMAP amplitude
  - Motor NCV

The following will be evaluated at Weeks 4, 8, 24 and 48 using the following measure:

- Change from baseline of MHQ Total Score

The following will be evaluated at Weeks 4, 8, 12, 24, 36 and 48 using the following measures:

- MRCC Motor Scale

- MRCC Sensory Scale
- SWMT Assessment
- Ratio of Affected to Contralateral Grip/Pinch Strength
- Change from baseline of NPRS Score

The following will be evaluated at Weeks 4, 8, 12, 24 and 48 using the following measures:

- Change from baseline of CISS Score
- PGIC Score

## **6.4 Safety Measures**

The following safety endpoints will be evaluated across 48 weeks following operative repair. Refer to individual sections for further details on complete analysis.

- Adverse events over various categories and characteristics (incidence rates)
  - Adverse events due to device (only available upon unblinding)
- Chemistry and hematology parameters
- Vital signs
- Prior and concomitant medications (listing only)
- Concomitant procedures (listing only)
- Physical examinations (listing only)

## **6.5 Baseline and Other Subject Characteristics**

The following baseline and subject characteristics will be evaluated:

- Screen failures (listing only)
- Populations (ITT, mITT, Safety and PP)
- Major protocol deviations (listing only if observed)
- Study disposition including completion and early withdrawal (incidence rates)

- Demographics (incidence rates, categorical and numerical descriptive stats)
- Medical history (listing only)
- Nerve/concurrent injury characteristics and nerve injury class (incidence rates)
- Surgical details (listing only available upon unblinding)
- Post-op product evaluation (listing only available upon unblinding)
- Splint assessments (listing only)
- Physical and occupational therapy compliance (visit rates and duration descriptive stats)
- Other collected data including during pregnancy testing, entry criteria, etc, (listing only)

## **7 STUDY POPULATIONS**

### **7.1 Analysis Populations**

This study will have the following population of interest:

- The Intent-to-Treat population (ITT Population) – Subjects who successfully pass screening criteria and are randomized for study treatment assignments. This will potentially include subjects who are randomized but not treated and/or did not complete surgery (listing will be created). Subjects will be analyzed according to the treatment assigned (NTX-001 or SoC).
- The Safety population (Safety Population) - Subjects from the ITT population who received or were exposed to at least one application of the topical IP (NTX-001) or completed surgery without study product. All subjects will be analyzed according to the treatment actually received (NTX-001 or SoC). The Safety population data set will be used for all the safety analyses.
- The Modified Intent-to-Treat Population (mITT Population) - Subjects who received or were exposed to at least one application of the topical study product (NTX-001) or completed surgery without study product, have a baseline visit for the Michigan Hand Questionnaire, and who provide at least up to week 8 of evaluable data for the Michigan Hand Questionnaire. All subjects will be analyzed according to the treatment procedure they actually received (NTX-001 or SoC). The mITT population data set will be used for all the efficacy analyses. All subjects who meet mITT criteria are considered evaluable subjects.
- The Per-Protocol Population (PP Population) - Subjects who received or were exposed to at least one application of the topical study product (NTX-001) or completed surgery

without study product, and who provide at least up to week 4 of evaluable data for the primary endpoint. Critical and major protocol deviations will be evaluated individually by the sponsor to decide whether it has a basis to exclude a participant from the PP population. All subjects will be analyzed according to the treatment procedure they actually received (NTX-001 or SoC). The PP population data set will be used for only a subset of the efficacy analyses as indicated in specific endpoint details later in this document.

## **7.2 Subgroups**

Subgroup analyses will be conducted on the primary endpoint of MHQ Total Score, if subgroup levels have sufficient sample size to justify it, based on the following factors:

- Age group (<18, 18-65, >65)
- Gender
- Smoking history (Non-smoker vs. previous or current smoker)
- Location of injury (Distal border of brachial plexus to wrist crease vs. Distal border of wrist crease to fingertip)

Additionally, subgroup analysis may be conducted for secondary endpoints if subgroups of interest are identified during the course of the study.

## **8 CHANGES IN CONDUCT OR PLANNED ANALYSES FROM THE PROTOCOL**

The baseline definition for MHQ and CISS was updated to include Week 4 as a possible baseline time point. The baseline period was expanded from up to Day 9 to up to Day 14 for other endpoints.

## **9 OVERALL STATISTICAL CONSIDERATIONS**

### **9.1 General Conventions**

- All statistical testing will be one-sided and performed at the 0.05 level.
- Change from baseline will always be calculated as T-B, where T is the value on treatment and B is the baseline value.
- Treatment differences will always be calculated as NTX-001 minus SOC.

- No adjustments will be made for testing multiple secondary outcome measures. Since it is possible that some significant results could occur by chance alone, undue consideration will not be given to isolated significant differences; rather, interpretation will be made based on patterns of significant differences and consistency with the primary parameter.

## 9.2 Baseline definition

Generally, baseline values are obtained from measurements/assessments taken at any time from a fully executed consent to before or at Day 14. If values for an endpoint are available prior to surgery, then the last available prior to surgery should be used in calculations for change from baseline. If no values are available prior to surgery, the value closest after surgery but still considered having occurred at Day 14 will be used as baseline.

The values for MRCC sensory and motor scales will use the highest value for each subject at the baseline visit when measurements are taken on multiple nerve sites at baseline.

For MHQ and CISS assessments, the baseline will be taken from the worst score at the Screening or Week 4 visit. The screening assessments for these endpoints are a measure of the condition up to two weeks prior to injury. This means that screening visit assessments can capture pre-injury status and ignore the severity of injury. To ensure that each subject's baseline captures a post-injury observation, the worst score from Screening and Week 4 visits will be used.

The following endpoints *do not require a baseline value identified* since they are comparative measures to prior to injury/surgery, or simply can only be performed after surgery:

- PGIC
- Splint Evaluations
- Grip/Pinch Strength
- PT/OT Compliance

## 9.3 Handling of Missing Data

Missing data will generally not be imputed in the analysis of this study's data with the exception of adverse events and prior/concomitant medication dates (see Appendices 4 and 5, respectively) and responder status (see Section 11.3 for endpoints using responder status). Please see below for specific handling of calculations in the presence of missing data.

### MHQ (Michigan Hand Questionnaire) Total Score

The MHQ contains 6 scales as described in section 11.1. If 50% or more of the items in a scale are missing, then that particular scale cannot be scored. For scales with less than 50% missing items, the average of the existing scale items may be used instead for normalizing to a 0-100 range. This implicit imputation of missing items assumes the missing items would have followed the same response trends as the average of the observed items. For example, if a subject is

missing 2 of the five item responses in the “Overall hand function” scale, then instead of using the following formula,  $100 \times (25 - \text{sum of all 5 item raw scores}) / 20$ , instead use the following formula,  $100 \times (15 - \text{sum of the 3 available item raw scores}) / 12$ . See Appendix 3 for more details in scoring the MHQ.

### **Responder/Non-Responder Status Imputation**

The secondary endpoints MRCC Sensory and Motor Scales, SWMT, and PGIC use responder/non-responder status to determine the effect of treatment. Missing responder status values for these endpoints will be imputed using repeated measures logistic regression on responder/non-responder status, with treatment, visit, and visit\*treatment as fixed effects, using an unstructured covariance structure for subject. The imputed values and imputation status will be included in the listing for these endpoints.

## **9.4 Interim Analysis**

An interim analysis will be performed to re-assess the adequacy of the study sample size based on the primary efficacy endpoint of interest, the change from baseline of MHQ total score at Week 12, after the first approximately 20 evaluable subjects (about 10 subjects in NTX-001 group and about 10 subjects in SOC group) have completed 12 weeks of treatment with a demonstrable balance between sites and injury location. If the balance between the sites and the injury location is statistically significantly different, interim analysis will be performed with additional subjects to get an approximate balance.

Sample size adjustment will be based on the primary endpoint, the change from baseline of MHQ total Score, if required. Additional subjects will be enrolled to have the desired number of completed subjects in each arm to achieve the desired power for the study (see Section 6.3). At the end of the study, the data will be analyzed using the Cui-Hung-Wang (CHW) method to reflect the fact of the sample size adjustment.

Interim sample size redetermination will be conducted by the unblinded sponsor statistician. The remaining interim analysis is to be conducted by an unblinded team of MMS Holdings, Inc. personnel to maintain blinding of blinded personnel throughout the course of the study. Agreement on method of distribution and details of whom the results will be provided to will be outlined in an unblinding request form (which will be finalized prior to the IA). Since this analysis will occur before formal unblinding, distribution of the results will be limited to those outside the blinded MMS study team and will not be shared with the blinded MMS study team.

The following summary tables will be provided for the interim analysis. No listings or graphs will be provided:

- Subject Disposition
- Subject Demographics
- Baseline Subject Characteristics

- Change from Baseline of MHQ Total Score (Mixed Model Results and Summary tables)
- Change from Baseline of MHQ Domain Scores (summary table only)
- Responder status for MRCC Two-Point Discrimination and Motor Function (Responder Analysis and summary tables)
- Responder status for SWMT (Responder Analysis and summary tables)
- Relative Grip/Pinch Strength (summary table only)

In addition to the tables listed above for the interim analysis, an Independent Data Monitoring Committee (IDMC) will examine drug safety at least 12 weeks after treatment.

An additional interim analysis will be conducted after all subjects have completed their Week 12 assessments. No sample size calculations or adjustments will be made for this interim analysis. The above-listed tables will be provided, with the addition of the following tables:

- Analysis Populations and Reasons for Exclusion
- Nerve Injury Characteristics
- Surgical Details and Treatment Characteristics
- Responder Status for SWMT (Responder Analysis and summary tables)
- Change from Baseline of NPRS Score (Mixed Model Results and summary tables)
- Change from Baseline of CISS Score (Mixed Model Results and summary tables)
- Responder Status for PGIC (Responder Analysis and summary tables)
- Sensory and Motor NCV Parameters (Mixed Model Results and summary tables)
- Overall Summary of Treatment-Emergent Adverse Events
- Treatment-Emergent Adverse Events
- Device-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- Serious Adverse Events by System Organ Class and Preferred Term
- Physical and Occupational Therapy Compliance and Duration

## **9.5 Pooling Strategy for Study Sites**

Due to the low sample size for this study and the anticipation that many sites will have at most one or two subjects, we are unlikely to have balanced or complete filling of all strata at all sites. If necessary, site pooling will be employed using available factors of interest.

# **10 BASELINE AND OTHER SUBJECT CHARACTERISTICS EVALUATION METHODS**

## **10.1 Subject Disposition**

A subject is considered to have completed the study if they have completed all phases of the study including the last visit planned for the study, Visit 8 (Week 48). Disposition characteristics will be summarized including the number (and percentage) of subjects randomized, completing the study, terminating the study early. For those subjects terminating early, the primary reason for terminating will be summarized. Individual subject disposition details will be provided in a listing. Disposition summary and listing will use the ITT Population set of subjects.

Subjects who fail to become randomized (i.e. screen failures) will be have their reasons for screen failure provided in a listing.

## **10.2 Analysis Populations**

The number of subjects (and percentages) in each analysis population will be summarized. Populations in this study include Intent-to-Treat (ITT), Safety, Modified Intent-to-Treat (mITT) and the Per-Protocol (PP) populations. This summary will be performed using the ITT Population. Individual subject membership, as well as reason for exclusions, will be provided in a listing.

## **10.3 Protocol Deviations**

All individual subject protocol deviations will be provided in a listing for subjects in the ITT Population. Protocol deviations that lead to the exclusion of a subject from the PP Population (significant protocol deviations) will be determined prior to final lock and unblinding of the database. Significant protocol deviations that lead to subject exclusion from the PP Population will be summarized and listed.

All subject data will be reviewed for the occurrence of protocol deviations; identified protocol deviations will be captured by the contract research organization (CRO) and identified as important or non-important, and categorized as follows:

- Inclusion Criteria
- Exclusion Criteria

- Study Drug
- Assessment
- Lab/Endpoint Data
- Visit Window
- Informed Consent Form (ICF)
- Prohibited Co-Medication
- Overdose/Misuse
- Other

#### **10.4 Demographics and Baseline Characteristics**

The following demographic and baseline characteristics will be summarized for the Safety and ITT populations. Demographic characteristics include:

- Age (years) and age group (<18, 18-65, >65)
- Sex
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- BMI (kg/m<sup>2</sup>)
- Smoking status

Baseline characteristics include:

- Vital signs
- Dominant side injured (Yes, No)\*
- Class of injury\*
- Location of injury\*

- MHQ Total Score
- STPD and MTPD
- Semmes-Weinstein Monofilament Test (SWMT)
- Numeric Pain Rating Scale (NPRS)
- Cold Intolerance Symptom Severity (CISS)

Individual subject demographics will be provided in a listing. Individual subject characteristics will be provided in the corresponding efficacy or safety endpoint listing, including the applicable baseline visit timepoint, except those indicated with an asterisk(\*), which will be provided in a listing of baseline characteristics using the Safety Population.

### **10.5 Medical History**

The number and percent of subjects reporting any medical history by SOC and PT for the Safety Population will be provided. A subject with multiple medical conditions (coded using MedDRA) will be counted once per SOC and PT. The summary table will be sorted by descending order of frequency of SOC (then alphabetically for ties), then by descending order of frequency of PT within each SOC (then alphabetically for ties), in the NTX-001 treatment group.

Individual subject medical history will be provided in a listing.

### **10.6 Prior and Concomitant Medications**

Prior and concomitant medication use will be summarized separately for the Safety Population using the World Health Organization Drug Dictionary (WHODD) for coding, organized by Anatomical Therapeutic Chemical Classification (ATC) Level 3 and generic drug name. A subject with multiple medication use will be counted once per ATC Level and generic name. A prior medication is any medication used during screening regardless of if the medication use was stopped prior to study drug administration. A concomitant medication is any medication in use from study drug administration to the end of the study (either Week 48 or Early Termination).

Individual subject medication use will be provided in a listing.

### **10.7 Surgical Details and Treatment Characteristics**

The following surgical details and characteristics will be summarized for the Safety Population:

- Time from injury to start of surgery (hours) = date/time of surgery start - date/time of injury
- Duration of surgery (hours) = date/time of surgery end - date/time of surgery start
- Type of Anesthesia (General, Monitored Anesthesia Care MAC, Local)
- Fusion duration (90-120 sec required)
- Surgery repeated? (Yes, No)
- Second fusion duration (90-120 sec required)
- Was nerve stimulation performed (Yes, No)
  - If No, specify reason (Sensory digital nerve, Other)
- Distal Motor Response
  - Was there a motor response (Yes, No)
  - Amplitude (mA)
  - Pulse duration (msec)
- Proximal to Captation: After Microsuture
  - Was there a motor response (Yes, No)
  - Amplitude (mA)
  - Pulse duration (msec)
- Proximal to Captation: After final rinse
  - Was there a motor response (Yes, No)
  - Amplitude (mA)
  - Pulse duration (msec)

## 10.8 Post-Operative Product Evaluation

Post-operative product evaluations are questions asked of the surgeons relating to the solutions, the retaining device, and a general response for the procedure as a whole. Responses to individual questions range on a 5-point ordinal scale (“1 – Strongly Disagree” to “5 – Strongly Agree”). Subjects in the Safety Population randomized to NTX-001 will be used categorically to descriptively summarize responses to these questions.

Additional questions asked may also be summarized. All individual subject responses to post-operative product evaluations will be provided in a listing using the Safety Population.

## 10.9 Nerve Injury Characteristics and Class

The following primary and concurrent secondary nerve injury characteristics will be summarized for the Safety Population. All individual nerve injury characteristics will be provided in a listing using the Safety Population as well.

- Primary nerve injury location (Left Upper Extremity, Right Upper Extremity, Left Digital)

- Left and Right Upper Extremity Primary injury sites will have more localized sites summarized as collected on the CRFs (Median, Median Cutaneous Forearm, Median Recurrent, etc., ...)
- Left and Right Digital Primary injury sites will have more localized sites summarized as collected on the CRFs (Thumb Radial, Thumb Ulnar, Index Radial, Index Ulnar, etc., ...)
- Other nerve site injury (not primary) will be provided in a listing.
- Class of injury at presentation (Sunderland degree/ Seddon class)
  - Fourth degree (Class III)
  - Fifth degree (Class III)

## 11 EFFICACY ENDPOINT EVALUATION METHODS

### 11.1 Primary Analysis

#### **Safety:**

Safety endpoints of adverse events and other safety data (vital signs, clinical labs, etc., ...) will be evaluated across the 48 weeks following operative repair. Details of the methods used to evaluate safety are described in [Section 12 \(Safety Assessment Evaluation Method\)](#).

#### **MHQ (Michigan Hand Questionnaire) Total Score:**

The MHQ is a patient-rated questionnaire assessing various subjective impressions of hand function. This assessment will be administered during the baseline period as well as follow-up assessments at Weeks 4, 8, 12, 24 and 48. The MHQ has a total of thirty-seven (37) questions/items among six distinct scales: (1) overall hand function, (2) activities of daily living (ADLs), (3) pain, (4) work performance, (5) aesthetics, and (6) subject satisfaction with hand function (Chung, 1998). There are 5 possible responses to each question/item within each scale ranging from best outcome to worst outcome (or vice-versa). Point values to individual item responses from each scale are summed and normalized (refer to Appendix 3) to a value between 0 and 100 (higher is better). The MHQ Total is calculated as the average of all 6 of the normalized scale scores, again ranging from 0 and 100 (higher is better). Please refer to Section 9.3 for handling of missing item responses for scoring and Appendix 3 for further details of calculating both the normalized and MHQ Total Score.

Some questions in the MHQ are split and assessed separately for the left and right sides for 1-handed function/pain. When a question has been split for left and right sides (1-handed items), the total score used for analysis in this study will be based on the question/item response for the side where the transection injury occurred. For the ADL scale, both 1-handed and 2-handed questions are assessed. ADL total score is calculated using the 2-handed scores and the 1-handed scores for affected side only.

The MHQ Total Score and change from baseline of MHQ Total Score, as well as normalized scores and change from baseline for each domain normalized score, will be summarized as

descriptive statistics at baseline and all post-baseline visits for the mITT population. MHQ Total Score, total score for each distinct scale, and individual question responses will be provided in by-subject data listings using the mITT population.

Analysis of the change from baseline in the MHQ Total Score will be performed using a repeated measures mixed model (Mixed Model Repeated Measures – MMRM) for the mITT population. Factors included in the model will be:

- Treatment
- Baseline MHQ Total Score
- Injury location
- Treatment by injury location interaction
- Visit
- Treatment by Visit interaction

Kenward-Rogers adjustment for degrees of freedom will be used to adjust for small sample sizes. An unstructured covariance structure will be used initially. If the model fails to converge, other covariance structures that fit the study design will be used. See Appendix 6 for sample code. The effect of treatment at each timepoint will be analyzed, focusing on Week 12 results as the primary timepoint of interest.

The effect of treatment at each visit will be determined using a one-sided test and an  $\alpha = 0.05$  and the null hypothesis  $H_0: \mu_{NTX001} = \mu_{SOC}$ .

### 11.1.1 Sensitivity Analysis for Primary Endpoint

The analysis described above for the change from baseline in the MHQ Total Score will be repeated for the PP population as a sensitivity analysis. The analysis for MHQ Total Score will also be repeated for the mITT population while removing any mITT subjects that dropped out prior to Week 48.

Additionally, sensitivity to type of nerve injury will be examined by separating the mITT population into two subpopulations: subjects with sensory only injuries and subjects with mixed sensory and motor injuries. The MMRM used in the primary analysis will be re-run separately for these subpopulations, removing the injury location and treatment by injury location interaction. Effects of treatment on change from baseline MHQ Total Score at each timepoint will be examined, focusing on Week 12.

## 11.2 Secondary Analysis

### Percent of Recovery of MHQ Total Score

Recovery to the pre-injury state will be examined as a secondary analysis for MHQ Total Score. The screening visit MHQ questionnaire will be used as the pre-injury status for each subject. The percent of recovery is defined as the ratio of the current score to the pre-injury score. Subjects without a pre-injury MHQ Total Score will be excluded from percent of recovery analysis.

Percent of meaningful recovery will be summarized at Weeks 12 and 24 and analyzed using responder analysis. For Week 12, a subject will be considered a responder if they recover to 50% of the pre-injury state. For Week 24, a subject will be considered a responder if they recover to 75% of the pre-injury state.

A Cochran-Mantel-Haenszel (CMH) test, stratified by injury location, will be conducted at Weeks 12 and 24 separately, testing a difference between responder status due to treatment (NTX-001 or SoC). Analysis will be conducted on the mITT population. See Appendix 6 for sample CMH code.

### **11.2.1 Sensitivity Analysis for Secondary Endpoint**

The CMH test will be repeated for the mITT population with any missing observations being treated as a non-responder.

A repeated measures logistic regression model will also be conducted on the percent recovery. Each post-baseline visit will be included in this model. The following factors will be included in the model:

- Treatment
- Pre-injury MHQ Total Score
- Injury location
- Treatment by injury location interaction
- Visit
- Treatment by Visit interaction

The effect of treatment on percent recovery will be analyzed at each timepoint.

## **11.3 Exploratory Secondary Analysis**

### **Week 12 Percent Change from Baseline Thresholds**

The proportion of subjects who have change from baseline score at the thresholds of greater than 25%, 50%, and 75% will be reported using descriptive statistics and 95% confidence intervals for the proportion.

### **Electrophysiology Assessments:**

The nerve conduction measurements performed in this study permit various assessments of function in both motor and sensory nerves. Of particular interest are the sensory nerve action potential (SNAP) amplitude and the nerve conduction velocity (NCV) associated with sensory nerves. Compound muscle action potential (CMAP) amplitude, CMAP, and NCV will also be examined.

Restoration of SNAP amplitude and NCV indicates the restoration of axon continuity and remyelination, respectively, with higher values indicating a better response (SNAP measured in milli-volts, NCV measured in meters per second). Electrophysiology assessments are only performed at Week 12.

Due to the complexity of electromyogram (EMG) measurements, it is not always possible to determine which assessment should be evaluated on a given subject and how best to programmatically determine improvement. To account for this, a central reader will blindly evaluate all the components of the electromyogram study performed at Week 12 to determine if the subject has recovered or still has evidence of nerve or muscle dysfunction. This test will only be performed in subjects whose injuries include nerves that impact motor function.

The following endpoints will be summarized using descriptive statistics for Week 12 measurements, following manual curation of relevant assessments, on the mITT population:

- SNAP amplitude (ratio of affected:contralateral)
- Sensory NCV (difference of contralateral – affected)
- CMAP amplitude (ratio of affected:contralateral)
- Motor NCV (difference of contralateral – affected)

A listing containing the nerve conduction measurements listed above, for both affected and contralateral sides, as well as the ratios/differences, will be provided using the mITT population.

In addition to the summaries and listings, the SNAP and CMAP amplitude ratios and sensory and motor NCVs will be analyzed using a mixed model. Each endpoint will be analyzed in a separate model containing a fixed effect for treatment and a random effect for subject. All statistical analysis will be conducted on the mITT population, following manual curation of the nerve sites of interest.

Needle electromyography (EMG) measurements will be provided in a listing only, using the mITT population.

### **British Medical Research Council Classification (MRCC) Sensory and Motor Scales:**

The MRCC sensory assessment includes using pain/touch sensibility as well as evaluating static and moving two-point discrimination grading (STPD and MTPD, respectively) as seen below in Tables 1 and 2, respectively.

STPD measures the innervation density (number of nerves present in an area) by testing the ability to discern the difference between one and two static pressure points. MTPD measures the innervation density by testing the ability to discern the difference between one or two pressure points when moved across the area. MTPD discrimination returns earlier than static 2-point discrimination. The scales are ordinal in nature with lowest value of “no sensibility recovery” (S0) up to “complete recovery” (S4). This assessment, including the supporting STPD/MTPD grading, will be evaluated during the baseline period as well as follow-up assessments at Weeks 4, 8, 12, 24, 36, and 48.

The percent of meaningful recovery responders will be summarized for STPD and MTPD (counts and percentages) at all post-baseline visits, where meaningful recovery is defined as a return of sensory score of S3+ or better (see Table 1 below for scoring details) (MacKinnon and

Dellon, 1990). Each subject may have more than one digital nerve tested. In the case that a subject has more than one nerve tested, the nerve with the highest baseline score will be used for analysis at each subsequent visit. Subjects with missing evaluations will imputed as detailed in Section 9.3.

A CMH test, stratified by injury location, will be conducted at each visit separately, testing a difference between responder status due to treatment (NTX-001 or SoC). The nerve with the highest scoring baseline value will be used to determine responder status for each visit. Only the injured side will be analyzed. Analysis will be conducted on the mITT population. See Appendix 6 for sample CMH code. Based on the evaluable data available for s2PD and m2PD assessments, additional models may be considered as sensitivity/supplementary analyses.

Individual subject results for MMRC sensory assessment, as well as the supporting STPD/MTPD grading, will be provided in listings using the mITT population.

**Table 1 MRCC Sensory Scoring**

| Grade           | Recovery of sensibility                                                                   | s2PD (mm) | m2PD (mm) |
|-----------------|-------------------------------------------------------------------------------------------|-----------|-----------|
| S0              | No recovery of sensibility in the autonomous zone of the nerve                            |           |           |
| S1              | Recovery of deep cutaneous pain sensibility within the autonomous area of the nerve       |           |           |
| S1 <sup>+</sup> | Recovery of superficial pain sensibility                                                  |           |           |
| S2              | Recovery of superficial pain and some touch sensibility                                   |           |           |
| S2 <sup>+</sup> | As in S2, but with over-response                                                          |           |           |
| S3              | Recovery of pain and touch sensibility with disappearance of over-response                | > 15      | > 7       |
| S3 <sup>+</sup> | As in S3; but localization of the stimulus is good and there is imperfect recovery of 2PD | 7-15      | 4-7       |
| S4              | Complete recovery                                                                         | 2-6       | 2-3       |

British Medical Research Council classification; MacKinnon and Dellon's modification of two-point discrimination. © Crown Copyright ("Used with the permission of the Medical Research Council")

The MRCC motor assessment evaluates muscle strength by isolating an individual muscle group and comparing power with that of the subject. Table 2 below details the possible 8 levels of response. The scale is ordinal in nature, ranging from “no contraction of any muscle” (M0) to “complete recovery” (M5). This assessment will be evaluated during the baseline period as well as follow-up assessments at Weeks 4, 8, 12, 24, 36, and 48.

The percent of meaningful recovery responders will be summarized (counts and percentages) at all post-baseline visits, where meaningful recovery is defined as a return of sensory score of M3 or greater. Each subject may have more than one digital nerve tested. In the case that a subject has more than one nerve tested, the nerve with the highest baseline score will be used for analysis at each subsequent visit. Subjects with missing evaluations will imputed as detailed in Section 9.3. Statistical analysis will follow the same approach as for the MRCC sensory assessment and be conducted using the mITT population. See Appendix 6 for sample CMH code.

Individual subject results for MMRC motor assessment will be provided in a listing.

**Table 2 MRCC Motor Scoring**

| <b>Grade</b> | <b>Motor Recovery (of muscles innervated by this nerve)</b> |
|--------------|-------------------------------------------------------------|
| M0           | No contraction of any muscle                                |
| M1           | Flicker/trace contraction                                   |
| M2           | Active movement with gravity eliminated                     |
| M3           | Active movement against gravity                             |
| M4-          | Slight movement against resistance                          |
| M4           | Moderate movement against resistance                        |
| M4+          | Strong movement against resistance                          |
| M5           | Complete recovery                                           |

British Medical Research Council classification Highet and Sanders’ modification. © Crown Copyright (“Used with the permission of the Medical Research Council”)

### **Semmes-Weinstein Monofilament Test (SWMT):**

The SWMT comprises of using a sequence of hand-held filaments that apply an increasing level of standardized forces to the surface of the skin of the hand until the sensation can be observed by the subject. This study uses a set of 5 monofilament sizes, measured in gauges/forces. The filament will the lowest gauge able to register sensation from the subject is recorded. Table 3 below provides the correspondence of gauge to cutaneous sensation level. Both the hand on the injured side (or affected side) as well as the non-injured side (or contralateral side) will be tested to allow the subject to be used as their own control. Further, each hand will be tested in the following regions (median, ulnar, radial).

**Table 3 SWMT Filaments**

| <b>Filament Gauge</b> | <b>Sensation Level</b>          |
|-----------------------|---------------------------------|
| 2.83                  | Normal                          |
| 3.61                  | Diminished Light Touch          |
| 4.31                  | Diminished Protective Sensation |
| 4.56                  | Loss of Protective Sensation    |
| 6.65                  | Deep Pressure Only              |

Counts and percentages for subjects scored for each gauge will be summarized for baseline and all post-baseline visits. Individual scores will be given in a by-subject data listing using the mITT population.

The SWMT will be analyzed using responder/non-responder status, where meaningful response (responder) is defined as normal sensation (filament gauge 2.83); all other gauges are considered non-responders. A Cochran-Mantel-Haenszel (CMH) test, stratified by injury location, will be used to provide p-values for each visit. Only the injured side will be analyzed. Analysis will be conducted in the mITT population.

### **Pinch and Grip Strength:**

Pinch and grip strength testing is a standard method for assessing isometric strength of the hand and forearm muscles. All measurements record results in force values (lbs) for the following:

- Grip
- Key pinch
- Two-point pinch
- Three-point pinch

Both hands are to be tested (injured and uninjured) so that each subject can serve as their own internal control. Each grip and pinch test are repeated 3 times and an average calculated for analysis purposes. Hence the endpoint for analysis in each of the grip/pinch tests above will be the percentage of the injured hand average test results compared to the uninjured side ( $100 * \frac{\text{Ave. Force Injured}}{\text{Ave. Force uninjured}}$ ). The individual pinch and grip strength tests will be assessed during the baseline period as well as follow-up assessments at Weeks 4, 8, 12, 24, 36, and 48. A subject's ability to begin testing must be approved by the investigator; thus, for some subjects the injured side may be missing responses up to a certain visit.

The injured hand's *relative strength*, the ratio between injured and un-injured side, in pinch and grip tests will be summarized by visit using continuous descriptive statistics in the mITT

population. Exploratory analyses will also be performed using the mITT population. For each of the four measurements, MMRM will be used, using the factors below. Kenward-Rogers adjustment for degrees of freedom will be used to adjust for small sample sizes. An unstructured covariance structure will be used initially. If the model fails to converge, other covariance structures that fit the study design will be used. Least square means, standard errors (SE), and one-sided p-values will be reported.

- Treatment
- Injury location
- Treatment by injury location interaction
- Visit
- Treatment by Visit interaction

Individual subject pinch and grip strength measurements for each side, as well as relative strength, will be provided in a listing using the mITT population.

### **Numeric Pain Rating Scale (NPRS):**

Subjects are asked to rate their pain based on an 11-point scale (0 = no pain, to 10 = worst pain imaginable). Subjects are asked to make three types of pain rating when considering the previous 24 hours: current pain, best pain, worst pain (Wang, 2013). The average of the 3 ratings will be used in analysis for representing a subject's level of pain. This pain assessment will be performed during the baseline period and follow-up assessments at Weeks 4, 8, 12, 24, 36 and 48. Subjects with missing post-baseline pain ratings at any visit will be excluded from particular visit results.

The change from baseline in the NPRS score will be summarized by visit using continuous descriptive statistics based on the mITT population. Analysis of the change from baseline in the NPRS score will be performed using MMRM. Model building and reporting will follow that performed for the primary endpoint, MHQ Total Score (see Section 11.1 and Appendix 6 for example SAS code).

Individual subject NPRS triplet of scoring results and the average result will be provided in a listing using the mITT population.

### **Cold Intolerance Symptom Severity (CISS):**

CISS is used to evaluate sensitivity of cold intolerance during daily life, and its onset is generally considered to occur within the first few months following injury. The CISS contains six questions with responses that have point values. Only questions 2 through 6 are used to add up individual question scores for a CISS total score. The table 4 below provides scoring per question and response. The CISS total score ranges from 0 to 100 (lower is better). This assessment will be performed during the baseline period and follow-up assessments at Weeks 4, 8, 12, 24, and 48. (Ruijs, 2006)

The change from baseline in the CISS total score will be summarized by visit using continuous descriptive statistics for the mITT population. Analysis of the change from baseline in the CISS will be performed using repeated measures mixed model (Mixed Model Repeated Measures – MMRM). Model building and reporting will follow that performed for the primary endpoint (MHQ, see Section 11.1).

Individual subject data collected for the CISS will be provided in a listing for the mITT population.

**Table 4 Cold Intolerance Symptom Severity (CISS) Scoring**

| Question                                                                                                                                                                                                        | Score <sup>*</sup> |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------|
| 1. Which of the following symptoms of cold intolerance do you experience in your injured limb on exposure to cold?<br>Pain, numbness, stiffness, weakness, aching, skin colour change (white/bluish white/blue) | Not scored         |
| 2. How often do you experience these symptoms? (Please tick)                                                                                                                                                    |                    |
| Continuously / all the time                                                                                                                                                                                     | 10                 |
| Several times a day                                                                                                                                                                                             | 8                  |
| Once a day                                                                                                                                                                                                      | 6                  |
| Once a week                                                                                                                                                                                                     | 4                  |
| Once a month or less                                                                                                                                                                                            | 2                  |
| Never <sup>†</sup>                                                                                                                                                                                              | 0                  |
| 3. When you develop cold induced symptoms, on your return to a warm environment are the symptoms relieved (please tick):                                                                                        |                    |
| Not applicable <sup>‡</sup>                                                                                                                                                                                     | 0                  |
| Within a few minutes                                                                                                                                                                                            | 2                  |
| Within 30 minutes                                                                                                                                                                                               | 6                  |
| After more than 30 minutes                                                                                                                                                                                      | 10                 |
| 4. What do you do to ease or prevent your symptoms occurring? (please tick)                                                                                                                                     |                    |
| Take no special action                                                                                                                                                                                          | 0                  |
| Keep hand in pocket                                                                                                                                                                                             | 2                  |
| Wear gloves in cold weather                                                                                                                                                                                     | 4                  |
| Wear gloves all the time                                                                                                                                                                                        | 6                  |
| Avoid cold weather / stay indoors                                                                                                                                                                               | 8                  |
| Other (please specify)                                                                                                                                                                                          | 10                 |
| 5. How much does cold bother your injured hand in the following situations (please score 0-10)                                                                                                                  |                    |
| Holding a glass of ice water <sup>‡</sup>                                                                                                                                                                       | 10                 |
| Holding a frozen package from the freezer <sup>‡</sup>                                                                                                                                                          | 10                 |
| Washing in cold water <sup>‡</sup>                                                                                                                                                                              | 10                 |
| When you get out of a hot bath/shower with air room temperature <sup>‡</sup>                                                                                                                                    | 10                 |
| During cold wintry weather                                                                                                                                                                                      | 10                 |
| 6. Please state how each of the following activities have been affected as a consequence of cold induced symptoms in your injured hand and score each (please score 0-4)                                        |                    |
| Domestic chores                                                                                                                                                                                                 | 4                  |
| Hobbies and interests                                                                                                                                                                                           | 4                  |
| Dressing and undressing                                                                                                                                                                                         | 4                  |
| Tying your shoe laces                                                                                                                                                                                           | 4                  |
| Your job                                                                                                                                                                                                        | 4                  |

<sup>\*</sup>In question one, patients are asked to score their symptoms as follows: "Please give each symptom a score between 0 and 10, where 0=no symptoms at all and 10=the most severe symptoms you can possibly imagine." However, the scores given in this question do not count towards the final CISS test score.

<sup>†</sup>These are two questions developed by Ruijs et al. to improve the scoring

<sup>‡</sup>These are the questions of the McCabe cold sensitivity test.

## Patient Global Impression of Change (PGIC):

The Patient Global Impression of Change (PGIC) assessment evaluates all aspects of subjects' health and assesses if there has been an improvement or decline in clinical status. This is a single question assessment asking, "Since beginning treatment at this clinic, how would you describe the change (if any) in ACTIVITY LIMITATIONS, SYMPTOMS, EMOTIONS, and OVERALL QUALITY OF LIFE, related to your painful condition?" There are 7 ordinal possible responses ranging from worst ("No change or condition as gotten worse") to best ("A great deal better and a considerable improvement that has made all the difference"). Please see Table 5 below for a full description. This assessment will be performed during the baseline period as well as follow-up assessments at Weeks 4, 8, 12, 24, and 48.

PGIC assessments will be summarized using categorical descriptive statistics by visit for the mITT population. Analysis of PGIC will use a responder analysis. A score of 5 through 7 will be categorized as a favorable response (responder), while responses 1 through 4 will be categorized as a non-favorable response (non-responder). A CMH test, stratified by injury location, will be used to provide p-values for responder status for each visit.

Individual subject PGIC assessments will be provided in a listing using the mITT population.

**Table 5 PGIC Responses**

| Response Number | Response                                                                            |
|-----------------|-------------------------------------------------------------------------------------|
| 1               | No change (or condition has gotten worse)                                           |
| 2               | Almost the same, hardly any change at all                                           |
| 3               | A little better, but no noticeable change                                           |
| 4               | Somewhat better, but the change has not made any real difference                    |
| 5               | Moderately better, and a slight but noticeable change                               |
| 6               | Better and a definite improvement that has made a real and worthwhile difference    |
| 7               | A great deal better and a considerable improvement that has made all the difference |

### **11.3.1 Sensitivity Analysis for Exploratory Secondary Endpoints**

The responder analysis models for SWMT, MRCC static and moving sensory scores, MRCC motor scores, and PGIC will be repeated as described in the above sections with all missing measurements being treated as non-responders. The NPRS and CISS analysis models will be repeated for the mITT population with any mITT subjects who dropped out prior to Week 48 removed.

## **12 SAFETY ASSESSMENT EVALUATION METHODS**

### **12.1 Adverse Events**

AEs will be recorded after a subject has received study medication. Therefore, all AEs recorded are considered to be treatment-emergent adverse events (TEAEs). Each verbatim AE term will be coded to a system organ class (SOC) and preferred term (PT) MedDRA version 21.0 or later.

Reported AEs will be summarized by the number of subjects reporting the events (and percentage), as well as by SOC, PT, severity, seriousness, and relationship to IP.

For the summary of AEs by severity, each subject will be counted only once within a SOC or a PT by using the AEs with the highest intensity within each category for each analysis. For the summary of AEs by relationship to study product, each subject will be counted only once within a SOC or PT by using the AEs with the greatest reported relationship within each category. For the summary of AEs by relationship to study product and severity, each subject will be counted only once within a SOC or PT by using (1) the greatest reported relationship followed by (2) the highest reported intensity.

Summaries of AEs by SOC and PT will be sorted by descending order of frequency of SOC within NTX-001 (then alphabetically for ties), then by descending order of frequency of PT within each SOC (then alphabetically for ties). Summaries of AEs by PT will be sorted by descending order of frequency of PT, then alphabetically for ties.

### **Overall Summary of AEs**

An AE overview containing the number of unique subjects and percentages will be provided for the following categories:

- Any TEAEs
- Any study drug related TEAEs
- Any TEAEs leading to study discontinuation
- Any study drug related TEAEs leading to study discontinuation
- Any serious adverse events (SAEs)
- Any study drug related SAEs
- Any TEAEs leading to death

## **Summary of AEs by SOC and PT**

The following will be summarized by SOC and PT if a meaningful number of AEs for each table are observed:

- Incidence of TEAEs
- Incidence of study drug related TEAEs
- Incidence of TEAEs leading to study discontinuation.
- Incidence of study drug related TEAEs leading to study discontinuation
- Incidence of TEAEs by worst severity (mild, moderate, severe)
- Incidence of SAEs
- Incidence of study drug related SAEs
- Incidence of TEAEs leading to death
- Incidence of TEASs by relationship to study product and severity
- Incidence of device-related TEAEs

All information pertaining to AEs noted during the study will be listed by subject, detailing verbatim term, SOC, PT, start date, stop date, intensity, outcome, and relationship to IP. The AE onset will also be shown relative (in number of days) to the day of IP administration.

Data listings of all TEAEs, all SAEs, TEAEs leading to death and TEAEs leading to study discontinuation will be provided.

## **12.2 Laboratory Tests**

### **Laboratory Values and Changes Over Time:**

Observed values of clinical chemistry and hematology, laboratory parameters at selected timepoints, and change from baseline in these parameters at each post-baseline time point, will be summarized descriptively. All laboratory test data will be listed by subject.

Potentially clinically significant (PCS) values will be summarized descriptively, including abnormal value criteria, which will be provided by the laboratories analyzing the samples.

## **12.3 Vital Signs**

### **Vital Sign Values and Change Over Time:**

Observed values of systolic blood pressure (SBP) (mmHg), diastolic blood pressure (DBP) (mmHg), pulse rate (bpm) and temperature (C), and change from baseline in these parameters at each post-baseline time point will be summarized descriptively by treatment group for the Safety Population.

Shift tables from baseline to each post-baseline visit and timepoint describing shifts in abnormality will be provided as well. See Table 6 below for abnormal ranges. Only subjects with a baseline result and a result at the specified post-baseline visit for the parameter will be considered.

Listings will be provided showing all subject level vital sign data collected.

**Table 6 Criteria for Abnormal Vital Signs**

| Parameter                | Flag | Criterion |
|--------------------------|------|-----------|
| Temperature              | High | >40°C     |
|                          | Low  | <35°C     |
| Weight                   | High | >150 kg   |
|                          | Low  | <38 kg    |
| Systolic Blood Pressure  | High | >140 mmHg |
|                          | Low  | <90 mmHg  |
| Diastolic Blood Pressure | High | >90 mmHg  |
|                          | Low  | <50 mmHg  |
| Pulse Rate               | High | >120 bpm  |
|                          | Low  | <40 bpm   |
| Respiratory Rate         | High | >30 bpm   |
|                          | Low  | <12 bpm   |

## 12.4 Physical and Occupational Therapy

Following upper extremity nerve reconstruction, rehabilitation is necessary to achieve optimal function and outcome. Compliance with post repair therapy will be assessed at each visit, Weeks 1, 4, 8, 12, 24, 36 and 48 as applicable. The data captured will be, did the subject attend prescribed PT/OT appointments as yes or no, as well as time from start to discontinuance of therapy in weeks (date of discontinuance – date of surgery).

A by-visit summary of the number of subjects attending physical therapy and occupational therapy. Percentage of subjects attending, especially at Week 12, will use the number of subjects

still in the study by that visit. Time from surgery to last therapy attended (date of last therapy – date of surgery) in weeks will also be summarized using univariate descriptive statistics.

## **12.5 Splint Assessments**

Splinting is required in a flexed or extended position as necessary to maintain minimal or acceptable tension. The splint assessment will consist of total splint time and if the subject complied with the splint post-operative instructions until removal based on clinical judgement. Splint assessments occur on Weeks 1, 4, 8, 12, 24, 36 and 48 as applicable.

A by-visit summary of the number of subjects with intact splints and compliant with it use. The percentages will be based on the number of subjects at that visit still in the study and who are still wearing a splint. Time from surgery to the removal of the splint (date of splint removal – date of surgery) will be summarized using univariate descriptive statistics.

## **13 REFERENCES**

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- MacKinnon SE, Dellon AL: Clinical nerve reconstruction with a bioabsorbable polyglycolic acid tube. *Plast Reconstr Surg* 85:419-424, 1990.
- Ruijs AC, Jaquet JB, Daanen HA, Hovius SE. Cold intolerance of the hand measured by the CISS questionnaire in a normative study population. *J Hand Surg Br.* 2006;31:533–6.
- Wang, Y., Sunitha, M., & Chung, K. (2013). How to Measure Outcomes of Peripheral Nerve Surgery. *Hand Clin*, 349-361

## 14 APPENDICES

### Appendix 1 Schedule of Assessments and Procedures

| Study Visit                               | V0                     | V1a    | V1b            | V1c     | V2                               | V3                               | V4                               | V5                                | V6                                | V7                                | V8                                |
|-------------------------------------------|------------------------|--------|----------------|---------|----------------------------------|----------------------------------|----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|
|                                           | <b>Baseline Period</b> |        |                |         |                                  |                                  |                                  |                                   |                                   |                                   |                                   |
|                                           | Screen                 | Pre-Op | Intra-Op       | Post-Op | W <sup>9</sup><br>1<br>+/-<br>2D | W <sup>9</sup><br>4<br>+/-<br>2D | W <sup>9</sup><br>8<br>+/-<br>2D | W <sup>9</sup><br>12<br>+/-<br>2D | W <sup>9</sup><br>24<br>+/-<br>5D | W <sup>9</sup><br>36<br>+/-<br>5D | W <sup>9</sup><br>48<br>+/-<br>5D |
| Informed Consent <sup>1</sup>             | X                      |        |                |         |                                  |                                  |                                  |                                   |                                   |                                   |                                   |
| Demographics                              | X                      |        |                |         |                                  |                                  |                                  |                                   |                                   |                                   |                                   |
| Inclusion/Exclusion                       | X                      | X      | X <sup>2</sup> |         |                                  |                                  |                                  |                                   |                                   |                                   |                                   |
| Smoking History                           | X                      |        |                |         |                                  |                                  |                                  |                                   |                                   |                                   |                                   |
| Class of Injury                           |                        |        | X <sup>2</sup> |         |                                  |                                  |                                  |                                   |                                   |                                   |                                   |
| Type-Nerve Injury                         | X                      |        |                |         |                                  |                                  |                                  |                                   |                                   |                                   |                                   |
| Medical History                           | X                      |        |                |         |                                  |                                  |                                  |                                   |                                   |                                   |                                   |
| Concurrent Injuries                       | X                      |        |                |         |                                  |                                  |                                  |                                   |                                   |                                   |                                   |
| Physical Exam                             | X                      |        |                |         |                                  |                                  |                                  | X                                 |                                   |                                   | X                                 |
| Vital Signs                               | X                      | X      | X              | X       | X                                | X                                | X                                | X                                 | X                                 | X                                 | X                                 |
| Labs (Pregnancy, Chem7, CBC)              | X                      |        |                |         |                                  |                                  |                                  | X                                 |                                   |                                   |                                   |
| Urine Pregnancy                           |                        |        |                |         |                                  |                                  |                                  | X                                 | X                                 | X                                 | X                                 |
| Date-Time Injury                          | X                      |        |                |         |                                  |                                  |                                  |                                   |                                   |                                   |                                   |
| EP <sup>8</sup>                           |                        |        |                |         |                                  |                                  |                                  | X <sup>8</sup>                    |                                   |                                   |                                   |
| CheckPoint <sup>®</sup> Stimulator        |                        |        | X              |         |                                  |                                  |                                  |                                   |                                   |                                   |                                   |
| MRCC s/m <sup>3, 4, 5, 6</sup>            | X <sup>4</sup>         |        |                |         |                                  | X                                | X                                | X                                 | X                                 | X                                 | X                                 |
| Grip/Pinch Strength <sup>3, 4, 6, 7</sup> | X <sup>4, 7</sup>      |        |                |         |                                  | X <sup>7</sup>                   | X <sup>7</sup>                   | X <sup>7</sup>                    | X <sup>7</sup>                    | X <sup>7</sup>                    | X <sup>7</sup>                    |
| SWMT <sup>3, 4, 5, 6</sup>                | X <sup>4</sup>         |        |                |         |                                  | X                                | X                                | X                                 | X                                 | X                                 | X                                 |
| MHQ <sup>4, 5, 6</sup>                    | X <sup>4</sup>         |        |                |         |                                  | X                                | X                                | X                                 | X                                 |                                   | X                                 |
| CISS <sup>4, 6</sup>                      | X <sup>4</sup>         |        |                |         |                                  | X                                | X                                | X                                 | X                                 |                                   | X                                 |
| PGIC <sup>4, 6</sup>                      | X <sup>4</sup>         |        |                |         |                                  | X                                | X                                | X                                 | X                                 |                                   | X                                 |
| NPRS <sup>4, 6</sup>                      | X <sup>4</sup>         |        |                |         |                                  | X                                | X                                | X                                 | X                                 | X                                 | X                                 |
| PT/OT Compliance until DC                 |                        |        |                |         | X                                | X                                | X                                | X                                 | X                                 | X                                 | X                                 |
| Splint Evaluation until DC                |                        |        |                |         | X                                | X                                | X                                | X                                 | X                                 | X                                 | X                                 |
| Concomitant Meds                          | X                      | X      | X              | X       | X                                | X                                | X                                | X                                 | X                                 | X                                 | X                                 |
| Adverse Events                            | X                      | X      | X              | X       | X                                | X                                | X                                | X                                 | X                                 | X                                 | X                                 |

1. No study related procedures conducted prior to obtaining ICF;
2. Intra-operative assessment, if the peripheral nerve injury does not meet Sunderland's, Fourth and Fifth Degree (Class III), the subject is considered a screen fail;
3. Assessments are conducted on the affected and contralateral sides;
4. Baseline values (except for Grip/Pinch Strength) are required assessments obtained at any time from fully executed consent to before or at Week 1 Visit
5. If the contralateral assessment of s2PD is > 10mm during baseline period; the subject will be a screen failure or early termination if done post-repair.
6. These assessments will be standardized in terms of sequence to mitigate questionnaire fatigue.
7. Grip/pinch strength will not be done until any type of splint is removed in digit or hand injuries and only with investigator approval.
8. Due to COVID restrictions, if still in place, the follow-up EP assessment will be done in the clinic at week 12.
9. Due to COVID-19 mitigations and restrictions remote in-home research visits will be conducted for all follow-up assessments, if the subject requests, or unless subject requires an in clinic due to adverse event or specific requirements for testing that cannot be done in the home.

## Appendix 2 Summary of Prospective Efficacy Analyses

The following efficacy analyses will be produced. Their methods and details are supported within the body of this document. The table below serves as a useful summary of all efficacy analyses prospectively declared by this statistical analysis plan.

**Table 1 Prospective Efficacy Analyses**

| Summary of Efficacy Analyses |              |                     |              |                  |
|------------------------------|--------------|---------------------|--------------|------------------|
| Parameter                    | Population   | Statistical Method  | Missing Data | Interpretation   |
| MHQ                          | mITT         | MMRM                | Implicit MAR | Primary analysis |
| MHQ                          | Per Protocol | MMRM                | Implicit MAR | Sensitivity      |
| MHQ                          | mITT         | CMH                 | Implicit MAR | Secondary        |
| MHQ                          | mITT         | Logistic Regression | Ignored      | Secondary        |
| EP                           | mITT         | Mixed Model         | Ignored      | Exploratory      |
| MRCC Sensory                 | mITT         | CMH                 | Ignored      | Exploratory      |
| MRCC Motor                   | mITT         | CMH                 | Ignored      | Exploratory      |
| SWMT                         | mITT         | CMH                 | Ignored      | Exploratory      |
| Pinch/Grip                   | mITT         | MMRM                | Implicit MAR | Exploratory      |
| NPRS                         | mITT         | MMRM                | Implicit MAR | Exploratory      |
| CISS                         | mITT         | MMRM                | Implicit MAR | Exploratory      |
| PGIC                         | mITT         | CMH                 | Ignored      | Exploratory      |
|                              |              |                     |              |                  |

## Appendix 3 Michigan Hand Questionnaire (MHQ) Scoring

The Michigan Hand Questionnaire (MHQ) contains 6 scales: (1) overall hand function, (2) activities of daily living, (3) work performance, (4) pain, (5) aesthetics and (6) satisfaction with hand function. Each scale contains generally 5 to 6 questions/items, and each item has responses that have five possible levels on an ordinal scale scored as numbers 1 through 5 (where ordinal values are inconsistent within these items and can present best to worst, or sometimes as worst to best). For this reason, the scoring calculation is different from scales that go best to worst vs. worst to best. Scoring direction is generally always consistent within a scale, with the exception of a couple of questions in the pain and aesthetics scales. For this reason, these items' scoring has to be recoded such that 1 becomes 5, 2 becomes 4, 3 remains a 3, 4 becomes a 2 and finally 5 becomes a 1.

The raw scale score for each of the 6 scales is the sum of the responses of each scale's individual items. The raw score is then converted to a normalized score range of 0 to 100. The scoring equation for each of the scales is listed below (refer to Table 8).

For MHQ items collected for both left- and right-hand, the affected side should be used for the final subscale score. Items where no differentiation is made between left- and right hand, scores

are used as is. For this study, when questions are differentiated between injured and non-injured side, only the side where the injury occurred will be used for scoring purposes.

Missing item responses may affect the validity of scoring. If 50% or more of the items for a subscale is missing, then that particular scale cannot be scored. For scales with less than 50% missing, the average of the existing scale items may be calculated. The MHQ Total Score is obtained by taking the average of the normalized scores of the individual non-missing scales scores. If scores for more than 2 scales are missing, the MHQ Total Score cannot be computed and will be missing.

Table 8 below provides a summary of the scoring features as well as the normalization formula when all items have been responded to in the scale. Please see section 9.3 (missing data handling) for the MHQ when scales have missing item responses. The normalization formulas must be adjusted to reflect a different range of raw scores in order to normalize correctly as 0 to 100.

**Table 8 MHQ Scoring Scales**

| <b>Scale</b>               | <b>Recode</b>                             | <b>Scale Direction</b> | <b>Raw Score Range</b> | <b>Normalization Formula (when all items have responses)</b>                                       |
|----------------------------|-------------------------------------------|------------------------|------------------------|----------------------------------------------------------------------------------------------------|
| Overall hand function      | None                                      | Best to worst          | 5 – 25                 | $100 \times (25 - \text{raw score}) / 20$                                                          |
| Activities of daily living | None                                      | Best to worst          | 5 – 25 1-handed        | $100 \times (25 - \text{raw score}) / 20$                                                          |
|                            |                                           |                        | 7 – 35 2-handed        | $100 \times (35 - \text{raw score}) / 28$                                                          |
|                            |                                           |                        | Overall ADL            | $(1\text{-handed} + 2\text{-handed}) / 2$                                                          |
| Work                       | None                                      | Worst to best          | 5 – 25                 | $100 \times (\text{raw score} - 5) / 20$                                                           |
| Pain                       | Item 2: (1→5), (2→4), (3→3), (4→2), (5→1) | Worst to best          | 5 – 25                 | If question 1 = 5, then score=0. If question 1 ≠ 5, then $100 \times (25 - \text{raw score}) / 20$ |

| <b>Scale</b>    | <b>Recode</b>                                   | <b>Scale Direction</b> | <b>Raw Score Range</b> | <b>Normalization Formula (when all items have responses)</b>                                        |
|-----------------|-------------------------------------------------|------------------------|------------------------|-----------------------------------------------------------------------------------------------------|
| Aesthetics      | Item 1: (1→5),<br>(2→4), (3→3),<br>(4→2), (5→1) | Worst to best          | 4 – 16                 | $100 * (\text{raw score} - 4) / 16$                                                                 |
| Satisfaction    | None                                            | Best to worst          | 6 – 30                 | $100 * (30 - \text{raw score}) / 24$                                                                |
| Total MHQ Score | None                                            | Best to worst          | None                   | [Overall Function + Activities of Daily Living + Work + (100- Pain) + Aesthetics + Satisfaction]/6* |

\*Use the normalized totals for each domain to calculate the normalized total MHQ score

#### Appendix 4 Imputation Rules for Missing or Partial Dates for AEs and Medical History

| Date          | Situation                                                                        | Imputation Rule                                    |
|---------------|----------------------------------------------------------------------------------|----------------------------------------------------|
| AE Start Date | Only month and year are known and month and year are prior to first dose date    | Use the first day of the month                     |
|               | Only month and year are known and month and year are the same as first dose date | Use the first administration date                  |
|               | Only month and year are known and month and year are after first dose date       | Use the first day of the month                     |
|               | Only year is known and year is before first dose date                            | Use Jan 1 of that year                             |
|               | Only year is known and year is after first dose date                             | Use Jan 1 of that year                             |
| AE End Date   | Only month and year are known and month and year are prior to last dose date     | Use the last day of the month                      |
|               | Only month and year are known and month and year are the same as last dose date  | Use the last observed date                         |
|               | Only month and year are known and month and year are after last dose date        | Use the last day of the month                      |
|               | Only year is known and year is before last dose date                             | Use Dec 31 of that year                            |
|               | The estimated stop date is before a complete or imputed AE start date            | Use the last day of the month of the AE start date |

AE = adverse event.

Note: The imputation of end date must be later than start date.

## Appendix 5 Imputation Rules for Missing or Partial Dates for Prior and Concomitant Medications and Medical Procedures

| Imputation rules for missing or partial dates (D = day, M = month, Y = year, T = time) |             |                                                                |                                      |
|----------------------------------------------------------------------------------------|-------------|----------------------------------------------------------------|--------------------------------------|
| Parameter                                                                              | Missing     | Additional conditions                                          | Imputation Rule                      |
| Start date                                                                             | D only      | M and Y same as M and Y of administration of study drug        | Date of administration of study drug |
|                                                                                        |             | M and/or Y not same as M and Y of administration of study drug | First day of month                   |
|                                                                                        | M and D     | Y same as Y of administration of study drug                    | Date of administration of study drug |
|                                                                                        |             | Y not same as Y of administration of study drug                | Use Jan 01 of Y                      |
| Stop date                                                                              | M, D, and Y | None--date completely missing                                  | Date of administration of study drug |
|                                                                                        | D only      | M and Y same as M and Y of last observation                    | Date of last observation             |
|                                                                                        |             | M and/or Y not same as M and Y of last observation             | Last day of month                    |
|                                                                                        | M and D     | Y same as Y of last observation                                | Date of last observation             |
|                                                                                        |             | Y not same as Y of last observation                            | Use Dec 31 of Y                      |
|                                                                                        | M, D, and Y | None--date completely missing                                  | Date of last observation             |

## Appendix 6            Select SAS code

### MHQ Total Score Repeated Measures Mixed Model:

```
proc sort data=MHQ_total_score;
  by usubjid visit;
run;

proc mixed data= MHQ_total_score maxiter=1000 maxfunc=5000;
  class trt visit inj_loc usubjid;
  model CHG = baseline trt visit trt*visit inj_loc trt*inj_loc / ddfm=kr;
  repeated visit/ type=un subject=usubjid;
  lsmeans trt*visit / diff CL;
  lsestimate trt*visit
    "Week 8" [1, 1 2] [-1, 2 2],
    "Week 12" [1, 1 3] [-1, 2 3],
    "Week 24" [1, 1 4] [-1, 2 4],
    "Week 48" [1, 1 5] [-1, 2 5]/ alpha = .05 upper;
run;
```

### CMH Test for Responder Analysis:

```
proc freq data=responder_data;
  tables inj_loc*trt*responder / cmh diff;
run;
```

# NTx20201\_SAP\_V3.0

Final Audit Report

2023-12-05

|                 |                                                |
|-----------------|------------------------------------------------|
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