Statistical Analysis Plan

Study Title:	A Phase 1/2a Dose Escalation Study of AST-OPC1 in Subjects with Subacute Cervical Spinal Cord Injury
Protocol Number:	AST-OPC1-01
Amendment:	Amendment 3 / 07 July 2017
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Version No./Date:	Version 1.0 / 03 Oct 2018

Signatory Page

This Statistical Analysis Plan was reviewed and approved by:

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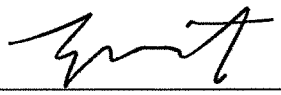

10/03/18

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Assistant Director, Biostatistics
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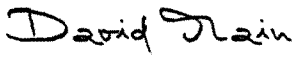

10/03/18

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10/5/18

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REVISION HISTORY

Version No.	Version Date	Description of Modifications
1.0	03 Oct 2018	Original Document

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1. LIST OF ABBREVIATIONS AND ACRONYMS

Abbreviations and Acronyms	Description
AE	Adverse Event
AIS	ASIA Impairment Scale
ASIA	American Spinal Injury Association
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
CDMS	Clinical Data Management System
CFB	Change From Baseline
CNS	Central Nervous System
CSR	Clinical Study Report
CSF	Cerebrospinal Fluid
DMC	Data Monitoring Committee
DPC	DP Clinical, Inc.
DVT	Deep Vein Thrombosis
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
GRASSP	Graded Redefined Assessment of Strength, Sensibility and Prehension
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ISNCSCI	International Standards for Neurological Classification of Spinal Cord Injury
kg	kilogram
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
ml	Milliliter
MRI	Magnetic Resonance Imaging
NLI	Neurological Level of Injury

Abbreviations and Acronyms	Description
ODS	Output Delivery System
PCFB	Percent Change From Baseline
PT	Preferred Term
QC	Quality Control
RTF	Rich Text File
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SCI	Spinal Cord Injury
SCIM	Spinal Cord Independence Measure
SD	Standard Deviation
SEM	Standard Error of the Mean
SOC	System Organ Class
SOP	Standard Operating Procedure
SPD	Syringe Positioning Device
TEAE	Treatment- Emergent Adverse Events
TLF	Tables, Listings, and Figures
UEMS	Upper Extremity Motor Score
WHODrug	World Health Organization Drug Dictionary
ZPP	Zone of Partial Preservation

2. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to document a more technical and detailed elaboration of the principal features stated in the protocol. This plan includes detail procedure for executing the efficacy analysis for the primary and secondary efficacy endpoints. Further analysis of safety variables (adverse events, clinical laboratory tests, vital signs, AST-OPC1 injection and MRI results) are described in greater detail in this document. Finally, the SAP will reasonably ensure that the tables which will be produced from these analyses, and the data listings, figures, and statistical methodologies that will be used, are complete and allow for the arrival of valid conclusions regarding the study objectives. In the development of this SAP, the following documents and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines were used:

- Protocol AST-OPC1-01, Amendment 3, 07 July 2017
- Electronic Case Report Form (eCRF) Casebook (31 Jul 2017)
- International Conference on Harmonisation (ICH) E3 (1995): Structure and Content of Clinical Study Reports (CSR)
- ICH E6 (R2) (2016): Guideline for Good Clinical Practice
- ICH E9 (1998): Statistical Principles for Clinical Trials

In the event that a discrepancy is found between the descriptions in the statistical section of the protocol and this document, the description in this document supersedes the descriptions in the statistical section of the protocol.

The DP Clinical, Inc. (DPC) Biostatistician is responsible for updating the SAP throughout the life of the study as needed. The responsible party at Asterias will be required to review and approve all versions of the SAP.

3. STUDY OVERVIEW

AST-OPC1-01 is an open-label, dose escalation, cross-sequential, multicenter Phase 1/2a study.

3.1 Study Objectives

3.1.1 Primary Objectives

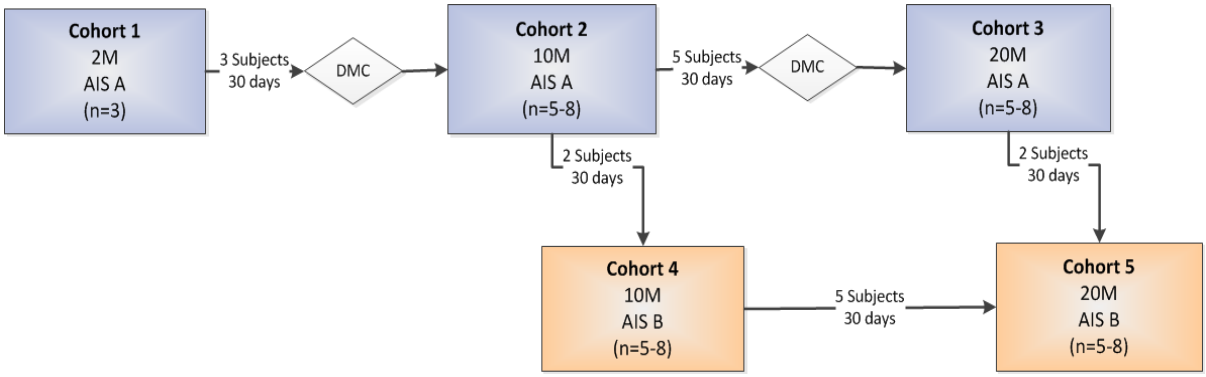
The primary objective of this study is to evaluate the safety of 3 sequential escalating doses of AST-OPC1 administered at a single time-point between 21 and 42 days post-injury, inclusive, to subjects with subacute cervical spinal cord injuries (SCI).

3.1.2 Secondary Objectives

The secondary objective is to evaluate changes in neurological function following administration of AST-OPC1.

3.2 Study Design

AST-OPC1-01 is an open-label, dose escalation, cross-sequential, multicenter Phase 1/2a study. Subjects with cervical AIS-A SCI will receive 1 of 3 sequential dose levels (2 x 10^6, 1 x 10^7 or 2 x 10^7) of AST-OPC1 injected directly into the spinal lesion within 21 and 42 days after the original injury. Subjects with cervical AIS-B SCI will receive 1 x 10^7, or 2 x 10^7 AST-OPC1 cells. All subjects will also receive low-dose tacrolimus for 60 days following injection to prevent immunological rejection. Subjects will be followed for safety and neurologic function for 1 year under this protocol and will then be required to participate in a companion long-term safety follow-up protocol for 14 years. In addition, eligible subjects who were enrolled and had pharmacological deep vein thrombosis (DVT) prophylaxis withdrawn in preparation for surgery, but who never received the AST-OPC1, will be followed for safety for 30 days and assessed separately. All adverse events (AE) will be monitored in an ongoing fashion by the Sponsor's medical monitor and by an independent Data Monitoring Committee.



Enrollment in Cohort 1 will be staggered such that there are at least 10 days between administrations of AST-OPC1 to each subject. Enrollment within Cohorts 2-5 will be staggered after the initial subject in each cohort is dosed, with at least 8 days between administration of AST-OPC1 to the first and second subjects. If the first two subjects are successfully dosed with no serious adverse events (SAE) that would trigger study suspension (per the study Suspension Rules), then the remaining subjects in that cohort may be dosed without further staggering.

An additional staggering rule for Cohorts 2-5 is that a minimum of 14 days must elapse between the dosing of any two consecutive subjects who both have a C4 neurological level of injury (NLI). This 14-day stagger for consecutive C4 NLI subjects applies throughout each of these cohorts and also would supersede the 8-day stagger noted above if the first two subjects in any cohort both have a C4 NLI.

Enrollment in Cohort 2 may commence after all three subjects in Cohort 1 have completed 30 days of follow up after AST-OPC1 administration and the safety data for Cohort 1 have been reviewed by the Data Monitoring Committee (DMC).

Enrollment in Cohort 3 may commence after at least five subjects in Cohort 2 have completed 30 days of follow up after AST-OPC1 administration and the safety data from Cohorts 1 and 2 have been reviewed by the DMC.

Enrollment in Cohort 4 may commence after at least two subjects in Cohort 2 have completed 30 days of follow up after AST-OPC1 administration and if there are no SAEs that would trigger study suspension.

Enrollment in Cohort 5 may commence after at least two subjects in Cohort 3 and at least five subjects in Cohort 4 have completed 30 days of follow up after AST-OPC1 administration and if there are no SAEs that would trigger study suspension.

For the planned DMC reviews noted above, the DMC will recommend whether enrollment of the next dose cohort can commence or whether additional follow up of the current cohort is needed prior to commencing enrollment in the next cohort.

The rationale for the 8-day stagger is that nearly all of the potential surgical complications, if they occur, will become clinically evident within the first few days after surgery. Thus, any serious complications (i.e., SAEs) would be evident within the first few days after surgery and would be reported within 24 hours of their occurrence (as required for all SAEs).

In addition, subjects in this study will receive a complete neurological exam and magnetic resonance imaging (MRI) scan for safety monitoring at 7 days after AST-OPC1 injection. The study suspension rules include several rules that could be triggered by potential complications of the AST-OPC1 injection procedure, such as: death or unexpected neurological deterioration, evidence of direct spinal cord damage related to the volume of injection, or any cerebrospinal fluid (CSF) infection or inflammation that is more than a transient reaction to AST-OPC1 injection.

On Injection Day subjects will receive the dose of AST-OPC1 as determined by cohort assignment (Table 1). AST-OPC1 may only be administered by a licensed surgeon who has both training and experience in performing intradural surgical procedures on the spine. In addition, each surgeon must be trained and qualified by the Sponsor on the use of the Syringe Positioning Device (SPD) and the injection procedure prior to their first administration of AST-OPC1.

Table 1: AST-OPC1 Dose Cohorts and Injection Preparation

Cohort	Dose (# of cells)	Concentration (cells/µL)	Volume per Injection (µL)	Number of Injections	Total Volume Administered (µL)
1	2×10^6	4×10^4	50	1	50
2	1×10^7	2×10^5	50	1	50
3	2×10^7	2×10^5	50	2	100
4	1×10^7	2×10^5	50	1	50
5	2×10^7	2×10^5	50	2	100

Between 6 and 12 hours after the AST-OPC1 dose, subjects will commence a course of the immunosuppressant tacrolimus, given orally at a starting dose of 0.03 mg/kg/day (divided into 2 daily doses) Days 1 through 46, tapered by 50% between Days 47 and 52 (rounding to the nearest 0.5 mg), tapered by another 50% on Day 53, and discontinued after 60 days.

If a subject is unable to take oral medication, tacrolimus may be given intravenously at a dose of 0.01 mg/kg/day as a continuous infusion, switching over to oral medication as soon as practicable. During intravenous infusion of tacrolimus, standard monitoring for acute anaphylaxis will be observed in accordance with approved labeling. Subjects will not be allowed to eat any grapefruit-containing food items through 60 days as this may alter the pharmacokinetics of tacrolimus.

Blood samples will be taken for monitoring blood levels of tacrolimus (immediately prior to the first daily dose if given orally) twice per week starting on Study Day 4 (+/- 1 day) and continuing for 30 days decreasing to once per week for 60 days (or through termination of tacrolimus) (see Section 7 of the protocol). Dosing of tacrolimus will be adjusted in order to maintain blood levels between 3 and 7 ng/mL. Additional monitoring of blood chemistry for possible tacrolimus toxicity will be as outlined in Section 7 of the protocol.

Tacrolimus dosing may be decreased or discontinued for unacceptable toxicity at the investigator's discretion; this might include infection or uncontrolled fever, liver function test elevation, creatinine elevation, seizure, or thrombotic thrombocytopenic purpura.

Subjects will receive a single administration of AST-OPC1. Subjects will be followed for 1 year post-injection of AST-OPC1 under this protocol and for an additional 14 years under a

companion long term follow-up protocol. Subjects must agree to and sign the informed consent for long-term follow-up in order to participate in this study.

All required tests and observations with their schedules are summarized in Section 3.2.2.

3.2.1 Sample Size Considerations

A total of 23-35 subjects were planned to receive AST-OPC1. Enrollment concluded on December 15, 2017 and a total of 25 subjects were enrolled and received AST-OPC1 across the five cohorts:

- Cohort 1: 3 Subjects
- Cohort 2: 6 Subjects
- Cohort 3: 6 Subjects
- Cohort 4: 6 Subjects
- Cohort 5: 4 Subjects

The sample size is based on the study design considerations for a Phase 1/2a study. This trial employs a cross-sequential cohort design for Phase 1 dose escalation in cervical AIS-A and AIS-B subjects. Power calculations have not been performed, as the primary objective is to collect safety and tolerability information on a limited number of subjects per dose level and AIS Grade, and an effect size cannot yet be estimated.

3.2.2 Study Assessments Schedules

Study assessments are described in detail in the protocol, and summarized below in Table 2.

Table 2: Summary of Study Procedures

Part A:

	Screen	Baseline	Surgery	Post-Injection		
	Days –11 to –3	Days –2 to –1	Injection Day	Days 1-6	Day 7	Days 8-29
Procedure					(+/- 1 day)	
Demographic data	X					
Past and current medical history	X					
Complete physical exam	X					
Brief physical exam		X		Day 1	X	
Vital signs	X	X[3]	X	Daily	X	
Neurological exam		X[5]			X	
ISNCSCI exam	X	X[1]			X	
GRASSP		X[5]				
SCIM		X[5]				
MRI[2]	Day -7 to -3				X	
ECG	X				X	
Hematology	X	X		Day 1	X	
Blood chemistry	X	X		Daily	X	2/week
Serology for HIV, HBV, HCV	X					
Panel reactive antibodies	X					
Pregnancy test, if applicable	X					
48-hour blood culture	Day –3					
Fasting blood glucose		X[4]				
Blood for HLA typing		X[5]				
Blood for immune response monitoring		X[5]			X	
Blood for xenotransplantation archival		X[5]				
Withhold DVT prophylaxis		Day -1				
CSF via lumbar puncture			X			
Begin tacrolimus			X			
Restart DVT prophylaxis				Day 1		
Tacrolimus blood levels				Day 3[6]	X	2/week
Concomitant medications	→					
Adverse events	→					

Part B:

Procedure	Day 30 (+/- 3 days)	Days 31-59	Day 60 (+/- 7 days)	Day 90 (+/- 7 days)	Day 180 (+/- 14 days)	Day 270 (+/- 14 days)	Day 365 (+/- 14 days)
Complete physical exam							X
Brief physical exam	X		X	X	X		
Vital signs	X		X	X	X		X
Neurological exam	X		X	X	X		X
ISNCSCI exam	X		X	X	X	X	X
GRASSP				X	X	X	X
SCIM questionnaire	X		X	X	X	X	X
Pain questionnaire	X			X	X		X
Bowel/Bladder questionnaire	X				X		X
MRI[2]	X				X		X
Hematology	X		X	X	X		X
Blood chemistry	X	1/week	X	X	X		X
Fasting blood glucose	X						
Blood for immune response monitoring	X		X	X	X		X
Tacrolimus blood level	X	1/week	X				
CSF via lumbar puncture			X				
Blood for xenotransplantation archival	X						X
Concomitant medications	→						
Adverse events	→						

Footnotes for Table 2, Parts A and B

1 ISNCSCI exam (may be performed on Day -3 to -1, unless the screening ISNCSCI was performed on Day -3)
2 MRI of cervical spine and brain at Screen & 1 Year; MRI of cervical spine only at Days 8, 31, 181
3 Vitals on day -2 and -1
4 May be done pre-op on Injection Day
5 May be performed as early as Day -4 if required to accommodate clinical site staff availability
6 Tacrolimus blood level on Day 4 may be obtained +/- 1 day

4. STUDY ENDPOINTS AND DEFINITIONS

4.1 Primary Endpoints

The primary endpoint of this Phase 1/2a study is safety and includes observations related to AST-OPC1 cells, the injection procedure, and the protocol-specified immunosuppression regimen. They include:

- Incidence, severity and relatedness of adverse events
- Changes in laboratory variables
- Changes at the injection site as monitored by MRI

Definitions relating to AEs and serious adverse events (SAE) are given in Section 10 of the protocol.

4.2 Secondary Endpoints

The secondary endpoints are changes in neurological function as measured on the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) examinations 30, 60, 90, 180, 270 and 365 days after AST-OPC1 injection. The endpoints will include:

- Upper Extremity Motor Scores (UEMS) - sum of motor score from C5 to T1
- Motor Level – defined by the lowest key muscle function that has a grade of at least 3 (on supine testing), providing the key muscle function represented by segments above that level are judged to be intact (graded as 5).

4.3 Exploratory Endpoints

Potential improvements in arm/hand function, self-care ability, and overall volitional ability will be evaluated by changes from baseline on the following endpoints:

- Graded and Redefined Assessment of Strength, Sensibility, and Prehension (GRASSP) is a quantitative measure of upper limb function in cervical SCI
- Spinal Cord Independence Measure (SCIM), particularly the SCIM self-care subscale, assesses the recovery of the ability of individuals with SCI to perform basic everyday tasks
- Changes in lower urinary tract and bowel function as assessed by the respective International Spinal Cord Injury Basic Data Set questionnaires
- Changes in post-treatment neuropathic pain as assessed by the International Spinal Cord Injury Pain Basic Data Set with regard to neuropathic pain.

4.4 Definitions

4.4.1 Study Day and Study Reference Period

Time will be measured as Study Day defined according to Clinical Data Interchange Standards Consortium (CDISC) standard. That is, the date of the AST-OPC1 injection is Study Day 0. The date before the AST-OPC1 injection is Study Day -1. Study day can be calculated as follows:

Study Day = visit date – date of AST-OPC1 injection

Last study day for a subject is the subject's last clinical visit date recorded on the subject status eCRF. If this date is missing for a subject, the last date found in the clinical database (e.g., clinical lab test date or date of vital sign collection) will be used as the last study date for the subject.

Total days on study are the total number of days a subject has been followed up after AST-OPC1 injection. Mathematically it can be calculated as follows:

Total days on study = last study date – date of AST-OPC1 injection + 1

4.4.2 Baseline and Change from Baseline

Unless indicated otherwise, change from baseline (CFB) will be calculated as follows, where the baseline assessment is the last assessment before AST-OPC1 injection:

- CFB = Value at Visit - Baseline

Percent change from baseline (PCFB) will be calculated as follow:

- PCFB (%) = 100*(Value at Visit - Baseline)/Baseline

5. STATISTICAL ANALYSIS GENERAL CONSIDERATIONS

5.1 Analysis Populations

Screened Population

The Screened Population will include all subjects who completed an informed consent form. This will be used for the purposes of summarizing disposition.

All Treated Population

The All Treated Population will include all subjects who received an injection of AST-OPC1. This will be used for all safety analyses.

Intent to Treat Population
The Intent to Treat Population will include all subjects who received an injection of AST-OPC1 in Cohorts 2 through 5. This population will be used for all efficacy analyses, and results will be presented for the overall, aggregated population.

Not Treated Population

The Not Treated Safety Population will include all subjects who have pharmacological deep vein thrombosis prophylaxis withdrawn in preparation for the surgery, but do not receive AST-OPC1. This population will have safety data collected for 30 days.

A topline summary of Adverse Events will be presented for the Not Treated Population, and no further data summaries will be presented for this population. The Not Treated Population will have the data listed with the Screen Failure subjects, separately from the All Treated Population.

5.2 Test Hypothesis and *P*-Value Justification

Because of the small sample size and study design, no formal statistical hypotheses will be tested.

5.3 Procedures for Handling Missing Data and Outliers

Missing or incomplete dates will be imputed per Section 6.2.2 for the purposes of determining treatment emergence. All other missing data will not be imputed, unless otherwise noted.

All unscheduled visit data will be included in data listings. In the data summary tables, the presence of missing data will be indicated by the inclusion of a ‘missing’ category with categorical data, and a count and percentage of missing observations for continuous numeric data, where applicable.

5.4 Interim Analysis

An interim analysis will be planned for September 2018 at the time of Cohorts 1-4 completing the Day 365 Visit and Cohort 5 completing the Day 180 Visit. All TLFs outlined in this SAP will be produced for the interim analysis.

5.5 Subgroup Analysis

Due to the small sample size and the design of the trial, no subgroup analyses will occur.

5.6 Multi-center Studies and Pooling of Centers

This is a multi-center study, but due to the small sample size and the design of the trial, no pooling of centers will occur.

6. STATISTICAL ANALYSIS METHODOLOGY

All data collected for this study will be presented in summary tables, listings, and figures (TLFs) as indicated in Appendix 1 of this SAP. Shells for TLFs with enough detail for programming will be provided as a guide to develop the programming SAS codes. These shells will be in sufficient detail to simulate the actual TLFs when they are created from the locked database.

Tabulations for continuous data will use a standard set of summary statistics: number of observations available (n), mean, standard deviation (SD), median, and range (minimum, maximum).

Categorical or dichotomous data will be tabulated using counts and percentages. The numerator and denominator for each percentage calculation will be specified in the footnotes of table shells.

Data listings will present all information recorded in eCRFs and any derived variable(s) included in the analysis datasets for all subjects and visits.

6.1 Study Subjects

6.1.1 Subject Disposition

Subject disposition will be presented for the Screened Population. The following will be presented in a disposition table:

- Number of subjects screened
- Number of subjects who enrolled but discontinued after DVT prophylaxis was withdrawn and before AST-OPC1 injection (Not Treated Safety Population)
- Number of subjects dosed with AST-OPC1 by cohort and overall (All Treated Population)
- Number and percentage of subjects who terminated prematurely before 1 Year Visit by cohort and overall
- Reason for premature termination before 1 Year Visit by cohort and overall
- Number and percentage of subjects who completed 1 Year Visit by cohort and overall

The number of subjects in the above categories will also be presented in a flow diagram figure.

A table with the number of screen failures and reason for screen failure will be produced.

6.1.2 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedure defined in the protocol.

The following categories will be used to group protocol deviations:

1. Eligibility not met
2. Study Assessment Noncompliance
3. Other

The following are categorical reasons used to document why a protocol deviation occurred:

1. Subject illness
2. Clinical error
3. Investigator/staff decision
4. Other

A subset of the protocol deviations can be identified as an important protocol deviation as described below:

> Important Protocol Deviation: An important protocol deviation that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being.

At a time prior to the interim analysis and again prior to soft lock of database, all documented protocol deviations in the study will be reviewed to identify all important protocol deviations by a data review team including representatives from clinical operations, medical, data management, and statistics, and sent to the sponsor for approval. Final decisions will be documented and maintained by DPC.

A summary table of protocol deviations will be presented for the number and percentage of subjects in the following categories by cohort and overall:

- ≥1 protocol deviation.
- ≥1 important protocol deviation
- Important protocol deviation category
- Important protocol deviation reason
- Protocol deviation category
- Protocol deviation reason

6.1.3 **Demographics**

A demographic and baseline characteristics table will be presented for the All Treated Population by cohort and overall. The summary will include descriptive statistics for age, sex, race, ethnicity, weight, height, and BMI at baseline, as well as the AIS grade and cause of spinal cord injury.

6.1.4 Medical and Surgical History

At the Screening visit, the general medical and surgical procedures history will be recorded on the eCRF. Medical/Surgical History data will be summarized by MedDRA version 18.0 System Organ Class (SOC) and Preferred Term (PT).

6.1.5 Concomitant Medications

All prior and concomitant medications, interventions and procedures will be tabulated. Prior and concomitant medications will be coded to the therapeutic drug classes and generic drug names using the World Health Organization Drug (WHODrug) classifications version March 2015.

6.2 Safety Analysis

6.2.1 Exposure

Investigational product exposure and injection day data will be listed, including injection, lumbar puncture, and product label data.

6.2.2 Adverse Events

The collection period for adverse events for the purposes of this protocol begins once the subject has signed the informed consent form and ends after 365 days of observation. All adverse events will be listed by subject. The Medical Dictionary for Regulatory Activities (MedDRA) (Version 18) will be used to classify all adverse events by system organ class (SOC) and preferred term (PT).

A treatment emergent adverse event (TEAE) will be considered as any adverse event that starts on or after the date and time of the AST-OPC1 injection, or if an adverse event that started before the AST-OPC1 injection worsened after the administration of the investigational product. For the purposes of determining treatment emergent adverse events, missing or partial AE start dates will be imputed with the following rules:

1) If onset date is completely missing, then onset date is set to date of first dose
2) If year is present and month and day are missing:
    a. If year = year of AST-OPC1 dose, then set date to AST-OPC1 dose date
    b. If year < year of AST-OPC1 dose and medication AE end month and year are available, then set to first of the AE end month
    c. Otherwise if year < year of AST-OPC1 dose, then set month and day to December 31st.
    d. If year > year of AST-OPC1 dose, then set month and day to January 1st.
3) If month and year are present and day is missing:
    a. If year = year of AST-OPC1 dose and
        i. If month = month of AST-OPC1 dose then set day to day of AST-OPC1 dose date

ii. If month ≠ month of AST-OPC1 dose then set day to first day of month

b. If year ≠ year of AST-OPC1 dose then set day to first day of month

4) If the AE start date is completely missing and the corresponding stop date is completely missing, the AE start date will remain missing.

A topline summary of treatment emergent adverse events with the number of events, number of subjects, and percentage of subjects for each category below will be tabulated by cohort and overall:

- Any TEAE and SAE
- Subjects Reporting at least one TEAE or TE SAE that has severity Grade 3 or higher that is also related to AST-OPC1, injection procedure, or tacrolimus
- TEAE and SAE Severity: Grade 1/Mild, Grade 2/Moderate, Grade 3/Severe, Grade 4/Life Threatening/Disabling, Grade 5/Fatal
- Categories for TEAE and TE SAE with possible relationship to: AST-OPC1, injection procedure, tacrolimus

The following tables will be presented for the number and percentage of subjects by cohort and overall:

- TEAE by preferred term sorted by descending number of overall events
- TEAE by SOC, PT, and maximum severity*
- Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Possible Relationship to AST-OPC1, Injection Procedure, and Tacrolimus Treatment emergent SAE by SOC, PT, and maximum severity*
- TEAE of special interest by SOC and PT, defined as Urinary Tract Infections, Spasticity, and Neuropathic Pain based on an adjudication of adverse events by the biostatistics, data management, clinical, and sponsor teams.

*Subjects with >1 AE in respective category will only be counted once. For maximum severity tabulations, subjects will be counted once in the SOC and PT in the maximum severity.

6.2.3 Clinical Laboratory Tests

Summary statistics (N, mean, standard deviation, median, minimum, and maximum) will be tabulated for chemistry, hematology, and liver function laboratory parameters during each period (Screening Visit, Baseline Visit, Post-Injection Days 1-6 Period, Day 7 Visit, Post-Injection Days 8-14 Period, Post-Injection Days 15-21 Period, Post-Injection Days 22-29 Period, Day 30 Visit, Post-Injection Days 31-37 Period, Post-Injection Days 38-44, Post-Injection Days 45-51 Period, Post-Injection Days 52-59 Period, Day 60 Visit, Day 90 Visit, and Day 180 Visit, and Day 365 Visit, as applicable by laboratory parameter) by cohort and overall. N will be calculated as the number of subjects with ≥1 assessment for the given parameter during the period. If a subject has >1 reading during a time period, the mean of the subject's results will be used for the calculation of the mean, SD, and median. For the

minimum and maximum summary statistics, the minimum and maximum results taken during any assessment within cohort and overall during the time period will be used.

A table counting abnormal flags of the most abnormal value by time period will be generated for each cohort and overall. For each subject, the most abnormal value for a parameter will be taken as the maximum of the absolute value of (lab result – lower reference range) and the absolute value of (lab result – upper reference range) during the time period. At each visit, for each parameter, the number of subjects with low, normal, high, and clinically significant assessments will be tabulated.

Other samples taken, including immune response, xenotransplantation, blood culture, blood glucose, antibodies, and tacrolimus blood level measurement will be listed.

6.2.4 Magnetic Resonance Imaging (MRI)

All study-driven MRI reading will be performed by a central group of neuroradiologists with extensive experience in MRI evaluation of spinal cord trauma. The screening/baseline MRI will be used for eligibility and to make a preliminary determination of the target site for AST-OPC1 injection. Following AST-OPC1 injection, the MRI images will be assessed according to standard practice and with specific attention to the following potential risks:

- intramedullary hemorrhage, CSF leak, epidural abscess, infection
- evidence of expanding cyst or mass at the injection site or elsewhere in CNS
- evidence of inflammatory lesion(s) at injection site or elsewhere in CNS
- evidence of CSF flow obstruction

Several additional parameters may be measured for future research analyses. These may include:

- Length of contusion (i.e., maximal extent of petechial hemorrhages)
- Presence/absence of intramedullary hemorrhage
- Length of intramedullary hemorrhage
- Length of edema
- Percent compression at epicenter

An MRI listing will be produced from the central reader data. All MRI data will be assessed qualitatively.

6.2.5 Vital Signs

Summary statistics (N, mean, standard deviation, median, minimum, and maximum) will be tabulated for vital sign parameters during each period by cohort and overall. N will be calculated as the number of subjects with ≥1 assessment for the given parameter during the period. If a subject has >1 reading during a time period, the mean of the subject's results will be used for the calculation of the mean, SD, and median. For the minimum and maximum

summary statistics, the minimum and maximum results taken during any assessment within cohort and overall during the time period will be used.

6.2.6 Physical Exam

The number and percentage of subjects with normal, abnormal non-clinically significant, and abnormal clinically significant physical exam results at the Screening visit will be tabulated by parameter for each cohort and overall. For visits after the Screening visit, no change, non-clinically significant change, and clinically significant change will be tabulated at each visit by parameter for each cohort and overall.

Neurological examination results will be listed.

6.2.7 Electrocardiogram

The number and percentage of subjects with normal, abnormal non-clinically significant and abnormal clinically significant electrocardiogram readings at Screening and the 1 Week visit will be tabulated.

6.2.8 International Spinal Cord Injury Pain Basic Data Set

Pain will be assessed using the International Spinal Cord Injury Pain Basic Data Set Data Collection Form Version 2.0. All pain data will be listed.

Neuropathic pain will be summarized by cohort and overall as follows:

- The number and percentage of subjects that report ≥1 neuropathic pain at each visit
- The number and percentage of subjects that report ≥1 at-SCI-level neuropathic pain at each visit
- The number and percentage of subjects that report ≥1 below-SCI-level neuropathic pain at each visit
- Summary statistics of the average neuropathic pain intensity reported at each visit. If a subject reports > 1 neuropathic pain at a visit, the mean intensity for the subject will be used when calculating the summary statistics.

6.3 Efficacy Analyses

All efficacy data will be listed for all subjects. Efficacy summaries will be presented for the Intent to Treat Population.

6.3.1 ISNCSCI

ISNCSCI score data of Sensory Score, Neurological Sensory and Motor Scores, Neurological level, ASIA Impairment Scale and Zone of Partial Preservation (ZPP) levels will be listed for

each ISNCSCI examination completed at the Screening Visit, Day 7 Visit, Day 30 Visit, Day 60 Visit, Day 90 Visit, Day 180 Visit, Day 270 Visit and Day 365 Visit. Results of the ISNCSCI Sensory Scores, Motor Scores, Neurological Level and Zone of Partial Preservation (ZPP), and Anorectal Examination will be presented in listings.

Baseline for the ISNCSCI assessment will be defined as the Baseline Visit on Day -2 or Day -1.

Upper Extremity Motor Score (0-50) and change from baseline will be summarized with N, mean, standard deviation, 95% confidence interval, median, minimum, and maximum by for the overall Intent to Treat population. A positive change is considered improvement and a negative change is considered worsening.

Motor and sensory level at each visit and changes in motor/sensory level from baseline will be defined as:

> Change in Level = the number of levels the motor/sensory level has changed from baseline visit, where a positive number represents a change in the caudal direction and a negative number represents a change in the rostral direction. A change in the caudal direction is considered improvement while a change in the rostral direction is considered worsening.

The change in motor and sensory level will be tabulated as follows:

- Percentage of subjects with an ascending motor level on either side of the body relative to baseline
- Percentage of subjects with no motor level change on either side of the body relative to baseline
- Percentage of subjects with one motor level improvement on at least one side of the body relative to baseline
- Percentage of subjects with one motor level improvement on both sides of the body relative to baseline
- Percentage of subjects with a two or more motor level improvement on at least one side of the body relative to baseline

6.3.2 Spinal Cord Independence Measure

The Spinal Cord Independence Measure (SCIM) III will be assessed. SCIM III results at Baseline Visit will be used as the reference time point to assess changes in subjects' quality of life at the follow-up visits. The Spinal Cord Independence Measure (SCIM) III covers 19 tasks, all activities of daily living, grouped into four areas of function: Self-Care (Questions 1-4, scored 0-20), Respiration and Sphincter Management (Questions 5-8, scored 0-40), Mobility in Room and Toilet (Questions 9-11) and Mobility Indoors and Outdoors on Even Surface (Questions 12-17) (Mobility Questions 9-17, Scored 0-40). The final total SCIM III is the sum of all scores and score ranges from 0 to 100, with 0 being requiring total assistance and 100 being completely independent.

SCIM III total score and each domain score, with changes from baseline, will be summarized at each visit for the overall Intent to Treat Population.

6.3.3 Lower Urinary Tract Function

Lower urinary tract function will be assessed using the questionnaire from the International Spinal Cord Injury Data Sets – Lower Urinary Tract Function Basic Data Set – Data Form. The lower urinary tract data will be listed, and any changes from baseline, where the 1 Month Visit is considered the baseline visit, will be assessed qualitatively.

6.3.4 Bowel Function

Bowel function will be assessed using the questionnaire from the International Spinal Cord Injury Data Sets – Bowel Function Basic Data Set – Data Form. The bowel function data will be listed, and any changes from baseline, where the 1 Month Visit is considered the baseline visit, will be assessed qualitatively.

6.3.5 The Graded Redefined Assessment of Strength, Sensibility and Prehension

The Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP) is a multimodal test comprising 5 subtests on the left and right side for each upper limb: dorsal sensation (3 subscores 0-4; total 0-12 for each side), palmar sensation (3 subscores 0-4; total 0-12 for each side), strength (tested with motor grading of 10 muscles 0-5; total 0-50 for each side), qualitative prehension (3 tasks 0-4; total 0-12 for each side), and quantitative prehension (6 tasks scored 0-5; total 0-30). Baseline GRASSP scores will be taken from the Baseline visit. A higher score represents improvement while a lower score represents worsening.

GRASSP subscores and subtest total scores will be presented in listings, where applicable. GRASSP subtest total scores for Total Strength (0-100), Total Quantitative Prehension (0-60), and Total Sensation (0-48), with changes from baseline (where the Baseline Visit on Day -2 to -1 will be considered the baseline), will be summarized at each visit for the overall Intent to Treat Population. Total Qualitative Prehension (0-24) summary statistics will be presented at each visit without change from baseline due to different baseline study visits across protocol amendments.

7. TESTING/QUALITY CONTROL PLAN AND SOFTWARE/SYSTEM

All statistical programs will be written in SAS® version 9.3. Statistical programs will be tested and reviewed for Quality Control (QC) by a second programmer/biostatistician not involved in the programming as per DP Clinical (DPC)'s standard operating procedure (SOP). In addition, DPC's SOP will be followed to ensure that the information is complete, consistent, and accurately reflects the data stored in Clinical Data Management System

(CDMS) database. Further all tables, listings, and figures (TLFs) will undergo a QC process by an independent biostatistician/programmer to ensure that the information is complete, consistent, and accurately reflects the data stored in CDMS.

7.1 Programming Specifications for TLFs

Appendix 1 provides a list of all the TLFs that are planned to be produced.

7.2 Formatting Conventions

The following formatting conventions will be used to output TLFs:

- TLFs are outputted by SAS Output Delivery System (ODS) into Rich Text File (RTF) format.
- Tables and Listings will include borders around all headings and data cells.
- Output will be in landscape orientation with margins of 1.5 inches on top, and 1 inch for right, left, and bottom.
- The default font to be in tables/listings/figures will be Courier New.
- Preferred and minimum font size:

Portion of Output	**Preferred**	**Minimum**
Page Header	10 pt	8 pt
Title	10 pt	8 pt
Column header	10 pt	8 pt
Cells	10 pt	8 pt
Footnote	10 pt	8 pt
Page Footer	10 pt	8 pt

- Data will be centered within columns when the maximum length of the data being displayed is less than or equal to the maximum width of the column heading. When the maximum length of the data being displayed exceeds the maximum width of the column heading, the data will be left-justified.
- Column headings should be in initial capital characters. For numeric variables, include “unit” in the column heading when appropriate.
- In figures, axes will be labeled appropriately.

7.3 Standard Text Conventions

7.3.1 Header

All output (table, listing, or figure) will have the following header:

[Sponsor Name]
Protocol: [Protocol Number] Page xx of XX

All output will have the date and time (date and time output was generated) and internal page number in the footer. Tables/Listings/Figures should be internally paginated (i.e., page numbers should appear sequentially within each output).

7.3.2 Title

At least three (3) lines, in general, will be reserved for the entire title.

- The first line is for the table/listing/figure number;
- The second line is for the actual title; and
- The third line is reserved for the analysis population descriptor.

All titles will be centered, as shown in the following example:

Table 14.3.2.1
Overall Incidence of Safety Events
Safety Population

7.3.3 Footnotes

Unless otherwise specified, footnotes will appear on all pages within the tables and listings as follows:

- Footnotes will be in the format of "NOTE: followed by 2 spaces, then the footnotes", as shown in the following example:

Note: SD = Standard Deviation; SEM = Standard Error of the Mean.

- Each line of a complete footnote should end with a period.
- When an abbreviation (e.g. AE, SAE, etc.) appears first time in the whole set of TLFs for a study, a footnote should be provided at least once; and it is up to the study statistician, to decide whether there is a need to repeat the same footnote for the rest of TLFs.
- A footnote serves as a brief explanation/clarification/definition /concept of a flag symbol or a character, an abbreviation, a terminology, etc., that appears in or relates directly to the displayed content of a table/listing/figure.
- Footnotes will not contain detailed/technical elaboration of, for example, a mathematical/statistical formula, a statistical term/test, or an algorithm for deriving a parameter value, which should be addressed in the text of the SAP.
- All footnotes will be at the lowest line of the page immediately above the footer. There will be one space between the last footnote and the footer.
- For Tables, first footnote will provide source listings and/or analysis datasets names for cross-referencing.

7.3.4 Footer

The following footer should appear at the very bottom of each page of a table, a listing, or a figure generated in SAS in the lower left corner:

Program: PGNAME.sas; Creation Date and Time: MMDDDYYYY HH:MM
Data Cutoff: DDMMMYY:HH:MM:SS – Listing Generated MMM DD, YYYY

Where PGNAME = SAS program name.

7.4 Statistical Conventions

7.4.1 Statistics Reported

- Unless otherwise specified, the mean and standard deviation (SD) will be displayed to one more decimal place than the original value, while minimum and maximum will be reported in the format of the original data, e.g.:

  Original: xx
  Mean and SD: xx.x
  Minimum and maximum: xx

- Descriptive statistics in this template include: **Mean, Median, Standard Deviation (SD), Standard Error of Mean (SEM), Minimum, Maximum, and N**. In addition, 95% CI will be presented when appropriate.

- Unless specified in the actual TLF shells for a study, all percentages will be rounded to 1 decimal place in all tables/listings/figures. Rounding will take place after all calculations have been performed.

- Use of N versus n:
  N = total number of subjects or subjects in the population.
  n = total number of subjects or subjects in the specific category.

7.4.2 SAS Procedure Output

If appropriate, SAS procedure output may be formatted and saved as source for references and will be included in Appendix.

7.4.3 Tables Summarizing Categorical Data

The following specifications apply to tables that summarize categorical data:

- Percent of events should be left blank (including the parentheses) if the number of events is zero.
- If the categories of a parameter are ordered, then all categories between the maximum possible category and the minimum category will be included, even if n=0 for a given category between the minimum and maximum level for that parameter.

- If the categories are not ordered, then only those categories for which there is at least one subject represented will be included.
- A missing category will be added to any parameter for which information is not available for any subjects.

7.4.4 **Subject Data Listings**

In general, individual subject data listings should include all subjects with data. However, if a subject data listing includes only subjects who met a certain condition, and there were no subjects who met that condition, then a "message" will appear indicating that no subjects met the condition for inclusion in that listing.

8. REFERENCES

ICH E3 (1995): Structure and Content of Clinical Study Reports. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

ICH E6 (R2) (2016): Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

ICH E9 (1998): Statistical Principles for Clinical Trials. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

MedDRA Version 18.0 (Mar 2015). International Federation of Pharmaceutical Manufacturers and Associations (IFPMA).

The WHO Drug Dictionary (WHO-DD) (Mar 2015). World Health Organization (WHO) Uppsala Monitoring Center (UMC).

SAS® for Windows® Version 9.3. SAS Inc. Cary, North Carolina USA.

9. APPENDICES

9.1 Planned Tables, Listings, and Figures

Table Number	Table Name	Population
Table 14.1.1.1	Subject Disposition	Screened Population
Table 14.1.1.2	Reasons for Screen Failures	Screened Population
Table 14.1.2	Demographics	All Treated Population
Table 14.1.3	Medical and Surgical History	All Treated Population
Table 14.1.4	Prior and Concomitant Medications	All Treated Population
Table 14.2.1.1	ISNCSCI Upper Extremity Motor Score and Change from Baseline	Intent to Treat Population
Table 14.2.1.2.1	ISNCSCI Motor Level and Improvement from Baseline	Intent to Treat Population
Table 14.2.1.2.2	ISNCSCI Sensory Level and Improvement from Baseline	Intent to Treat Population
Table 14.2.2	Spinal Cord Independence Measure III and Changes from Baseline	Intent to Treat Population
Table 14.2.3	GRASSP and Changes from Baseline	Intent to Treat Population
Table 14.3.1.1.1	Topline Summary of Treatment Emergent Adverse Events	All Treated Population
Table 14.3.1.1.2	Topline Summary of Adverse Events Prior to Treatment	Not Treated Population
Table 14.3.1.2	Treatment Emergent Adverse Events by Preferred Term in Descending Order of Total Events	All Treated Population
Table 14.3.1.3	Treatment Emergent Adverse Events by System Organ Class, Preferred Term and Possible Relationship to AST-OPC1, Injection Procedure, and Tacrolimus	All Treated Population
Table 14.3.1.4	Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity	All Treated Population
Table 14.3.2.1	Treatment Emergent Serious Adverse Events by System Organ Class, Preferred Term, and Maximum Severity	All Treated Population
Table 14.3.2.2	Treatment Emergent Adverse Events of Special Interest	All Treated Population
Table 14.3.4.1.1	Chemistry Laboratory Summary	All Treated Population
Table 14.3.4.1.2	Chemistry Laboratory Result Flags	All Treated Population
Table 14.3.4.1.3	Chemistry Laboratory Results By Subject	All Treated Population
Table 14.3.4.2.1	Hematology Laboratory Summary	All Treated Population
Table 14.3.4.2.2	Hematology Laboratory Result Flags	All Treated Population
Table 14.3.4.2.3	Hematology Laboratory Results By Subject	All Treated Population
Table 14.3.4.3.1	Liver Function Chemistry Laboratory Summary	All Treated Population
Table 14.3.4.3.2	Liver Function Chemistry Laboratory Result Flags	All Treated Population
Table 14.3.4.3.3	Liver Function Laboratory Results By Subject	All Treated Population
Table 14.3.5	Vital Signs Summary	All Treated Population
Table 14.3.6	Electrocardiogram Summary	All Treated Population
Table 14.3.7	Physical Examination Summary	All Treated Population
Table 14.3.8.1	Neuropathic Pain Assessments	All Treated Population
Table 14.3.8.2	Average Neuropathic Pain Intensity	All Treated Population

Figure Number	Figure Name	Population
Figure 14.1.1.1	Subject Disposition	Screened Population

Listing Number	Listing Name	Population
Listing 16.2.1.1	Subjects Not Meeting Inclusion/Exclusion Criteria	Screened
Listing 16.2.1.2	Disposition/Subject Status	Screened
Listing 16.2.1.3	Reconsent to Long Term Follow Up	All Treated
Listing 16.2.2.1-.2	Protocol Deviations	All Treated / Screen Failure and Not Treated
Listing 16.2.4.1.1-.2	Demographics	All Treated / Screen Failure and

		Not Treated
Listing 16.2.4.2.1.1-.2	Medical and Surgical History	All Treated / Screen Failure and Not Treated
Listing 16.2.4.2.1.2-.2	Deep Vein Thrombosis (DVT) Pharmacological Prophylaxis	All Treated / Screen Failure and Not Treated
Listing 16.2.4.3.1.1-.2	Concomitant Medications	All Treated / Screen Failure and Not Treated
Listing 16.2.4.3.2.1-.2	Tacrolimus Administration Log	All Treated
Listing 16.2.4.3.3.1-.2	Tacrolimus Blood Level	All Treated
Listing 16.2.5.1	Lumbar Puncture	All Treated
Listing 16.2.5.2	AST-OPC1 Injection	All Treated
Listing 16.2.5.3	Product Label	All Treated
Listing 16.2.6.1.1.1-.2	ISNCSCI Sensory	All Treated / Screen Failure and Not Treated
Listing 16.2.6.1.2.1-.2	ISNCSCI Motor	All Treated / Screen Failure and Not Treated
Listing 16.2.6.1.3.1-.2	ISNCSCI Summary	All Treated / Screen Failure and Not Treated
Listing 16.2.6.1.4.1-.2	ISNCSCI Anorectal/Non-Key Muscles	All Treated / Screen Failure and Not Treated
Listing 16.2.6.2.1.1-.2	GRASSP Strength/Prehension	All Treated / Not Treated
Listing 16.2.6.2.2.1-.2	GRASSP Sensibility	All Treated / Not Treated
Listing 16.2.6.3.1.1-.2	SCIM Scores	All Treated / Not Treated
Listing 16.2.6.4.2.1-.2	SCIM Summary	All Treated / Not Treated
Listing 16.2.6.4	Pain Assessment	All Treated
Listing 16.2.6.5	Bowel Function Assessment	All Treated
Listing 16.2.6.6	Lower Urinary Tract Function	All Treated
Listing 16.2.7.1.1-.2	Adverse Events	All Treated / Screen Failure and Not Treated
Listing 16.2.7.2.1-.2	Serious Adverse Events	All Treated / Screen Failure and Not Treated
Listing 16.2.8.1.1-.2	Chemistry Labs	All Treated / Screen Failure and Not Treated
Listing 16.2.8.2.1-.2	Hematology Labs	All Treated / Screen Failure and Not Treated
Listing 16.2.8.3.1-.2	Liver Function Labs	All Treated / Screen Failure and Not Treated
Listing 16.2.8.4.1-.2	Antibody Tests	All Treated / Screen Failure and Not Treated
Listing 16.2.8.5.1-.2	Blood Cultures	All Treated / Screen Failure and Not Treated
Listing 16.2.8.6.1-.2	Blood Glucose	All Treated / Not Treated
Listing 16.2.8.7.1-.2	Human Leukocyte Antigen (HLA) Typing	All Treated / Not Treated
Listing 16.2.8.8.1-.2	Serum Pregnancy	All Treated / Screen Failure and Not Treated
Listing 16.2.9.1.1-.2	Vital Signs	All Treated / Screen Failure and Not Treated
Listing 16.2.9.2.1-.2	Vital Signs Outside of Normal Range	All Treated / Screen Failure and Not Treated
Listing 16.2.10.1-.2	MRI	All Treated / Screen Failure and Not Treated
Listing 16.2.11.1-.2	ECG	All Treated / Screen Failure and Not Treated
Listing 16.2.12.1-.2	Physical Exam	All Treated / Screen Failure and Not Treated
Listing 16.2.13.1-.2	Neurological Exam	All Treated / Not Treated
Listing 16.2.14	Pain Assessment	All Treated
Listing 16.2.15.1-.2	Comments	All Treated / Screen Failure and Not Treated