COVER PAGE

FAST STUDY (NCT04231409)
Study to Demonstrate the Value of Fast-Acting Subperception (FAST) using the Spectra WaveWriter™ Spinal Cord Stimulator System in the Treatment of Chronic Pain (A4070)

This serves as a cover page for the FAST Study – A Sub-study of COMBO Study (NCT03689920)

Version E (Current Version): 31 Jan 2020

Sponsored By
Boston Scientific Neuromodulation Corporation
25155 Rye Canyon Loop
Valencia, CA 91355
United States of America
Study to Demonstrate the Value of Fast-Acting Subperception (FAST) using the Spectra WaveWriter™ Spinal Cord Stimulator System in the Treatment of Chronic Pain

FAST Study
COMBO Sub-Study

A4070

CLINICAL INVESTIGATION PLAN

NCT03689920

Sponsored By
Boston Scientific Neuromodulation Corporation
25155 Rye Canyon Loop
Valencia, CA 91355
United States of America

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<td>To evaluate the effectiveness of Spinal Cord Stimulation (SCS) with fast-acting subperception (FAST) as compared to subperception SCS in patients with chronic pain when using the Boston Scientific Spectra WaveWriter SCS System.</td>
</tr>
<tr>
<td><strong>Secondary Objectives</strong></td>
<td>To determine the impact of Spectra WaveWriter SCS System on global patient outcomes including quality of life, patient preference, etc.</td>
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<tr>
<td><strong>Indication(s) for Use</strong></td>
<td>The Spectra WaveWriter Spinal Cord Stimulator (SCS) System is indicated as an aid in the management of chronic intractable pain of the trunk and/or limbs, including unilateral or bilateral pain associated with the following: failed back surgery syndrome, Complex Regional Pain Syndrome (CRPS) Types I and II, intractable low back pain and leg pain.</td>
</tr>
<tr>
<td><strong>Commercial Device/System</strong></td>
<td>BSC Spectra WaveWriter™ SCS System</td>
</tr>
<tr>
<td><strong>Study Design</strong></td>
<td>Prospective, multi-center, parallel-group randomized controlled trial with an adaptive design</td>
</tr>
<tr>
<td><strong>Planned Number of Subjects</strong></td>
<td>Up to 148 randomized subjects</td>
</tr>
<tr>
<td><strong>Planned Number of Sites / Countries</strong></td>
<td>Up to 25 sites in the United States.</td>
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# FAST Study

A Study to Demonstrate the Value of Fast-Acting Subperception (FAST) using the Spectra WaveWriter™ Spinal Cord Stimulator System in the Treatment of Chronic Pain

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<th>Safety Parameters</th>
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</tr>
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<td>Proportion of subjects with 50% or greater reduction from Baseline Visit in average overall pain intensity at 3 months post-randomization, with no increase in baseline average daily opioid medications used to treat pain.</td>
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<td>Secondary Effectiveness Endpoint</td>
<td>Proportion of subjects who report clinically significant improvement in overall pain post-activation (Activation Questionnaire), change in average overall pain intensity from pre-activation to post-activation (Activation Questionnaire), change in overall pain intensity from Baseline Visit to 3 mo. post-randomization Visit (VRS), percent Pain Relief in overall pain at 3 mo. post-randomization Visit (PPR), patient global impression of change at 3 mo. post-randomization Visit (PGI-C), clinician global impression of change at 3 mos. post-randomization Visit (CGI-C), treatment satisfaction at 3 months post-randomization Visit (TSQM-9m), change in disability from Baseline Visit to 3 mos. post-randomization Visit (ODIv2.1a), change in sleep from Baseline Visit to 3 mos. post-randomization Visit (PSQI).</td>
</tr>
<tr>
<td>Exploratory Endpoints</td>
<td>Proportion of subjects who report clinically significant improvement in overall pain post-activation (Activation Questionnaire), change in average overall pain intensity from pre-activation to post-activation (Activation Questionnaire), change in overall pain intensity from Baseline Visit to 3 mo. post-randomization Visit (VRS), percent Pain Relief in overall pain at 3 mo. post-randomization Visit (PPR), patient global impression of change at 3 mo. post-randomization Visit (PGI-C), clinician global impression of change at 3 mos. post-randomization Visit (CGI-C), treatment satisfaction at 3 months post-randomization Visit (TSQM-9m), change in disability from Baseline Visit to 3 mos. post-randomization Visit (ODIv2.1a), change in sleep from Baseline Visit to 3 mos. post-randomization Visit (PSQI).</td>
</tr>
<tr>
<td>PRIMARY OUTCOME measure(s)</td>
<td>secondary outcomes</td>
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<tr>
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<tr>
<td>Change in average low back pain intensity from pre-activation to post-activation (Activation Questionnaire)</td>
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<td>Change in average leg pain intensity from pre-activation to post-activation (Activation Questionnaire)</td>
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<td>Change in average overall pain intensity from Baseline Visit to 6, 9, 12 and 24 months post-randomization Visits (VRS)</td>
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<td>Change in average low back pain intensity from Baseline Visit to 6, 9, 12 and 24 months post-randomization Visits (VRS)</td>
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<tr>
<td>Percent pain relief of overall pain at 6, 9, 12 and 24 months post-randomization Visits (PPR)</td>
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<tr>
<td>Percent pain relief of low back pain at 6, 9, 12 and 24 months post-randomization Visits (PPR)</td>
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<tr>
<td>Percent pain relief of leg pain at 6, 9, 12 and 24 months post-randomization Visits (PPR)</td>
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<tr>
<td>Clinician global impression of change at 6, 9, 12 and 24 months post-randomization Visits (CGI-C)</td>
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<tr>
<td>Patient global impression of change at 6, 9, 12 and 24 months post-randomization Visits (PGI-C)</td>
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<tr>
<td>Treatment satisfaction at 6, 9, 12 and 24 months post-randomization Visits (TSQM-9m)</td>
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<tr>
<td>Change in quality of life from Baseline Visit to 6, 9, 12 and 24 months post-randomization Visits (SF-36v2)</td>
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</tbody>
</table>
# FAST Study

A Study to Demonstrate the Value of Fast-Acting Subperception (FAST) using the Spectra WaveWriter™ Spinal Cord Stimulator System in the Treatment of Chronic Pain

## Follow-up Schedule

Study events occur at the following time points:
- Screening
- Opioid Medication Lock Visit (Up to 35 days following Informed Consent)
- Baseline Period (14 days)
- Baseline Visit (0 - 7 days post Baseline Period)
- Implant Procedures (up to 90 days post Baseline Visit)
- Healing Period (0 - 28 days)
- Randomization Visit (Day 0)
- Programming Lock Visit (70 - 14 days post-randomization Visit)
- 3 Month Visit (90 + 14 days post-randomization Visit)
- 6-Month Visit (180 ± 30 days post-randomization Visit)
- 9-Month Visit (270 ± 30 days post-randomization Visit)
- Year 1 Visit (365 ± 30 days post-randomization Visit)
- Year 2 Visit (730 ± 30 days post-randomization Visit)

## Study Duration

Enrollment is expected to be completed in approximately 14 months; therefore, the total study duration is estimated to be approximately 41 months.

## Participant Duration

The study duration for each subject is expected to be approximately 27 months.

## Inclusion Criteria

IC1. Chronic pain of the trunk and/or limbs for at least 6 months with back pain greater or equal to leg pain.
<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>IC3. No back surgery within 6 months prior to Screening</td>
<td></td>
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<tr>
<td>IC4. Average overall pain intensity (leg and/or low back pain) of 6 or greater on a 0-10 numerical rating scale at Baseline Visit based on 7-day recall</td>
<td></td>
</tr>
<tr>
<td>IC5. If taking prescription opioids for primary chronic pain complaint (low back and/or leg pain), must have been on a stable prescription (same drug(s) and dose(s)) 30 days prior to Screening</td>
<td></td>
</tr>
<tr>
<td>IC6. Consumed an average total daily morphine equivalent of ≤200 mg during the 30 days prior to Screening</td>
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<tr>
<td>IC7. Willing and able to comply with all protocol-required procedures and assessments/evaluations</td>
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<tr>
<td>IC8. Baseline Oswestry Disability Index score ≥40 and ≤80</td>
<td></td>
</tr>
<tr>
<td>IC9. 22 years of age or older when written informed consent is obtained</td>
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<tr>
<td>IC10. Eligible candidate for SCS from a psychological and psychiatric standpoint as determined within 180 days prior to Baseline Visit, per site’s routine screening process</td>
<td></td>
</tr>
<tr>
<td>IC11. Able to independently read and complete all questionnaires and assessments provided in English</td>
<td></td>
</tr>
<tr>
<td>IC12. If female of childbearing potential: not pregnant, as evidenced by a negative pregnancy test at Screening</td>
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<tr>
<td>IC13. Subject signed a valid, IRB-approved informed consent form (ICF) provided in English</td>
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<table>
<thead>
<tr>
<th>Exclusion Criteria</th>
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</thead>
<tbody>
<tr>
<td>EC1. Average leg pain intensity is greater than average low back pain intensity as reported during Baseline Period</td>
<td></td>
</tr>
<tr>
<td>EC2. Patient exhibits catastrophization based on physician evaluation (e.g., average overall daily pain intensity of 10 on a 0-10 numerical rating scale, every day during the 7 days prior to Screening, based on patient recall)</td>
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</tbody>
</table>
EC7. Any pain-related diagnosis or medical/psychological condition that, in the clinician’s best judgment, might confound reporting of study outcomes (e.g. pelvic pain, anginal pain, chronic migraine, brain or spinal cord tumor)

EC15. Significant cognitive impairment at Screening that, in the opinion of the Investigator, would reasonably be expected to impair the study candidate’s ability to participate in the study

EC16. Participating (or intends to participate) in another drug or device clinical trial that may influence the data that will be collected for this study
FAST Study
A Study to Demonstrate the Value of Fast-Acting Subperception (FAST) using the Spectra WaveWriter™ Spinal Cord Stimulator System in the Treatment of Chronic Pain

### Statistical Methods

| **Primary Statistical Hypothesis** | The primary statistical hypothesis in this study is that the proportion of subjects with 50% or greater reduction from Baseline Visit in average daily overall pain intensity at 3 months post randomization in the FAST group is non-inferior compared to the Control (i.e. subperception) group.

\[
\begin{align*}
H_0: \pi_t - \pi_c & \leq -0.20 \\
H_1: \pi_t - \pi_c & > -0.20
\end{align*}
\]

Where \(\pi_t\) and \(\pi_c\) are the proportion of subjects with 50% or greater reduction from Baseline in average daily overall pain intensity at 3 months post randomization with no increase in baseline average daily opioid pain medications using FAST and subperception settings, respectively. The study’s non-inferiority margin is 0.20. |
| **Statistical Test Method** | The 95% confidence interval of \(\pi_t - \pi_c\) will be computed. The study will be considered a success if, using the Intent-To-Treat (ITT) analysis, the lower bound of the two-sided 95% confidence interval for the difference is greater than -0.20. |
FAST Study
A Study to Demonstrate the Value of Fast-Acting Subperception (FAST) using the Spectra WaveWriter™ Spinal Cord Stimulator System in the Treatment of Chronic Pain

<table>
<thead>
<tr>
<th>Sample Size Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test significance level (α)</td>
</tr>
<tr>
<td>1 or 2 sided test</td>
</tr>
<tr>
<td>Difference in Response (πₜ - πₖ)</td>
</tr>
<tr>
<td>Non-inferiority margin (δ)</td>
</tr>
<tr>
<td>Proportion of Responder in Control group (πₖ)</td>
</tr>
<tr>
<td>Power (1- β)</td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>Attrition (%)</td>
</tr>
<tr>
<td>N</td>
</tr>
</tbody>
</table>

Interim Analysis
The study will have a total of four looks, with three interim analyses at:
- 20 randomized subjects at 3-Month Visit: futility stopping
- 60 randomized subjects at 3-Month Visit: futility and effectiveness stopping
- 100 randomized subjects at 3-Month Visit: effectiveness stopping

The adaptive design will use the Lan-DeMets group sequential method (Lan and DeMets 1983) with the O'Brien-Flemming α-spending function (O'Brien and Fleming 1979) and Pocock β-spending function (Pocock 1977).
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4. Introduction

This is an appendix to the COMBO Study and only contains information that is unique to this sub-study.

Information that is common to both is not repeated in this document.

5. Commercial Device Description (part of Standard of Care)

This is an appendix to the COMBO Study and only contains information that is unique to this sub-study.

Information that is common to both is not repeated in this document.

6. Study Objectives and Endpoints

6.1. Primary Objective

The primary objective of this study is to evaluate the effectiveness of Spinal Cord Stimulation (SCS) with fast-acting subperception (FAST) as compared to subperception SCS in patients with chronic pain when using the Boston Scientific Spectra WaveWriter SCS System.

6.2. Secondary Objective

The secondary objective of this study is to determine the impact of Spectra WaveWriter SCS System on global patient outcomes including quality of life, patient preference, etc.

6.3. Primary Endpoint

The primary endpoint is the proportion of subjects with 50% or greater reduction from the Baseline Visit in average overall pain intensity at 3 months post randomization, with no increase in baseline average daily opioid medications used to treat pain.

6.4. Secondary Endpoints
6.5. Exploratory Endpoints

The following exploratory endpoints will be evaluated. Assessments required for deriving each endpoint are denoted in parentheses.

- Change in average low back pain intensity from pre-activation to post-activation (Activation Questionnaire)
- Change in average leg pain intensity from pre-activation to post-activation (Activation Questionnaire)
- Change in average overall pain intensity from Baseline Visit to 6, 9, 12, and 24 months post-randomization Visits (VRS)
- Change in average low back pain intensity from Baseline Visit to 6, 9, 12, and 24 months post-randomization Visits (VRS)
- Change in average leg pain intensity from Baseline Visit to 6, 9, 12, and 24 months post-randomization Visits (VRS)
- Change in average overall pain intensity from Baseline Visit to 6, 9, 12, and 24 months post-randomization Visits (NRS)
- Change in average low back pain intensity from Baseline Visit to 6, 9, 12, and 24 months post-randomization Visits (NRS)
- Change in average leg pain intensity from Baseline Visit to 6, 9, 12, and 24 months post-randomization Visits (NRS)
- Percent pain relief of overall pain at 6, 9, 12, and 24 months post-randomization Visits (PPR)
- Percent pain relief of low back pain at 6, 9, 12, and 24 months post-randomization Visits (PPR)
- Percent pain relief of leg pain at 6, 9, 12, and 24 months post-randomization Visits (PPR)
6.6. **Safety Parameters**

Safety parameters include the rates of occurrence of all device hardware, device stimulation and procedure related non-serious adverse events, all serious adverse events, and unanticipated adverse events through the end of the study.

7. **Study Design**

The study is a prospective, multi-center, parallel group randomized controlled trial with an adaptive design. All participants will receive the Spectra WaveWriter Spinal Cord Stimulator (SCS) system and followed per the study schedule as shown in study schematic Figure 7.1-1.

7.1. **Scale and Duration**

The study will randomize up to 148 subjects at up to 25 investigational sites in the United States. Enrollment is expected to take approximately 14 months and a subject's participation in the study, from the point of enrollment until study completion, should last approximately 27 months. The study is expected to last approximately 41 months from the first patient enrolled until the end of study close-out activities.

Figure 7.1-1: FAST Study Design
7.2. Treatment Assignment

All enrolled subjects who pass eligibility criteria will receive a trial. Subjects with a positive trial will proceed to receive permanent implant. Following permanent implant, all subjects’ device will be randomized in a 1:1 ratio to either receive:

- WaveWriter Settings: Fast-acting subperception (FAST)
- Conventional Settings: Subperception

7.3. Justification for the Study Design

The study is a prospective, multi-center, parallel group randomized controlled trial with an adaptive design. The study is designed to demonstrate the value of fast-acting subperception for sustained clinically significant pain relief in patients with chronic pain when using the Boston Scientific Spectra WaveWriter SCS System. Additionally, the impact of the Spectra WaveWriter SCS System on global patient outcomes, quality of life and patient preference will also be evaluated.

A prospective study design will eliminate the bias associated with case selection in a retrospective review and will ensure that identical procedures are followed for data capture and review.
A multi-center design will minimize the impact on treatment outcome that may potentially result from differences in patient selection, regional differences in the patient demographic, and differences in investigator technique and patient management.

The study design includes two groups (arms) – WaveWriter group and Conventional group. The WaveWriter group will receive fast-acting subperception (FAST) as available in the WaveWriter SCS System while the conventional group will receive subperception programming. The Conventional group will serve as a control in this study. Randomization (1:1) will minimize selection bias and impact of demographic variables.

The primary endpoint is the proportion of subjects with 50% or greater reduction (responder rate) from the Baseline Visit in average overall pain intensity at 3 months post-randomization, with no increase in baseline average daily opioid medications used to treat pain. A 3-month endpoint was chosen as 3 months provides adequate time for a subject to have their programming parameters optimized.

8. Subject Selection

8.1. Study Population and Eligibility

Study candidates will be drawn from the population of patient’s resident in pain management or surgical medical practices. The study eligibility criteria are listed below.

8.2. Inclusion Criteria

Subjects who meet all of the following criteria (see Table 8.2-1) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see Section 8.3-1) is met.
### Table 8.2-1: Inclusion Criteria

<table>
<thead>
<tr>
<th>Clinical Inclusion Criteria</th>
<th>IC1. Chronic pain of the trunk and/or limbs for at least 6 months with back pain greater or equal to leg pain.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IC2. Chronic, intractable pain of the trunk and/or limbs which has been refractory to conservative therapy (E.g. pain medications, physical therapy, facet joint/medial branch nerve blocks.)</td>
</tr>
<tr>
<td></td>
<td>IC3. No back surgery within 6 months prior to Screening</td>
</tr>
<tr>
<td></td>
<td>IC4. Average overall pain intensity (leg and/or low back pain) of 6 or greater on a 0-10 numerical rating scale at Baseline Visit based on 7-day recall</td>
</tr>
<tr>
<td></td>
<td>IC5. If taking prescription opioids for primary chronic pain complaint (low back and/or leg pain), must have been on a stable prescription (same drug(s) and dose(s)) 30 days prior to Screening</td>
</tr>
<tr>
<td></td>
<td>IC6. Consumed an average total daily morphine equivalent of ≤200 mg during the 30 days prior to Screening</td>
</tr>
<tr>
<td></td>
<td>IC7. Willing and able to comply with all protocol-required procedures and assessments/evaluations</td>
</tr>
<tr>
<td></td>
<td>IC8. Baseline Oswestry Disability Index (ODI) score ≥40 and ≤80</td>
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<tr>
<td></td>
<td>IC9. 22 years of age or older when written informed consent is obtained</td>
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<tr>
<td></td>
<td>IC10. Eligible candidate for SCS from a psychological and psychiatric standpoint as determined within 180 days prior to Baseline Visit, per site’s routine screening process</td>
</tr>
<tr>
<td></td>
<td>IC11. Able to independently read and complete all questionnaires and assessments provided in English</td>
</tr>
<tr>
<td></td>
<td>IC12. If female of childbearing potential: not pregnant, as evidenced by a negative pregnancy test at Screening</td>
</tr>
<tr>
<td></td>
<td>IC13. Subject signed a valid, IRB-approved informed consent form (ICF) provided in English</td>
</tr>
</tbody>
</table>

### 8.3. Exclusion Criteria

Subjects who meet any one of the following criteria cannot be included in this study or will be excluded from this clinical study.

### Table 8.3-1 Exclusion Criteria
<table>
<thead>
<tr>
<th>Clinical Exclusion Criteria</th>
<th>EC1. Average leg pain intensity is greater than average low back pain intensity as reported during Baseline Period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EC2. Patient exhibits catastrophization based on physician evaluation (e.g., average overall daily pain intensity of 10 on a 0-10 numerical rating scale, every day during the 7 days prior to Screening, based on patient recall)</td>
</tr>
<tr>
<td></td>
<td>EC3. Radiographic evidence of spinal instability requiring fusion</td>
</tr>
<tr>
<td></td>
<td>EC4. Primary pain complaint of vascular origin (e.g. peripheral vascular disease)</td>
</tr>
<tr>
<td></td>
<td>EC5. Spinal pain secondary to neoplasm, infection, autoimmune disorder with spinal involvement, or a spinal metabolic disorder</td>
</tr>
<tr>
<td></td>
<td>EC6. Visceral pain referred to the low back and/or legs</td>
</tr>
<tr>
<td></td>
<td>EC7. Any pain-related diagnosis or medical/psychological condition that, in the clinician’s best judgment, might confound reporting of study outcomes (e.g. pelvic pain, anginal pain, chronic migraine, brain or spinal cord tumor)</td>
</tr>
<tr>
<td></td>
<td>EC8. Require implantation of lead(s) in the cervical epidural space</td>
</tr>
<tr>
<td></td>
<td>EC9. Current systemic infection, or local infection in close proximity to anticipated surgical field, at Screening</td>
</tr>
<tr>
<td></td>
<td>EC10. High surgical risk</td>
</tr>
<tr>
<td></td>
<td>EC11. Body mass index ≥ 45 at Screening</td>
</tr>
<tr>
<td></td>
<td>EC12. Terminal illness with anticipated survival &lt; 12 months</td>
</tr>
<tr>
<td></td>
<td>EC13. Current condition associated with risk of immunocompromise that might increase risk of infection during study duration</td>
</tr>
<tr>
<td></td>
<td>EC14. Currently on any anticoagulant medications that cannot be discontinued during perioperative period</td>
</tr>
<tr>
<td></td>
<td>EC15. Significant cognitive impairment at Screening that, in the opinion of the Investigator, would reasonably be expected to impair the study candidate’s ability to participate in the study</td>
</tr>
<tr>
<td></td>
<td>EC16. Participating (or intends to participate) in another drug or device clinical trial that may influence the data that will be collected for this study</td>
</tr>
<tr>
<td></td>
<td>EC17. Previous spinal cord stimulation trial or is already implanted with an active implantable device(s) (e.g. pacemaker, drug pump, implantable pulse generator)</td>
</tr>
<tr>
<td></td>
<td>EC18. A female who is breastfeeding</td>
</tr>
<tr>
<td></td>
<td>EC19. A female of childbearing potential planning to get pregnant during the course of the study or not using adequate contraception</td>
</tr>
</tbody>
</table>
9. Subject Accountability

9.1. Point of Enrollment

This is an appendix to the COMBO Study and only contains information that is unique to this sub-study.

Information that is common to both is not repeated in this document.

9.2. Withdrawal

This is an appendix to the COMBO Study and only contains information that is unique to this sub-study.

Information that is common to both is not repeated in this document.

9.3. Subject Status and Classification

This is an appendix to the COMBO Study and only contains information that is unique to this sub-study.

Information that is common to both is not repeated in this document.

9.4. Enrollment Controls
The study will implement a formal *Enrollment Communication Plan*. The plan will outline the specific activities, as well as the nature and timing of communications to investigators in order to minimize the risk of enrollment beyond the protocol-specified enrollment caps determined by the statistical analysis plan.

### 9.5. End-of-Study Action Plan

This is an appendix to the COMBO Study and only contains information that is unique to this sub-study.

Information that is common to both is not repeated in this document.

### 10. Study Methods

#### 10.1. Data Collection

The data collection schedule is shown in table below.
# Table 10.1-1: Data Collection Schedule

<table>
<thead>
<tr>
<th>Screening</th>
<th>Opioid Medication Lock Visit</th>
<th>Baseline Period</th>
<th>Baseline Visit</th>
<th>Implant Procedures (Trial and Permanent)</th>
<th>Randomization/Activation Visit</th>
<th>Programming Lock Visit</th>
<th>3-Month Visit</th>
<th>6-Month Visit</th>
<th>9-Month Visit</th>
<th>1-Year Visit</th>
<th>2-Year Visit</th>
<th>End of Study</th>
<th>Unscheduled Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed Consent (ICF)</td>
<td>X</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Inclusion/Exclusion Criteria Evaluation</td>
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</tr>
<tr>
<td>Demography</td>
<td>X</td>
<td></td>
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<tr>
<td>Medical History</td>
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<tr>
<td>Beck Depression Inventory (BDI-II)</td>
<td>X</td>
<td></td>
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<tr>
<td>Oswestry Disability Index (ODI v2.1a)</td>
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<td></td>
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<tr>
<td>Short Form Health Survey 36 Item (SF-36v2)</td>
<td>X</td>
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<tr>
<td>EQ-5D-5L</td>
<td>X</td>
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<tr>
<td>Pain Intensity (NRS)</td>
<td>X</td>
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<tr>
<td>Pain Intensity (VRS)</td>
<td>X</td>
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<tr>
<td>Pittsburgh Sleep Quality Index (PSQI)</td>
<td>X</td>
<td></td>
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<tr>
<td>Procedure Information</td>
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<tr>
<td>End of Trial Assessment</td>
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</tr>
<tr>
<td>Programming Parameters***</td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>
| Activation Questionnaire | | | | | | | | | | | | | X**
| Clinician Global Impression of Change (CGI-C) | | | | | | | | | | | | | X
| Patient Global Impression of Change (PGI-C) | | | | | | | | | | | | | X
| Percent Pain Relief (PPR) | | | | | | | | | | | | | X
| Preference Questionnaire | X | | | | | | | | | | | | |
| Treatment Satisfaction Questionnaire (TSQM-9m) | X | | | | | | | | | | | | |
| Concomitant Medications (opioid pain medications) | X | X | X | | | | | | | | | | X
| Adverse Events (AE) | X | X | X | X | | | | | | | | | X

* For unscheduled visits where procedures are performed.
** Only when device programming is performed.
* The device will remain off after permanent implant until the Activation Visit.
10.2. Study Candidate Screening

Subjects’ eligibility for the study will be assessed based on study Inclusion and Exclusion criteria listed in Sections 9.2 and 9.3, respectively. Subjects who have provided informed consent and who have been determined to not meet all eligibility requirements will be withdrawn.

10.3. Informed Consent

This is an appendix to the COMBO Study and only contains information that is unique to this sub-study.

Information that is common to both is not repeated in this document.

10.3.1. Screening Period

This is an appendix to the COMBO Study and only contains information that is unique to this sub-study.

Information that is common to both is not repeated in this document.

10.4. Opioid Medication Lock Visit (Up to 35 days following informed consent)

The Opioid Medication Lock Visit will occur within 35 days following informed consent. However, this visit may occur on the same day as that of the Informed consent as well following completion of consent.

At this visit, the subject’s opioid pain medications will be locked, with no increase in type/dose/route/frequency, until the 3-Month post-randomization Visit.

At this visit (or during the screening period), the investigator will convert the subject’s opioid medication prescriptions from PRN to a fixed dose, as needed.

10.5. Baseline Period (14 days)

The Baseline Period will last for 14 consecutive days following the Opioid Medication Lock Visit. At the end of the Baseline Period, subjects will return to the clinic for their Baseline Visit.

Subjects are to not make any increases to their opioid pain medications during this period.

10.6. Baseline Visit (0 – 7 days post Baseline Period)

At the Baseline Visit, subjects will return to the clinic to complete remaining screening requirements. Any adverse since the last study visit will be collected.

The following assessments, as outlined in Table 11.1-1, will be conducted:

- Demographics
• Medical history
• Beck Depression Inventory (BDI-II)
• Oswestry Disability Index (ODIv2.1a)
• Short Form Health Survey 36 (SF-36v2)
• EQ-5D 5-Level
• Pain Intensity: VRS
• Pain Intensity: NRS
• Pittsburg Sleep Quality Index (PSQI)

Subjects that meet all study criteria will be scheduled for the device implant procedures (trial and permanent implant of the SCS system). If a subject fails to meet all the eligibility criteria, they will be withdrawn from the study.

**End of Visit Information:**

- Subjects should be reminded not to make any increases to their opioid medications.

10.7. **Implant Procedures (Up to 90 days following the Baseline Visit)**

Subjects will have up to 90 days following the Baseline Visit to receive their Spectra WaveWriter System. Subjects will undergo a trial procedure per standard of care. Following a successful trial, i.e. at least 50% pain reduction in their overall pain as compared with Baseline, the subject will proceed to permanent implantation. Subjects with an unsuccessful implant procedure will be followed for 2 weeks for procedure related adverse events then withdrawn from the study. Acute opioid pain medications may be taken.

10.8. **Healing Period (0 - 28 days following Implant Procedures)**

The subject’s device will remain inactivated (device OFF) for up to 28 days following the permanent implantation procedure to allow for healing. Acute opioid pain medications may be taken during this period. No additional scheduled assessments will be completed during this period.

For those subjects receiving the surgical (paddle) lead, it is recommended that their device remain inactivated (device OFF) as part of healing for 21-28 days.

10.9. **Randomization Visit (Day 0)**

At the Randomization Visit, subjects will be randomized in a 1:1 ratio to either receive

- WaveWriter Settings: Fast-acting subperception
- Conventional Settings: Subperception

Subjects will receive their assigned treatment settings up to 3 Mo. Visit. Any protocol required adverse events since the last study visit will be collected.
The Activation Questionnaire must be completed prior to and post-activation to document pain scores, time taken, etc.

Subjects must stop taking acute opioid pain medications, as applicable, and are not to increase their opioid pain medications up to the 3-Month Visit.

Information regarding programming parameters will be collected. To aid in programming it is recommended that thoracic and/or lumbar imaging is obtained at this visit or up to 7 days prior to the visit to show the position(s) of the study device lead(s). In the event of suspected lead migration, imaging may be performed to document lead positions.

**End of Visit Information:**
- Subjects will receive instructions on the use of the device including the Remote Control and charging system.
- Subjects are to contact the site in an event that any additional intervention is warranted, to report a complaint and/or a suspected adverse event, reprogramming, etc.
- Subjects should be reminded not to make any increase in their opioid pain medications.

10.10. **Programming Lock Visit (Day 70 - 14 days post randomization Visit)**

At the Programming Lock Visit, subjects will return to the clinic to have their programs locked. Any protocol required adverse events since the last study visit will be collected.

No further changes to the subject’s programs (for e.g. electrode configuration) will be allowed except to resolve a device and/or stimulation-related AE.

Information regarding programming parameters and device information may be collected.

**End of Visit Information:**
- Subjects will receive instructions on the use of the device including the Remote Control and charging system, as needed.
- Subjects are to contact the site in an event that any additional intervention is warranted, to report a complaint and/or a suspected adverse event, reprogramming, etc.
- Subjects should be reminded not to make any increase in their opioid medications.

10.11. **3-Month Visit (90 + 14 days post randomization Visit)**

During the 3-Month Visit, subjects will return to the clinic for study evaluations and programming. Any protocol required adverse events since their last study visit will be collected.

The following assessments will be completed as summarized in Table 11.1-1:
- Beck Depression Inventory (BDI-II)
- Oswestry Disability Index version 2.1a (ODI v2.1a)
- Short Form Health Survey 36 items (SF-36 v2)
- EQ-5D 5-Level
- Pain Intensity: VRS
- Pain Intensity: NRS
- Clinical Global Impression of Change (CGI-C)
- Patient Global Impression of Change (PGI-C)
- Percent Pain Relief (PPR)
- Pittsburg Sleep Quality Index (PSQI)
- Treatment Satisfaction Questionnaire for Medication - modified (TSQM-9m)

Following completion of assessments, subjects’ device will be programmed as needed and programming information may be collected. At this visit, all subjects may receive programming as available on the device with no restrictions.

- In the event of suspected lead migration or to aid programming the subject’s device, imaging may be performed to document lead position.
- Any additional instructions related to charging of the device and/or use of Remote Control may be provided.

**End of Visit Information:**
- Subjects will receive instructions on the use of the device including the Remote Control and charging system, as needed.
- Subjects are to contact the site in an event that any additional intervention is warranted, to report a complaint and/or a suspected adverse event, reprogramming, etc.
- Subjects’ opioid medications are no longer locked and can be changed, if needed for the remainder of the study

10.12. 6-Month Visit (180 ± 30 days post randomization Visit)

During the 6-Month Visit, subjects will return to the clinic for study evaluations and programming. Any protocol required adverse events since their last study visit will be collected.

The following assessments will be completed as summarized in Table 11.1-1:

- Oswestry Disability Index version 2.1a (ODI v2.1a)
- Short Form Health Survey 36 items (SF-36 v2)
- EQ-5D 5-Level
- Pain Intensity: NRS
- Pain Intensity: VRS
- Clinical Global Impression of Change (CGI-C)
- Patient Global Impression of Change (PGI-C)
- Percent Pain Relief (PPR)
- Pittsburg Sleep Quality Index (PSQI)
- Preference Questionnaire
- Treatment Satisfaction Questionnaire for Medication - modified (TSQM-9m)

Following completion of assessments, subjects’ device will be programmed as needed and programming information may be collected.

- In the event of suspected lead migration or to aid programming the subject’s device, imaging may be performed to document lead position.
- Any additional instructions related to charging of the device and/or use of Remote Control may be provided.

End of Visit Information:

- Subjects will receive instructions on the use of the device including the Remote Control and charging system, as needed.
- Subjects are to contact the site in an event that any additional intervention is warranted, to report a complaint and/or a suspected adverse event, reprogramming, etc.
- Changes to opioid pain medications are allowed up to End of Study Visit.

10.13. 9-Month Visit (270 ± 30 days post randomization Visit)

During the 9-Month Visit, subjects will return to the clinic for study evaluations and programming. Any protocol required adverse events since their last study visit will be collected.

The following assessments will be completed as summarized in Table 11.1-1:

- Oswestry Disability Index version 2.1a (ODI v2.1a)
- Short Form Health Survey 36 items (SF-36 v2)
- EQ-5D 5-Level
- Pain Intensity: NRS
- Pain Intensity: VRS
- Clinical Global Impression of Change (CGI-C)
- Patient Global Impression of Change (PGI-C)
- Percent Pain Relief (PPR)
- Pittsburg Sleep Quality Index (PSQI)
- Preference Questionnaire
- Treatment Satisfaction Questionnaire for Medication - modified (TSQM-9m)

Following completion of assessments, subjects’ device will be programmed as needed and programming information may be collected.
In the event of suspected lead migration or to aid programming the subject’s device, imaging may be performed to document lead position.

Any additional instructions related to charging of the device and/or use of Remote Control may be provided.

**End of Visit Information:**

- Subjects will receive instructions on the use of the device including the Remote Control and charging system, as needed.
- Subjects are to contact the site in an event that any additional intervention is warranted, to report a complaint and/or a suspected adverse event, reprogramming, etc.

**10.14. Year 1 and Year 2 Visit (365 ± 30 days post randomization Visit and 730 ± 30 days post-randomization Visit)**

During the 1 and 2 Year Visits, subjects will return to the clinic for study evaluations and programming. Any protocol required adverse events since their last study visit will be collected.

The following assessments will be completed as summarized in Table 11.1-1:

- Beck Depression Inventory (BDI-II)
- Oswestry Disability Index version 2.1a (ODI v2.1a)
- Short Form Health Survey 36 items (SF-36 v2)
- EQ-5D 5-Level
- Pain Intensity: NRS
- Pain Intensity: VRS
- Clinical Global Impression of Change (CGI-C)
- Patient Global Impression of Change (PGI-C)
- Percent Pain Relief (PPR)
- Pittsburg Sleep Quality Index (PSQI)
- Preference Questionnaire
- Treatment Satisfaction Questionnaire for Medication - modified (TSQM-9m)

Following completion of assessments, subjects’ device will be programmed as needed and programming information may be collected.

- In the event of suspected lead migration or to aid programming the subject’s device, imaging may be performed to document lead position.
- Any additional instructions related to charging of the device and/or use of Remote Control may be provided.

**End of Visit Information:**
Subjects will receive instructions on the use of the device including the Remote Control and charging system, as needed.

Subjects are to contact the site in an event that any additional intervention is warranted, to report a complaint and/or a suspected adverse event, reprogramming, etc.

The 2 Year Visit is the End of Study Visit and End of Study Action Plan (ESAP) will be followed as described in Section 10.5.

10.15. **Unscheduled Visit**

This is an appendix to the COMBO Study and only contains information that is unique to this sub-study.

Information that is common to both is not repeated in this document.

10.15.1. **Revision or Replacement of Leads, Extensions and/or IPGs**

This is an appendix to the COMBO Study and only contains information that is unique to this sub-study.

Information that is common to both is not repeated in this document.

10.15.2. **Interventional Pain Procedures**

This is an appendix to the COMBO Study and only contains information that is unique to this sub-study.

Information that is common to both is not repeated in this document.

10.16. **Medication Requirements**

**Opioid Medication Lock Period (Medication Lock visit to 3-Month Visit):**

Investigators/Subjects will not be allowed to increase opioid pain medications from the Medication Lock visit until completion of the 3-Month Visit.

The use of acute opioid pain medication for procedural discomfort is allowed during the Procedures and Healing Period and in the event of the revision or replacement of leads, extensions and/or IPG, per site’s routine care.

**Opioid Medication Open Period (3-Month Visit to End of Study visit)**

Investigators/Subjects may change opioid pain medications during the pain medication open period, from the 3-Month Visit to the End of Study Visit as needed.
10.17. **Study Completion**

All randomized subjects permanently implanted will be followed through completion of the 2-Year Visit or study withdrawal. The End of Study Action Plan defines the actions to be taken when the subject reaches the end of their study participation.

10.18. **Source Documents**

This is an appendix to the COMBO Study and only contains information that is unique to this sub-study.

Information that is common to both is not repeated in this document.

11. **Statistical Considerations**

11.1. **Endpoints**

11.1.1. **Primary Endpoint**

The primary endpoint for this study is the proportion of subjects with 50% or greater reduction from Baseline Visit in average overall pain intensity at 3 months post randomization with no increase in baseline average opioid medications used to treat pain.

11.1.1.1. **Hypotheses**

The primary statistical hypothesis in this study is that the proportion of subjects with 50% or greater reduction from Baseline Visit in average daily overall pain intensity at 3 months post randomization in the FAST group is non-inferior compared to the Control (i.e. subperception) group

\[
H_0: \pi_t - \pi_c \leq -0.20
\]

\[
H_1: \pi_t - \pi_c > -0.20
\]

Where \(\pi_t\) and \(\pi_c\) are the proportion of subjects with 50% or greater reduction from Baseline in average daily overall pain intensity at 3 months post randomization with no increase in baseline average daily opioid pain medications using FAST and subperception settings, respectively. The study’s non-inferiority margin is 0.20.
11.1.1.2. Sample Size

The required sample size for this study was calculated based on the following assumptions in East 6.5:

- Test significance level (α) 0.025
- 1 or 2 sided test 1
- Difference in Response (π_t - π_c) 0.05
- Non-inferiority margin (δ) 0.20
- Proportion of Responder in Control group (π_c) 0.60
- Power (1- β) 0.80

N 140 with three interim looks
Attrition (%) 5%

Therefore, a total of 148 randomized subjects are required.

11.1.1.3. Statistical Methods

The 95% confidence interval of π_t - π_c will be computed. The study will be considered a success if, using the Intent-To-Treat (ITT) analysis, the lower bound of the two-sided 95% confidence interval for the difference is greater than -0.20.

11.1.2. Efficacy Endpoints

The following secondary endpoints will be analyzed as a comparison between the two groups. Assessments required for deriving each endpoint are denoted in parentheses.

- Percentage of subjects who report clinically significant improvement in overall pain post-activation (Activation Questionnaire)
- Change in average overall pain intensity from pre-activation to post-activation (Activation Questionnaire)
- Change in overall pain intensity from Baseline Visit to 3 mo. post-randomization Visit (VRS)
- Percent Pain Relief in overall pain at 3 mo. post-randomization Visit (PPR)
- Patient global impression of change at 3 mo. post-randomization Visit (PGI-C)
- Clinician global impression of change at 3 mos. post-randomization Visit (CGI-C)
- Treatment Satisfaction at 3 months post-randomization Visit (TSQM-9m)
- Change in disability from Baseline Visit to 3 mos. post-randomization Visit (ODIv2.1a)
- Change in sleep from Baseline Visit to 3 mos. post-randomization Visit (PSQI)
11.1.3. Exploratory Endpoints

The following exploratory endpoints will be evaluated. Assessments required for deriving each endpoint are denoted in parentheses.

- Change in average low back pain intensity from pre-activation to post-activation (Activation Questionnaire)
- Change in average leg pain intensity from pre-activation to post-activation (Activation Questionnaire)
- Change in average overall pain intensity from Baseline Visit to 6, 9, 12 and 24 months post-randomization Visits (VRS)
- Change in average low back pain intensity from Baseline Visit to 6, 9, 12 and 24 months post-randomization Visits (VRS)
- Change in average leg pain intensity from Baseline Visit to 6, 9, 12 and 24 months post-randomization Visits (VRS)
- Change in average overall pain intensity from Baseline Visit to 6, 9, 12 and 24 months post-randomization Visits (NRS)
- Change in average low back pain intensity from Baseline Visit to 6, 9, 12 and 24 months post-randomization Visits (NRS)
- Change in average leg pain intensity from Baseline Visit to 6, 9, 12 and 24 months post-randomization Visits (NRS)
- Percent pain relief of overall pain at 6, 9, 12 and 24 months post-randomization Visits (PPR)
- Percent pain relief of low back pain at 6, 9, 12 and 24 months post-randomization Visits (PPR)
- Percent pain relief of leg pain at 6, 9, 12 and 24 months post-randomization Visits (PPR)
- Clinician global impression of change at 6, 9, 12 and 24 months post-randomization Visits (CGI-C)
- Patient global impression of change at 6, 9, 12 and 24 months post-randomization Visits (PGI-C)
- Treatment satisfaction at 6, 9, 12 and 24 months post-randomization Visits (TSQM-9m)
- Change in quality of life from Baseline Visit to 6, 9, 12 and 24 months post-randomization Visits (SF-36v2)
- Change in disability from Baseline Visit to 6, 9, 12 and 24 months post-randomization Visits (ODIv2.1a)
11.2. General Statistical Methods

This is an appendix to the COMBO Study and only contains information that is unique to this sub-study.

Information that is common to both is not repeated in this document.

12. Data Management

This is an appendix to the COMBO Study and only contains information that is unique to this sub-study.

Information that is common to both is not repeated in this document.

12.1. Data Collection, Processing, and Review

This is an appendix to the COMBO Study and only contains information that is unique to this sub-study.

Information that is common to both is not repeated in this document.

12.2. Study Assessments

This is an appendix to the COMBO Study and only contains information that is unique to this sub-study.

Information that is common to both is not repeated in this document.

12.2.1. Activation Questionnaire

The Activation Questionnaire is administered by site personnel at the activation/randomization visit and will collect information related to subject’s overall improvement in pain scores, time taken to achieve pain relief, etc.

12.3. Data Retention

This is an appendix to the COMBO Study and only contains information that is unique to this sub-study.
13. Deviations

This is an appendix to the COMBO Study and only contains information that is unique to this sub-study.

Information that is common to both is not repeated in this document.

14. Compliance

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Information that is common to both is not repeated in this document.

15. Monitoring

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16. Potential Risks and Benefits

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17. Safety Reporting

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Information that is common to both is not repeated in this document.
18. Informed Consent

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Information that is common to both is not repeated in this document.

19. Committees

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Information that is common to both is not repeated in this document.

19.1. Safety Monitoring Process

This is an appendix to the COMBO Study and only contains information that is unique to this sub-study.

Information that is common to both is not repeated in this document.

20. Suspension or Termination

20.1 This is an appendix to the COMBO Study and only contains information that is unique to this sub-study.

Information that is common to both is not repeated in this document.

21. Publication Policy

This is an appendix to the COMBO Study and only contains information that is unique to this sub-study.

Information that is common to both is not repeated in this document.

22. Bibliography

This is an appendix to the COMBO Study and only contains information that is unique to this sub-study.

Information that is common to both is not repeated in this document.
23. Abbreviations and Definitions

23.1. Abbreviations

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New abbreviations shown below.

<table>
<thead>
<tr>
<th>Abbreviation/Acronym</th>
<th>Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAST</td>
<td>Fast Acting Subperception</td>
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</table>

23.2. Definitions

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