BENEFIT-02 Study

Statistical Analysis Plan

Version 1.0

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1 INTRODUCTION

The purpose for this Statistical Analysis Plan (SAP) is to provide additional detail regarding the primary and secondary endpoint analyses, and analysis of additional data of interest conducted for the 2020 BENEFIT-02 Final Report. This SAP is a supplement to the information contained within the Clinical Protocol for the BENEFIT-02 Study (final version 19-Apr-2019). Refer to the study protocol for more background and analysis details not included in this SAP.

2 STUDY DESIGN

The BENEFIT-02 Study is a prospective, multi-center, randomized, parallel assignment, single-blind, interventional feasibility study that is designed to investigate the effects of two study spinal cord stimulation (SCS) therapies on subject reported pain and paresthesia perception.

Figure 1 provides an overview of the clinical study design.

Figure 1: Study Design Flowchart

3 SUBJECT POPULATION

Subjects eligible for the study include those with chronic low back and/or leg pain who plan to undergo trial testing of a commercially available SCS system including an SCS trial stimulator and percutaneously implanted SCS trial lead(s). Prior to enrollment procedures, subjects will be screened to ensure study eligibility and will sign an informed consent form.

3.1 Study Participation Status Definitions

Screen failure – Subject that is unsuitable for enrollment following protocol required laboratory/psychological assessments or implanted with SCS trial lead(s) that are incompatible with the study stimulation system. These subjects will be exited from the study once screen failure is confirmed. Subject informed consent forms will be kept in the site's administrative files.

Provisionally enrolled – Subject who is fully informed about the specifics of the study by authorized site personnel and provides informed consent by properly signing an informed consent form after confirmation of the initial enrollment criteria.

Fully enrolled (Randomized) – Provisionally enrolled subject who meets all clinical eligibility criteria, and has been randomized. These subjects will be followed in accordance with the protocol requirements.

Study exit - Early termination of study participation applicable to subjects that have signed an informed consent form.

Study completion - Subject who completes all protocol-required study procedures.

4 STUDY ASSESSMENT DATA SOURCES

The BENEFIT-02 Study collected pain assessments, questionnaires, paresthesia perception assessments, and other data, both remotely and in-office. Table 2 provides an overview of the study assessment data sources stratified by assessment type (in-office vs. remotely collected).

Table 1: Study Assessment Data Sources

Source	Assessment Type	Description
Study Source Documentation Worksheets/ Electronic Capture Database (EDC) Data	In-office Assessment	Datasets contain in-office pain assessments, questionnaires, paresthesia perception assessments, and other data collected via study worksheets and other source documents that are uploaded and have each required data point entered in the EDC by study personnel. For analysis, this data is extracted directly from the EDC.
Subject Diary	Remote Assessment	Datasets consist of paper-based Subject Diary data, including information regarding pain medication usage, Numerical Rating Scale (NRS) for Pain score and Patient Global Impression of Change logged by subjects during the study. Paper-based Subject Diary scans are uploaded in EDC, but each data point is not entered directly by study personnel. Therefore, Subject Diary data will require transcription by sponsor personnel for analysis.
CamNtech PRO-Diary Watch	Remote Assessment	Datasets consist of acute NRS scores, pain events, pain medication events, sleep quality, and activity data electronically logged by subjects that is collected via the study data collection watch. Files containing this electronically collected data are uploaded in the EDC by study personnel, for later systematic analysis.

In-office data is used for analysis of the study primary and secondary endpoints (See Section 6.1 and Section 6.2) while analysis of additional data of interest (See Section 7) may include both in-office and remotely collected data. Further details for data collected for the study can be found in the study protocol.

5 SAMPLE SIZE ANALYSIS

The BENEFIT-02 Study is designed to limit the number of subjects involved and the duration of intervention, while ensuring sufficient preliminary data regarding the effectiveness and safety of the study SCS therapies is collected in order to accomplish the study objectives.

Since the effect size of each study SCS therapy on the primary outcome measure (NRS for overall pain) is unknown, statistically driven sample size estimation is not possible. A reduction of approximately two points on an NRS for chronic pain represents a clinically relevant difference.[1]

In order to detect a difference of approximately two in mean change in NRS pain score (from baseline to the final study visit) between the two study SCS therapies, a target of 70 subjects should complete the 12 day study stimulation period (~35 subjects for each study SCS therapy).

Therefore, to account for expected attrition due to subject withdrawal following consent but prior to completion of the study testing period:

- Up to 226 subjects will be provisionally enrolled
    - Assumed 51% drop out rate between consent and the randomization visit (e.g. failed commercial trial, withdrawn consent, etc.)
- Approximately 110 subjects will undergo randomization (fully enrolled)
    - Assumed 15% drop out rate following randomization prior to initiation of the assigned study SCS therapy (e.g. subject doesn't meet post-washout inclusion criteria)
- Approximately 93 subjects will initiate the randomly assigned study SCS therapy
    - Assumed 25% drop out rate following initiation of the randomly assigned study SCS therapy (e.g. non-compliance with study assessment schedule, withdrawn consent, subject lost to follow-up, etc.)
- Approximately 70 subjects will complete the study testing period

[1] J. T. Farrar *et al.*, "Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale," *Pain,* vol. 94, pp. 149-158, Nov 2001.

6 STUDY ENDPOINTS

The BENEFIT-02 Study includes the assessment of two primary endpoints and two secondary endpoints that are designed to provide preliminary information regarding the effectiveness and safety of the two study SCS therapies under investigation. There are no formal tests of hypotheses or other pre-specified statistical tests associated with the study primary endpoints.

6.1 Primary Endpoints

6.1.1 Primary Endpoint 1

The purpose of primary endpoint 1 is to evaluate the change since baseline in Numerical Rating Scale (NRS) for pain (overall) for each study SCS therapy.

The evaluation of primary endpoint 1 will be based on the NRS for pain (overall) obtained at the final study testing visit (NRS_{Final}) compared with the baseline measurement obtained prior to initiation of the commercial trial therapy ($NRS_{Baseline}$) (Note: $NRS_{Baseline}$ data collection may occur on the same date as the trial lead implant), for subjects randomized to each study SCS therapy.

Primary endpoint 1 analyses include all subjects with measurements for both NRS_{Final} and $NRS_{Baseline}$; therefore, subjects must have completed the study to be included in the primary endpoint 1 analyses.

Subject's re-assigned and/or re-programmed to receive the alternative therapy during the study testing period will be excluded from primary endpoint 1 analyses.

6.1.2 Primary Endpoint 2

The purpose of primary endpoint 2 is to provide an inter-therapy comparison of change since baseline in Numerical Rating Scale (NRS) for pain (overall). The evaluation of primary endpoint 2 will be based on a comparison of the results of primary endpoint 1 between the two study SCS therapies.

Primary endpoint 2 analyses include all subjects included in primary endpoint 1 analyses. Therefore, subject's re-assigned and/or re-programmed to receive the alternative therapy during the study testing period will be excluded from primary endpoint 2 analyses.

6.2 Secondary Endpoints

6.2.1 Secondary Endpoint 1

The purpose of secondary endpoint 1 is to evaluate the change in Numerical Rating Scale (NRS) for pain (overall) since conclusion of the commercial trial for each study SCS therapy.

The evaluation of secondary endpoint 1 will be based on the NRS for pain (overall) obtained at the final study testing visit (NRS_{Final}) compared with the measurement obtained following conclusion of the commercial trial but prior to initiation of the randomized study SCS therapy ($NRS_{Commercial\ Trial}$), for subjects randomized to each study SCS therapy.

Secondary endpoint 1 analyses will include all subjects with measurements for both NRS_{Final} and $NRS_{Commercial\ Trial}$.

Subject's re-assigned and/or re-programmed to receive the alternative therapy during the study testing period will be excluded from secondary endpoint 1 analyses.

6.2.2 Secondary Endpoint 2

The purpose of secondary endpoint 2 is to collect preliminary safety information regarding the investigational device and study SCS therapies (stimulation parameters are within the ranges of existing commercial therapies).

The evaluation of secondary endpoint 2 will be based on the adverse event-free rate (AEFR), calculated based on the total number of subjects free from any AEs classified by the investigator as clearly related to the investigational device. AEs that are resolved without any medical procedure or surgical intervention (e.g. through device reprogramming) will not be included in the analysis of secondary endpoint 2. The observed AEFR will be presented, along with a summary of all reported secondary endpoint 2 adverse events.

$$\textbf{Adverse event-free rate (AEFR)} = \frac{\textbf{(Number of subjects without an investigational device-related AE)}}{\textbf{(Total number of subjects)}}$$

Evaluable subjects for secondary endpoint 2 will include all subjects who undergo randomization and have the investigational stimulation system connected to their SCS trial lead(s).

6.3 Endpoint Results Example Tables and Figures

The results of primary and secondary endpoints will be analyzed as described in this Statistical Analysis Plan and the Clinical Protocol for the BENEFIT-02 Study.

Example tables and figures representative of how the data will be presented in the final study results are provided below. As applicable, descriptive statistics may also be used to present and summarize the data collected during the study. Means and standard error of the mean will be used to describe results from primary endpoints 1 and 2, and secondary endpoint 1. Change in NRS and Percent Pain Relief (PPR) will be evaluated using paired T-test or two-sample T-test, as applicable. For all analyses, $p < 0.05$ is considered significant. Frequency distributions will be used to describe secondary endpoint 2.

6.3.1 Primary Endpoint 1

Figure 2: Therapy A/B Change in NRS for Pain (Overall) Since Baseline

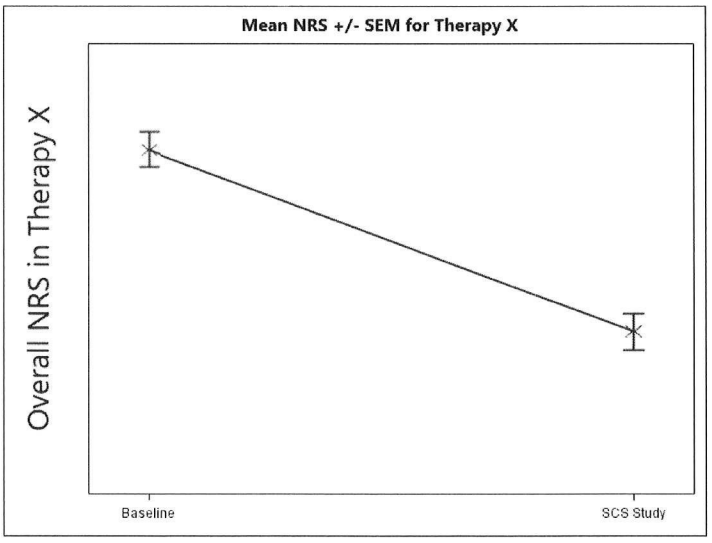


Table 2: Primary Endpoint 1 Summary

Numerical Rating Scale for Pain (Overall)	Therapy A n = XX	Therapy B n = XX	Total (A+B) n = XX
Mean NRS at Baseline ± SEM	X.X ± X.XX	X.X ± X.XX	X.X ± X.XX
Mean NRS at Final Study Visit ± SEM	X.X ± X.XX	X.X ± X.XX	X.X ± X.XX
Mean Change in NRS ± SD	**X.X ± X.XX**	**X.X ± X.XX**	**X.X ± X.XX**
Paired T-Test (Final Mean NRS vs Baseline)	**p = 0.XXX**	**p = 0.XXX**	**-------**

Figure 3: Percent Pain Relief (PPR) per Therapy

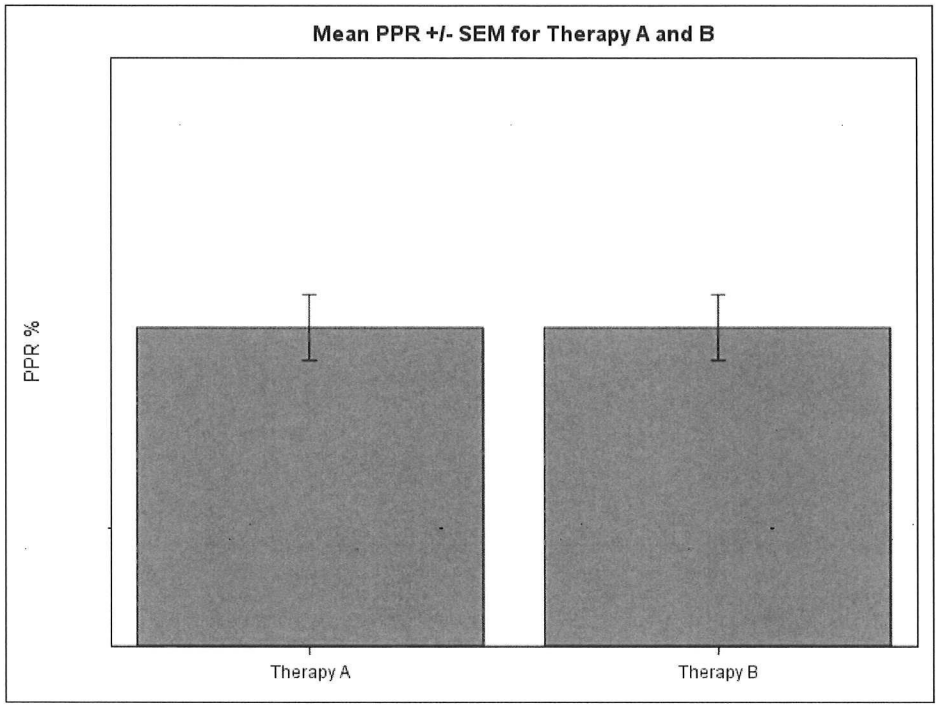


Table 3: Percent Pain Relief (PPR)

Percent Pain Relief	Therapy A n = XX	Therapy B n = XX	Therapy (A+B) n = XX
Mean PPR ± SEM	XX.X% ± X.XX%	XX.X% ± X.XX%	XX.X% ± X.XX%

6.3.2 Primary Endpoint 2

Figure 4: Inter-therapy Comparison

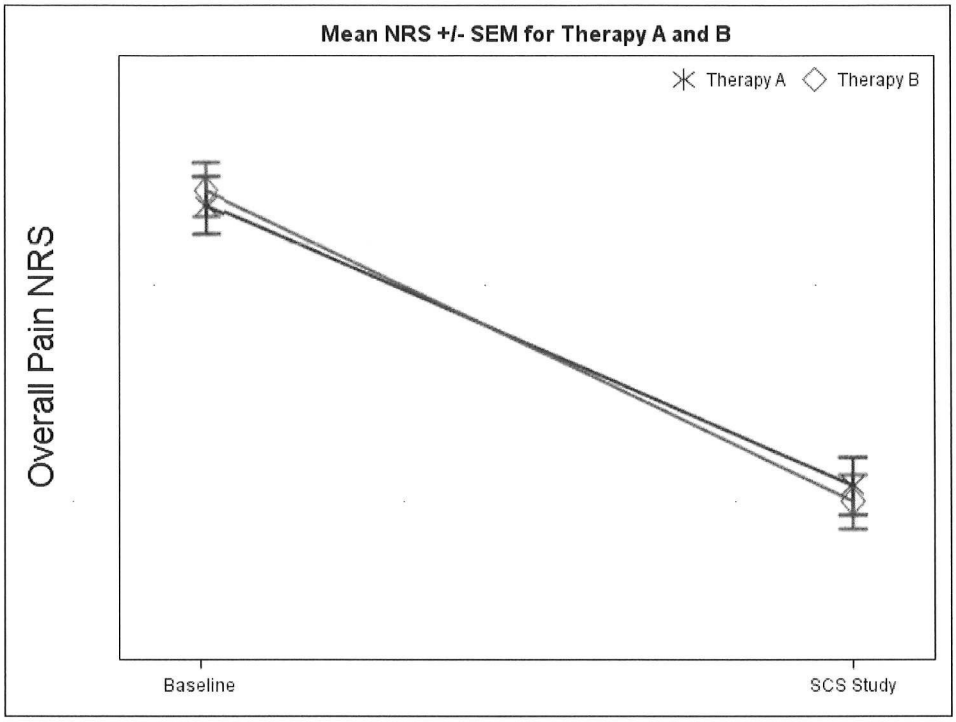


Table 4: Inter-therapy Comparison of Change since Baseline

Primary Endpoint 2	Two-Sample T-Test on NRS	Two-Sample T-Test on Percent Pain Relief (PPR)
p value: equal var	X.XXXX	X.XXXX
p value: unequal var	X.XXXX	X.XXXX

6.3.3 Secondary Endpoint 1

Table 5: Secondary Endpoint 1 Summary

Numerical Rating Scale for Pain (Overall)	Therapy A n = XX	Therapy B n = XX	Total (A+B) n = XX
Mean NRS at Study Visit 1 ± SEM	X.X ± X.XX	X.X ± X.XX	X.X ± X.XX
Mean NRS at Study Visit 3 ± SEM	X.X ± X.XX	X.X ± X.XX	X.X ± X.XX
Mean Change in NRS ± SEM	**X.X ± X.XX**	**X.X ± X.XX**	**X.X ± X.XX**
Paired T-Test (Visit 3 Mean NRS vs Visit 1)	**p = 0.XXX**	**p = 0.XXX**	**------**

6.3.4 Secondary Endpoint 2

Table 6: Investigational Device-Related Adverse Events

Adverse Event Type	Number of AEs	Subjects with AE, n	Subjects with AE, %
Event type 1	X	X	X.XX%
Event type 2	X	X	X.XX%
Event type 3	X	X	X.XX%
Event type 4	X	X	X.XX%
Total	**X**	**X**	**X.XX%**

Number of subjects = XX

7 ADDITIONAL DATA OF INTEREST

As outlined in the Clinical Protocol for the BENEFIT-02 Study, to supplement the analysis of the study primary and secondary endpoints, additional data of interest will be collected.

Further details regarding how these additional data of interest may be analyzed, and example tables and figures illustrating how the data may be presented are provided below. Frequency distributions will be used to describe adverse events excluded from secondary endpoint 2 and device complaints.

For remote pain assessments, descriptive statistics including means and standard error of the mean will be used to describe results. Comparison of remote and in-office assessments will be performed with a paired T-test, when applicable. For comparison between commercial trials and investigational study phase, overall change in NRS will be evaluated by ANOVA while comparisons between therapies will be evaluated by a paired T-test. Change in NRS between therapies will be evaluated using paired T-test. For all analyses, $p < 0.05$ is considered significant.

7.1 Adverse Events Excluded from Secondary Endpoint 2

Adverse events that are classified by the investigator as related to the SCS trial lead implant procedure, related to the commercial trial period, or related to the investigational device that are not included in secondary endpoint 2 will be summarized.

Table 7: Summary of Adverse Events Excluded from Secondary Endpoint 2

Adverse Event Type	Number of AEs	Subjects with AE, n	Subjects with AE, %
SCS Trial Lead Implant Procedure-Related			
Event type 1	X	X	X.XX%
Event type 2	X	X	X.XX%
Commercial Trial Period Related			
Event type 3	X	X	X.XX%
Event type 4	X	X	X.XX%
Possibly Related to the Investigational Device			
Event type 5	X	X	X.XX%
Event type 6	X	X	X.XX%
Unknown Relationship to the Investigational Device			
Event type 7	X	X	X.XX%
Event type 8	X	X	X.XX%
Total Non-Endpoint Adverse Events	**X**	**X**	**X.XX%**

Number of subjects = XXX

7.2 Device Complaints

Potential complaints associated with the study investigational devices will be summarized.

Table 8: Summary of Device Complaints

Device Complaint Type	Number of Complaints
Complaint type 1	X
Complaint type 2	X
Complaint type 3	X

7.3 Remote Pain Assessments

As described in Table 1, remote pain assessments are recorded daily by the subject using the CamNtech PRO-Diary Watch and paper-based Subject Diary. The remotely assessed NRS scores for overall pain collected from the PRO-Diary Watch and Subject Diary may be combined and compared to the In-Office assessments to evaluate the consistency across the in-office and remote data collection settings, and supplement the primary and secondary endpoints.

7.3.1 Remote NRS Data Processing Steps

Data from the PRO-Diary Watch data files will be combined with data manually transcribed from the Subject Diary by sponsor personnel. When available, the NRS score recorded on the watch will the primary source used for analysis of the remote assessments. Paper-based subject diary NRS scores will be used when the watch data is unavailable.

7.3.2 Data Structure

A data file with the combined watch and transcribed paper diary NRS scores will be constructed from the raw data files from the EDC, and archived. The combined file will be formatted as follows:

- Column 1: Subjects (e.g. '001-001')
- Column 2: Dates (format 'MM/DD/YYYY')
- Column 3: Data (NRS values range 0-10, note some values are not integers due to the averaging of watch data)

7.3.3 Calculation of 2-day pain score for comparison between investigational therapy and commercial trial

The remote NRS scores in the combined file may be used to compute a two-day pain score. The two-day pain score will be defined as the second lowest pain score which was achieved by the therapy (equal to the minimum if the minimum occurs more than once). This metric is preferred over the minimum score because it reduces the effect of random factors resulting in a minimum pain score that is a statistical outlier. The two-day pain score will be used to evaluate the performance of the therapy in the commercial trial phase and the investigational phase relative to baseline. The baseline pain score (Phase 1) is the overall NRS score collected at the study enrollment visit. It is not computed from the remote NRS scores.

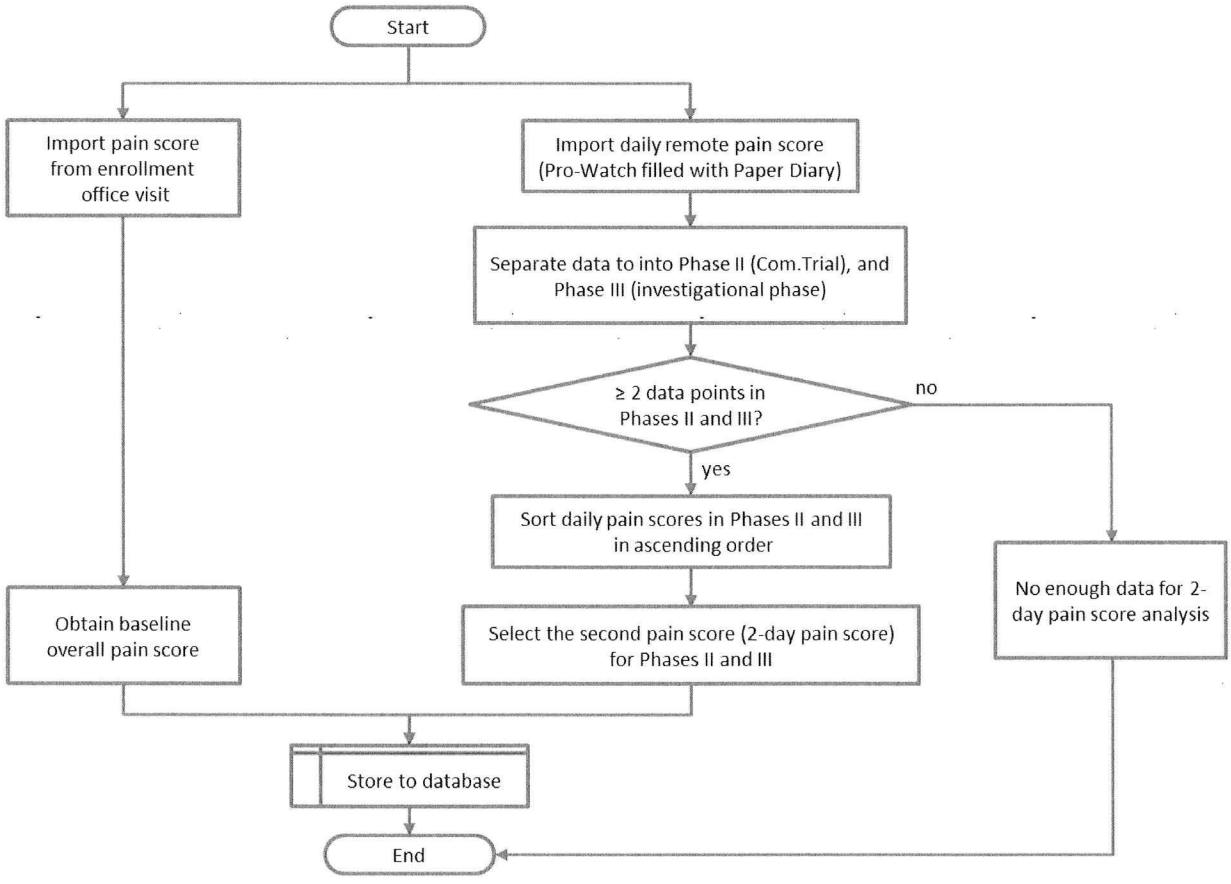
The integrated pain score data from the watch and paper diary may be separated into phases:

- Phase II: Commercial Trial
  - Inclusive dates: date of trial lead implant through the date of office visit 1 (randomization)
- Phase III: Investigational Therapy
  - Inclusive dates: (Randomization date + 3 days) until the end of the study period (office visit 3 = study exit).
- Additional notes:
  - Randomization arms in the investigational therapy phase are combined (both A and B)

In order to calculate 2-day pain scores in the commercial trial phase and investigational phase, at least 2 data points (2 test days with recordings) will be required in each phase. Otherwise, the subject will be excluded from the analysis.

The daily pain scores in Phases II and III will be sorted in ascending order. Then, the second value (2-day pain score) will be obtained for both the commercial trial phase and investigational phase. Figure 5 provides an overview of this process.

Figure 5: Flow Chart for Calculation of 2-day Pain Score



7.3.4 Calculation of 2-day pain score for comparison between investigational therapies A and B

For comparisons of remote assessment data between investigational therapies A and B the two-day pain score is calculated as described in Section 7.3.3 with the following exceptions:

- A 2-day pain score for the Commercial Trial Phase is not computed
- The 2-day pain score is only computed from remotely collected NRS values on days prior to cross-over (if it occurs). Specifically, all NRS scores on days following the initial cross-over will be excluded. Note: The Titration Procedures Therapy Block Re-Assigned variable recorded in EDC will be used to verify cross-over (e.g. therapy switches from A to B or from B to A). Examples of cross-over patterns are provided by Table 9.

Table 9: Example Therapy Cross-over of Randomized Subjects

Date	Initial Therapy	Final Therapy	Block Re-Assigned	NRS included?
24-Oct-2019	A	A	unchecked	Yes
25-Oct-2019	A	B	checked	Yes
26-Oct-2019	B	B	unchecked	No
27-Oct-2019	B	A	checked	No
28-Oct-2019	A	A	unchecked	No

7.3.5 Data Validation for Combined Remote Pain Assessment Data Set and 2-day Pain Score

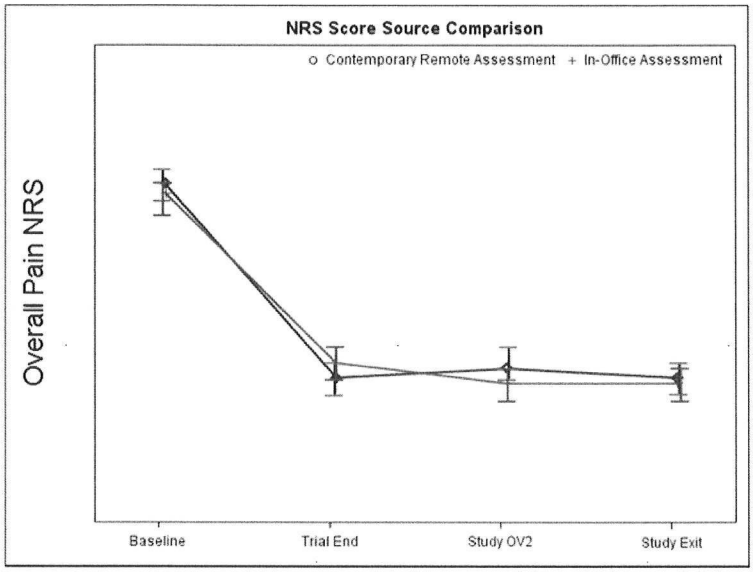
In order to validate the calculation process of the 2-day pain score, 2 SCS experts will develop programs to calculate 2-day pain scores independently. The results obtained for every subject will be compared. Prior to analysis, it will be confirmed that both independent analysis programs generate the same 2-day pain score results, indicating that the calculation processes are correct and the data is accurate. The same process will be used to validate the Pro-Diary Watch and Merged Pro-Diary/Subject Diary datasets. The values contained within the transcribed Paper Diary will also be cross-validated by sponsor personnel, with a minimum of a random 10% sample reviewed for accuracy, with any discrepancies verified, and corrected prior to final analysis.

7.3.6 Remote Pain Assessments Example Tables and Figures

Table 10: NRS Score Source Comparison

Overall NRS	Baseline/Enrollment (n=XX/XX)	Trial End/Rand (n=XX)	Midpoint Evaluation (Study OV2) (n=XX)	Study Exit (n=XX)
Mean In-Office Assessment ± SEM	X.X ± X.XX	X.X ± X.XX	X.X ± X.XX	X.X ± X.XX
Mean Remote Assessment ± SEM	X.X	X.X ± X.XX	X.X ± X.XX	X.X ± X.XX
Paired T-Test	-----	X.XX	X.XX	X.XX

Figure 6: NRS Score Source Comparison



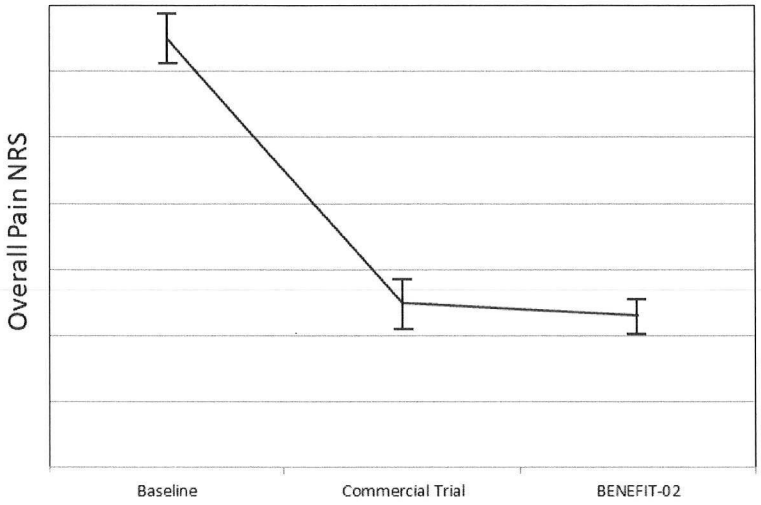
7.4 Comparison between Commercial Trial and Investigational Study Phase

A comparison between commercial trial and investigational study phase may be completed for the entire sample of subjects with Therapy A and Therapy B combined including any subjects that were re-assigned and/or reprogrammed to the alternative therapy. Only subjects with data available in each study interval will used to compare across study time points.

Table 11: Overall NRS (Mean ± SEM, XX Subjects)

Overall NRS	Mean NRS ± SEM	P-value Baseline vs. (post hoc paired t-test)	P-value Commercial vs. (post hoc paired t-test)
Baseline (In-Office Assessment) (N=XX)	X.X ± X.XX	-----	-----
Commercial Trial (Remote Assessment) (N=XX)	X.X ± X.XX	X.XXXXX	-----
BENEFIT-02 Study (Remote Assessment) (N=XX)	X.X ± X.XX	X.XXXXX	X.XXXXX
Overall NRS P-value (ANOVA)	**p = 0.XXX**	-----	-----

Figure 7: Overall NRS (Mean ± SEM, XX Subjects)



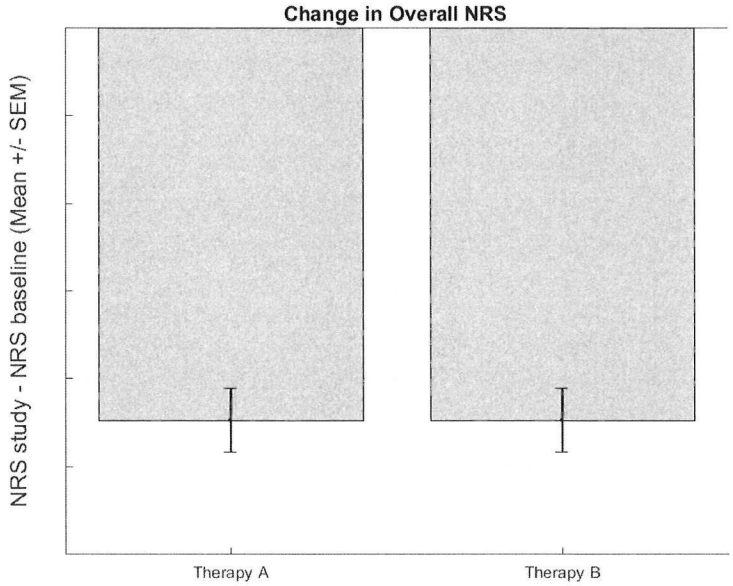
7.5 Comparison between Investigational Therapy Randomization Arms

A comparison between investigational therapy arms may be completed to determine the change in overall NRS for all subjects completing the study, including subjects actively re-assigned to the alternative therapy. For subjects that are actively re-assigned, only NRS values prior to cross-over will be used.

Table 12: Change in Overall NRS

Change in Overall NRS	Therapy A (N=XX)	Therapy B (N=XX)	Therapy A vs Therapy B (two sample t-test)
Mean NRS ± SEM	X.X ± X.XX	X.X ± X.XX	p = 0.XXX
		-----	-----

Figure 8: Change in Overall NRS



8 SIGNATURES

Personnel	Signature and Date
[redacted] Clinical Studies BIOTRONIK, Inc.	
[redacted] Clinical Studies BIOTRONIK, Inc.	
[redacted] Clinical Studies BIOTRONIK, Inc.	
[redacted] Clinical Studies BIOTRONIK, Inc.	

Personnel	Signature and Date
[redacted] Clinical Studies BIOTRONIK, Inc.	
[redacted] Technical Expert	
[redacted] Technical Expert	