Outcomes in Adults with Mixed or Conductive Hearing Loss Implanted with the BONEBRIDGE

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LIST OF ABBREVIATIONS

BC-FMT	Bone Conduction – Floating Mass Transducer
BCI	Bone Conduction Implant
CFR	Code of Federal Regulations
CNC	Consonant-Nucleus-Consonant
CRF	Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HDSS	Hearing Device Satisfaction Scale
HL	Hearing Level
IC	Informed Consent
IRB	Investigational Review Board
PI	Principal Investigator
PTA	Pure-Tone Average
SAP	Statistical Analysis Plan
SIN	Speech In Noise
SNR	Signal-to-Noise Ratio
SOP	Standard Operating Procedure
SPL	Sound Pressure Level
SSQ	Speech, Spatial and Qualities of Hearing

STATEMENT OF COMPLIANCE

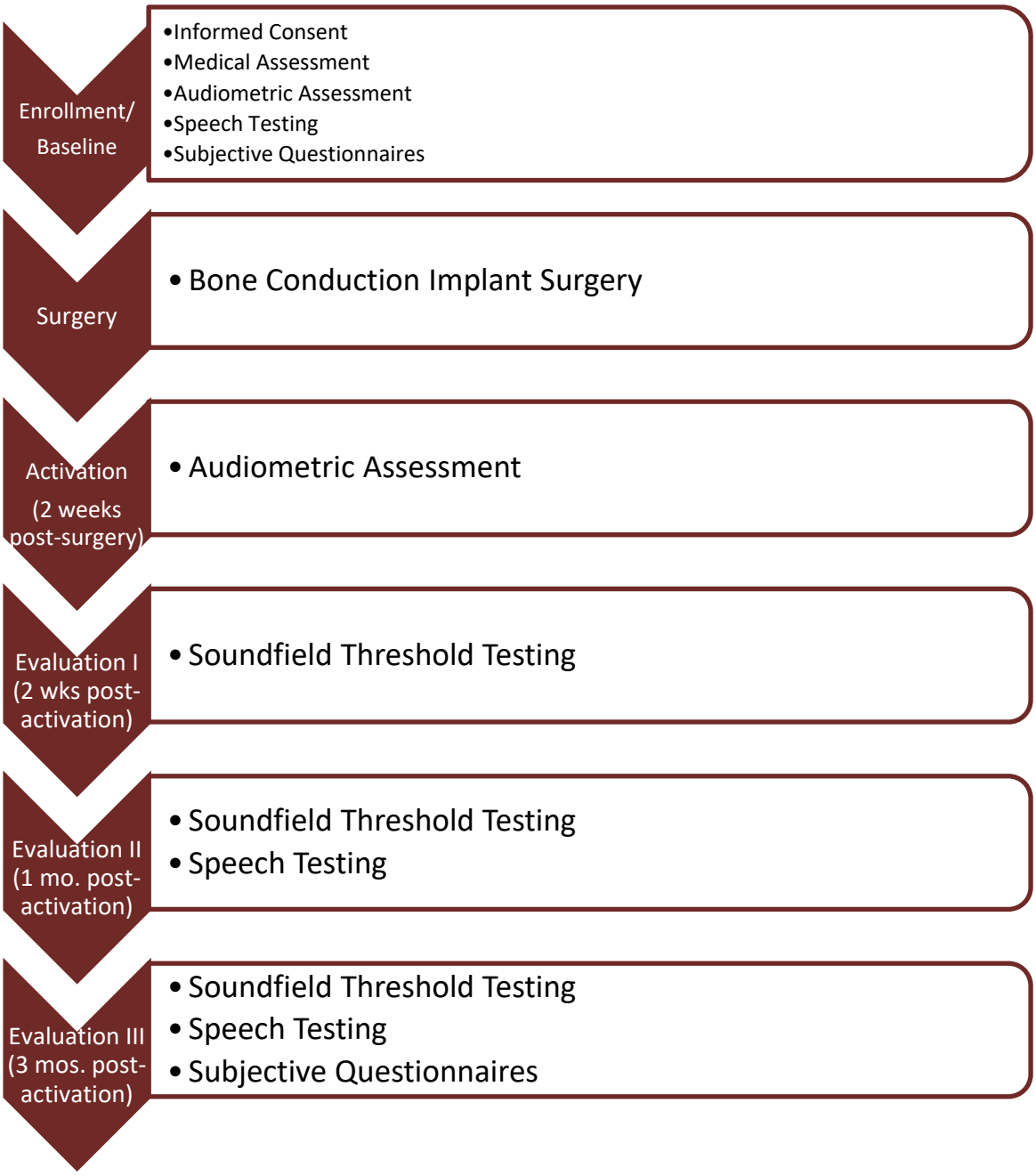
The trial will be carried out in accordance with Good Clinical Practice (GCP), as required by the following:

- United States Code of Federal Regulations (CFR) applicable to clinical studies (21 CFR Part 50, 21 CFR Part 54, 21 CFR Part 56)
- Good Clinical Practices

All investigators involved in the conduct of this study will be informed about their obligations in meeting the above commitments.

PROTOCOL SUMMARY	
Title:	Outcomes in Adults with Mixed or Conductive Hearing Loss Implanted with the BONEBRIDGE
Study Description:	Approximately thirty subjects with mixed or conductive hearing loss, meeting FDA-cleared candidacy criteria for the BONEBRIDGE, will be implanted and followed for three (3) months post-activation to assess safety and effectiveness of the BONEBRIDGE implant.
Objectives:	Primary: To assess safety and effectiveness of the BONEBRIDGE implant in adults with mixed or conductive hearing loss.
	Secondary: To assess post-operative audiometric and speech perception outcomes with BONEBRIDGE, compared to unaided pre-operative performance as well as report on intraoperative experience.
Endpoints: (Primary)	1. Subjects will demonstrate significant improvement in AzBio Sentence score in noise in the implanted ear at three (3) months post-activation, compared to unaided pre-operative performance.
	2. Safety data will be collected and reported as the number and proportion of subjects experiencing known risks of the BONEBRIDGE implant through three (3) months post-activation.
(Secondary)	1. Subjects will demonstrate similar or better scores on CNC words in quiet in the implanted ear at three (3) months post-activation, compared to unaided pre-operative performance.
	2. Subjects will demonstrate similar or better soundfield thresholds in the implanted ear at three (3) months post-activation, compared to pre-operative unaided soundfield thresholds.
	3. Subjects will demonstrate similar or better performance on the QuickSIN in the implanted ear at three (3) months post-activation, compared to unaided pre-operative performance.
	4. Subjects will demonstrate stable bone conduction thresholds at the device activation interval compared to pre-operative bone conduction thresholds.
Study Population:	Approximately thirty (30) total subjects, 18 years of age and older, will be implanted across three study sites in the United States and Canada. Fifteen (15) subjects with mixed hearing loss and fifteen (15) subjects with conductive hearing loss will be recruited.
Description of Sites Enrolling Participants:	Three (3) sites will participate in the clinical trial. Two (2) sites will be located in the United States, and one (1) site will be in Canada.
Description of Study Device:	Subjects will be implanted with the MED-EL BONEBRIDGE Bone Conduction Implant (BCI 601 or BCI 602). Subjects will be fit with the SAMBA Audio Processor using SYMFIT software. The system is commercially available in the United States and Canada.
Study Duration:	Enrollment is expected to last eighteen (18) months, while subject follow-up will last an additional four (4) months. Therefore, the study duration is anticipated to be twenty-two (22) months, from opening of enrollment to completion.
Participant Duration:	Each subject's participation in the clinical trial will last approximately four (4) months.

SCHEMATIC OF STUDY DESIGN



1 PURPOSE

The purpose of this investigation is to assess safety and effectiveness of the BONEBRIDGE Bone Conduction Implant for adults with mixed or conductive hearing loss. Study candidates will demonstrate bone conduction thresholds better than 45 dB. Surgical and performance outcomes will be collected through three months post-activation.

2 INTRODUCTION

2.1 BACKGROUND INFORMATION

The MED-EL BONEBRIDGE Bone Conduction Implant is a transcutaneous, active bone conduction implant that was first implanted in 2011 in a European multicenter clinical trial. (Sprinzl, et al., 2013) Results from the initial clinical trial demonstrated effectiveness in restoring hearing and a low number of adverse events for subjects with mixed and conductive hearing loss. The BONEBRIDGE consists of an implantable part, the Bone Conduction Implant (BCI), and the external audio processor. The BCI consists of a magnet surrounded by the receiver coil, the electronics, a bendable transition, and the Bone Conduction-Floating Mass Transducer (BC-FMT).

A long history of experience with other available bone conduction implants, such as percutaneous BAHA devices, resulted in positive audiological outcomes but a high number of adverse events such as skin reactions, loss of osseointegration, and revision surgery. (Badran, Bunstone, Arya, Suryanarayanan, & Mackinnon, 2006) Development of the transcutaneous BONEBRIDGE system offers an intact skin solution that does not require osseo-integration and, thus, provides an active bone conduction implant with fewer post-operative complications.

In 2016, Schmerber et al. published on 13 adult patients with mixed or conductive hearing loss implanted with the BONEBRIDGE. (Schmerber, et al., 2016) No complications, device failures, or revision surgeries were reported in this patient group through 12 months post-implantation. Subjects demonstrated significant improvements in functional gain, speech perception in quiet, and speech perception in noise. These results were further confirmed by Weiss et al., who published data on 18 subjects implanted with BONEBRIDGE for mixed or conductive hearing loss. (Weiss, et al., 2016) No cases of infection or other complications were reported in this study. Riss et al. demonstrated similar results in subjects with mixed hearing loss and with atresia. (Riss, et al., 2014) On average, subjects with mixed hearing loss demonstrated 24.7 dB of functional gain, while subjects with atresia demonstrated 32.5 dB of functional gain. The authors hypothesized that the group with atresia demonstrated higher functional gain because they had a larger pre-operative air-bone gap.

A variety of surgical approaches can be used to properly place the BONEBRIDGE, and pre-operative imaging is recommended in the planning of BONEBRIDGE placement. A review published in 2015 reported on five publications including 20 patients. (Zernotti & Bravo Sarasty,

2015) Surgical approaches encompassed transmastoid, retrosigmoid, and middle fossa or "above the temporal line." Patient anatomy and history of prior ear surgery can influence the decision on which surgical approach is most appropriate. Functional gain ranging from 24 to 43 dB was reported in these five publications.

As published by Sprinzl & Wolf-Magele in 2015, 29 studies reported improvements in audiological outcomes and low complication rates. (Sprinzl & Wolf-Magele, 2016) Twelve studies reporting safety outcomes showed a total of six minor complications across three studies, with nine studies reporting no adverse events through at least six months of follow-up. These studies included a wide range of demographic and surgical factors, indicating that BONEBRIDGE is safe for use in the approved population and with the recommended surgical techniques. Additionally, 11 studies demonstrated improved audiological outcomes in both short-term and long-term data, indicating that BONEBRIDGE is also effective in the approved population.

The current study proposes to collect multicenter safety and effectiveness data across North America. Audiological and surgical outcomes will be collected and reported, as well as the occurrence of any known risks with BONEBRIDGE implantation. The subject population will meet the current indication criteria and investigators will follow the recommended surgical techniques.

2.2 POTENTIAL RISKS AND BENEFITS

2.2.1 KNOWN POTENTIAL RISKS

The known potential risks of implantation in the currently approved population are as follows:

- Post-surgery displacement of the implant
- Post-surgical translocation of the BC-FMT
- Extrusion of the implant
- Skin-related issues
- Infection
- Tinnitus
- Vertigo
- Headache
- Dural erosion/compression
- CSF leak
- Meningitis
- Bleeding/hematoma or subdural hematoma
- Facial nerve injury
- Intra-operative complications, including from anesthesia

In rare cases, post-operative device failure or decrease in device performance may occur. Some serious complications may result in revision surgery.

It is recommended that bone conduction implant recipients receive age-appropriate vaccinations, including a pneumococcal meningitis vaccine prior to implantation.

2.2.2 KNOWN POTENTIAL BENEFITS

Subjects may experience an improvement in sound detection and speech perception abilities, as compared to preoperative abilities with or without acoustic amplification.

Subjects may also obtain subjective benefit after implantation, as compared to their experience with or without acoustic amplification.

3 OBJECTIVES

All subjects will receive a MED-EL BONEBRIDGE Bone Conduction Implant.

The primary objective is to assess safety and effectivenss of the MED-EL BONEBRIDGE Bone Conduction Implant for adults with mixed or conductive hearing loss.

Secondary objectives will assess post-operative audiometric and speech perception outcomes with BONEBRIDGE, compared to unaided pre-operative performance as well as report on intraoperative experience.

4 STUDY DESIGN AND ENDPOINTS

4.1 DESCRIPTION OF THE STUDY DESIGN

Approximately 30 subjects will be enrolled across three centers in this single-arm, repeated measures study, where each subject serves as his or her own control. Of the 30 subjects recruited into the study, 15 subjects with mixed hearing loss and 15 subjects with conductive hearing loss will be recruited across all three sites. After enrollment/baseline assessment confirms candidacy, qualified individuals will receive a BONEBRIDGE Bone Conduction Implant. Each subject will subsequently be fit with a SAMBA Audio Processor.

Activation will occur at two weeks post-implantation. Follow-up evaluations will occur at two weeks, one month, and three months post-activation. Soundfield thresholds, as well as speech perception testing in quiet and in noise, will be measured at the follow-up intervals. Results will be compared to the pre-operative unaided condition. In addition to any complications reported on a surgical questionnaire, safety outcomes will be collected and reported as the number and proportion of subjects experiencing a known risk. The three-month interval will be considered the primary safety and effectiveness endpoint.

4.2 STUDY ENDPOINTS

4.2.1 PRIMARY ENDPOINTS

Primary endpoints are as follows:

1. Comparison of AzBio sentence score in noise with the BONEBRIDGE at three months post-activation to the pre-operative unaided score. Testing will be completed in the soundfield at 60 dB SPL with a +5 dB signal-to-noise ratio (SNR). Improvement will be defined as equal to or greater than 10 percentage points.
2. Number and proportion of subjects experiencing known risks, as listed above in Section 2.2.1.

4.2.2 SECONDARY ENDPOINTS

Secondary endpoints are as follows:

1. CNC word score in quiet with the BONEBRIDGE at three months post-activation in the individual implant ear(s), compared to the pre-operative unaided score in the same ear. Testing will be completed in the soundfield at 60 dB SPL. Scores at three months will be similar to or better than scores at the pre-operative interval. Similar is defined as within 10 percentage points, while better than is defined as equal to or greater than a 10-percentage-point change. Subjects will be classified as improved, similar, or worse at three months post-activation.
2. Soundfield thresholds with the BONEBRIDGE at three months post-activation in the individual implant ear(s) at 500-4000 Hz, compared to pre-operative soundfield thresholds in the same ear. Thresholds at three months will be similar to or better than scores at the pre-operative interval. Similar is defined as thresholds within 15 dB at five or more of the frequencies tested, while better is defined as a 15 dB improvement in thresholds at three or more frequencies tested. Subjects will be classified as improved, similar, or worse at three months post-activation.
3. QuickSIN score with the BONEBRIDGE at three months post-activation in the individual implant ear(s), compared to the pre-operative unaided score in the same ear. Scores at three months will be similar to or better than scores at the pre-operative interval. Similar is defined as within 1 dB SNR, while better than is defined as equal to or greater than than a 1 dB SNR decrease. Subjects will be classified as improved, similar, or worse at three months post-activation.
4. Bone conduction thresholds from the device activation interval will be compared to the pre-operative interval to assess stability in the implant ear(s). A worsening in bone conduction thresholds is defined as a 15 dB or greater decrease. Bone conduction thresholds will be considered stable if no more than two frequencies demonstrate a worsening.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 PARTICIPANT INCLUSION CRITERIA

Individuals must meet all of the inclusion criteria set forth below in order to qualify for inclusion in this study.

- Adults, 18 years of age or older at the time of implantation
- Conductive or mixed hearing loss, defined as:
  - Conductive hearing loss with pure-tone average (PTA) for bone conduction thresholds better than or equal to 25 dB at 500, 1000, 2000 and 3000 Hz
  - Mixed hearing loss with PTA for bone conduction thresholds better than or equal to 45 dB at 500, 1000, 2000, and 3000 Hz
- Sufficient air-bone gap at 500, 1000, 2000, and 3000 Hz to demonstrate potential for improvement
- Ability to benefit from amplification as defined by an unaided word recognition score of 30% correct or better
- Bilateral BONEBRIDGE can be considered if the difference in PTA for bone conduction thresholds is 10 dB or less between the right and left ears
- Prior experience with acoustic or bone conduction hearing aids, unless candidate is unable to wear amplification for medical reasons
- Able to complete testing materials in English
- CT scan indicating the patient's anatomy is adequate to enable placement of the implant
- Ability to undergo general anesthesia
- Appropriate motivation and expectation levels
- Stated willingness to comply with all study procedures for the duration of the study

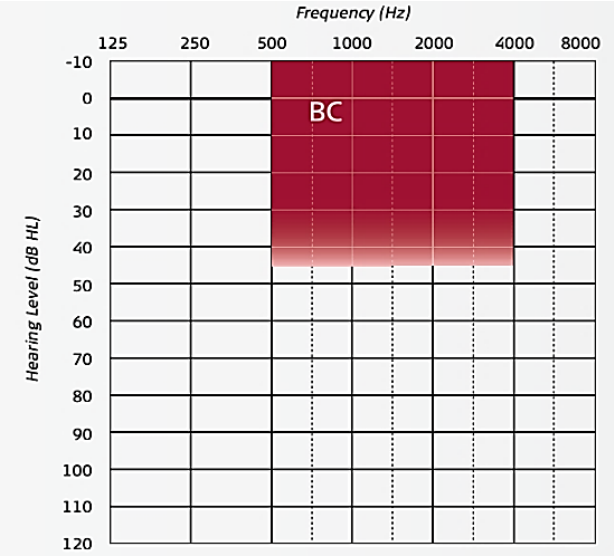


FIGURE 1 – Example inclusion audiogram showing audiometric threshold criteria.

NOTE: Subjects may fall outside of the shaded area but still meet the PTA criteria.

5.2 PARTICIPANT EXCLUSION CRITERIA

Any individual meeting the below exclusion criteria at the candidacy evaluation will be excluded from study participation.

- Evidence that hearing loss is retrocochlear in origin
- Skin or scalp condition precluding use of external audio processor
- Suspected cognitive impairment or organic brain dysfunction

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Participants in the study will be enrolled at the three clinical trial sites involved. Each site should aim to recruit 10 subjects in order to reach the sample size of 30 subjects. Two investigative sites from within the United States will be included; one site will be located in Canada. Sites should recruit candidates with both conductive and mixed hearing loss, with the intention of enrolling 15 subjects with mixed hearing loss and 15 subjects with conductive hearing loss. If needed, the total number of subjects enrolled may exceed 30 in order to have roughly equal subgroups based on type of hearing loss.

Subject recruitment is expected to take approximately 18 months. Each site should expect to enroll one to two subjects per six-month period throughout the duration of the study. At this rate, we expect to have 30 subjects enrolled in the trial within 18 months.

5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

Subjects may voluntarily withdraw from the study at any point. Subjects who choose to withdraw or are terminated from the study should be reported to study monitors as soon as possible. Subjects who are considered lost-to-follow-up should also be reported to study monitors immediately.

5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

Withdrawn subjects will continue to be seen by their clinical audiologist and surgeon for regular follow-ups, but no additional data will be collected. Subjects may voluntarily withdraw from the study at any time without fear of repercussion or loss of benefit from the study device. When withdrawing, the subject should contact study personnel at their implanting site, who will contact the study monitor. Reasons for withdrawal will be described in study reports.

6 STUDY DEVICE

The MED-EL BONEBRIDGE Bone Conduction Implant is a commercially marketed device consisting of the Bone Conduction Implant (BCI 601 or BCI 602) and the Audio Processor. The BCI is the implantable part of the BONEBRIDGE and can only be used together with compatible MED-EL external components. The device is an osseo-integrated bone conduction implant system, intended to provide a level of useful sound perception for individuals with conductive and mixed hearing loss. The BCI is surgically implanted into the mastoid bone.

The externally-worn audio processor is attached to the user's head, behind the ear. A magnet in the audio processor is attracted to an opposing magnet within the implant. The audio processor includes two microphones to pick up sound from the environment, sound processing circuitry to modify the output signal to the user's specific requirements, and a digital compression processor. The device is powered by a single standard battery. The BONEBRIDGE system is activated by fitting the audio processor to the patient.

The implanted part of the BONEBRIDGE system consists of the internal coil and the Bone Conduction Floating Mass Transducer (BC-FMT). A signal from the audio processor is transferred across the skin to the internal coil. The internal coil then relays the signal to the BC-FMT. The BC-FMT converts the signal to vibrations, which are interpreted by the user as sound.

7 STUDY PROCEDURES AND SCHEDULE

7.1 STUDY PROCEDURES

7.1.1 STUDY SPECIFIC PROCEDURES

The following procedures will be performed over the duration of the study and will be documented for each subject enrolled in the study.

- Informed Consent (IC): Investigators will review the IC with potential subjects and obtain signature prior to initiating study activities.
- Medical Assessment: Subjects should be evaluated for their ability to undergo surgery. This should include a chart review to document prior surgeries and known health conditions, as well as ear-related history. All subjects should also undergo a complete otologic exam and radiologic assessment, for proof of adequate anatomy to enable placement of the implant.
- Surgery: BONEBRIDGE surgery will be performed once a subject has consented to participating in the study and completed pre-operative assessment.
- Unaided Thresholds: Unaided air conduction thresholds will be measured pre- and post-operatively at 250, 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz. Bone conduction thresholds will also be measured at 500, 1000, 2000, 3000, and 4000 Hz in order to determine whether hearing loss is conductive or mixed.

- Sentence Testing: AzBio sentences in noise will be administered at 60 dB SPL with a signal-to-noise ratio of +5 dB SNR as the primary outcome measure. Sentence testing will occur in the unaided condition pre-operatively and with the BONEBRIDGE post-operatively. One list will be presented per condition.
- Monosyllabic Word Testing: CNC words in quiet will be administered at 60 dB SPL as a secondary outcome measure. Word testing will occur in the unaided condition pre-operatively, and with the BONEBRIDGE post-operatively. One list will be presented per condition.
- Soundfield Thresholds: soundfield thresholds will be measured in the implant ear only at 500, 1000, 2000, 3000, and 4000 Hz pre-operatively and post-operatively.
- Signal-to-Noise Ratio Testing: The QuickSIN will be administered at 60 dB SPL pre-operatively in the unaided condition and post-operatively with the BONEBRIDGE. This will be reported as a Signal-to-Noise Ratio Loss.
- Subjective Questionnaires: Subjects will complete the SSQ12 questionnaire (Noble, Jensen, Naylor, Bhullar, & Akeroyd, 2013) and HDSS questionnaire (Luetje, et al., 2002) pre-operatively and post-operatively.
- BONEBRIDGE Programming: Programming of the audio processor should occur at each interval after device activation.
- Occurrence of Known Risks: occurrence of risks should be monitored throughout the duration of the study and reported as appropriate.

7.1.2 STUDY INTERVALS

- Enrollment/baseline
- Surgery (within 4 months of baseline)
- BONEBRIDGE implant activation (2-4 weeks post-operative)
- 2-weeks post-activation (1.5-3 weeks post-activation)
- 1-month post-activation (3-6 weeks post-activation)
- 3-months post-activation (10-14 weeks post-activation)

Testing can occur outside of the provided window with prior approval from MED-EL.

7.2 STUDY SCHEDULE

7.2.1 ENROLLMENT/BASELINE

Prior to completing any candidacy or baseline testing, subjects will sign an informed consent (IC) form.

All testing should occur in a sound-treated booth under insert earphones or in the soundfield with the subject seated one meter from the speaker, depending on the test condition. Speaker output should be calibrated prior to conducting study-related testing to ensure consistency

across clinical trial sites. During soundfield measures, the contralateral ear should be plugged or masked, as needed, taking special consideration for unilateral conductive or mixed hearing losses.

If a subject qualifies for bilateral BONEBRIDGE implantation, each ear will be treated separately.

Baseline testing will include the following outcome measures:

- Unaided audiogram, insert earphones (if patent ear canal)
  - Pure-tone air conduction thresholds (250 – 8000 Hz)
  - Pure-tone bone conduction thresholds (500 – 4000 Hz)
- Unaided speech testing in noise, soundfield
  - AzBio Sentences in noise at 60 dB SPL with an SNR of +5 dB
  - Speech and noise will be presented at 0° azimuth
  - One list of 20 sentences will be presented to the individual implant ear(s) alone
  - Lists will be randomized at each clinical trial site
  - Contralateral ear plugged or masked, as needed
- Unaided speech testing in quiet, soundfield
  - CNC Words in quiet at 60 dB SPL
  - One list of 50 words will be presented to the individual implant ear(s) alone
  - Lists will be randomized at each clinical trial site
  - Contralateral ear plugged or masked, as needed
- Unaided audiogram, soundfield
  - Soundfield thresholds (500 – 4000 Hz) in the individual implant ear(s) alone
  - Contralateral ear plugged or masked, as needed
- Unaided signal-to-noise ratio testing, soundfield
  - QuickSIN at 60 dB SPL in the individual implant ear(s) alone
  - Speech and noise will be presented at 0° azimuth
  - Lists will be randomized at each clinical trial site
  - Reported as a signal-to-noise ratio loss
  - Contralateral ear plugged or masked, as needed
- Subjective questionnaires
  - SSQ12 & HDSS

7.2.2 SURGERY

Surgery will be completed within four months of the above pre-operative testing. If surgery is not completed within four months of baseline testing, the testing should be repeated to ensure accuracy. The surgical steps to be followed are drawn from the MED-EL BONEBRIDGE Surgical Guide. These same steps are also detailed in *Appendix A*.

7.2.3 DEVICE ACTIVATION

Device activation will occur two to four weeks after surgery. Prior to fitting the device, the following testing should be completed:

- Unaided audiogram, insert earphones (if patent ear canal)
  - Pure-tone air conduction thresholds (250 – 8000 Hz)
  - Pure-tone bone conduction thresholds (500 – 4000 Hz)

Investigators should fit the SAMBA Audio Processor in accordance with the instructions in the IFU for SYMFIT software.

7.2.4 TWO WEEKS POST-ACTIVATION

The two-week follow-up visit will occur 1.5 to three weeks following activation of the audio processor. All audiometric testing should occur in a sound-treated booth in the sound field, with the subject seated one meter from the speaker. During soundfield measures, the contralateral ear should be plugged or masked as needed, taking special consideration for unilateral conductive or mixed hearing losses. In the case of bilateral implantation, each ear should be tested separately.

Testing should occur with the SAMBA Audio Processor and be completed prior to making programming changes to the subject's processor. Testing should be conducted using the patient's preferred program and volume settings. The following testing should be completed:

- Aided audiogram, soundfield
  - Soundfield thresholds (500 – 4000 Hz) in the individual implant ear(s) alone
  - Contralateral ear plugged or masked, as needed

Programming of the SAMBA Audio Processor should be completed in accordance with the recommendations in the IFU for SYMFIT software.

7.2.5 ONE MONTH POST-ACTIVATION

The one-month follow-up visit will occur three to six weeks post-activation. All audiometric testing should occur in a sound-treated booth in the sound field, with the subject seated one meter from the speaker. Speaker output should be calibrated prior to conducting study-related testing to ensure consistency across study sites. During soundfield measures, the contralateral ear should be plugged or masked as needed, taking special consideration for unilateral conductive or mixed hearing losses. In the case of bilateral implantation, each ear should be tested separately.

Testing should occur with the SAMBA Audio Processor and be completed prior to making programming changes to the subject's processor. Testing should be conducted using the patient's preferred program and volume settings. The following testing should be completed:

- Aided speech testing in noise, soundfield
  - AzBio Sentences in noise at 60 dB SPL with an SNR of +5 dB
  - Speech and noise will be presented at 0° azimuth
  - One list of 20 sentences will be presented to the individual implant ear(s) alone
  - Lists will be randomized at each clinical trial site
  - Contralateral ear plugged or masked, as needed
- Aided speech testing in quiet, soundfield
  - CNC Words in quiet at 60 dB SPL
  - One list of 50 words will be presented to the individual implant ear(s) alone
  - Lists will be randomized at each clinical trial site
  - Contralateral ear plugged or masked, as needed
- Aided signal-to-noise ratio testing, soundfield
  - QuickSIN at 60 dB SPL in the individual implant ear(s) alone
  - Speech and noise will be presented at 0° azimuth
  - Lists will be randomized at each clinical trial site
  - Reported as a signal-to-noise ratio loss
  - Contralateral ear plugged or masked, as needed

Programming should be completed according to the IFU for SYMFIT software.

7.2.6 THREE MONTHS POST-ACTIVATION

The three-month follow-up visit will occur 10 to 14 weeks post-activation. All audiometric testing should occur in a sound-treated booth in the sound field, with the subject seated one meter from the speaker. Speaker output should be calibrated prior to conducting study-related testing to ensure consistency across study sites. During soundfield measures, the contralateral ear should be plugged or masked as needed, taking special consideration for unilateral conductive or mixed hearing losses. In the case of bilateral implantation, each ear should be tested separately.

Testing should occur with the SAMBA Audio Processor and be completed prior to making programming changes to the subject's processor. Testing should be conducted using the patient's preferred program and volume settings. The following testing should be completed:

- Aided speech testing in noise, soundfield
  - AzBio Sentences in noise at 60 dB SPL with an SNR of +5 dB
  - Speech and noise will be presented at 0° azimuth
  - One list of 20 sentences will be presented to the individual implant ear(s) alone
  - Lists will be randomized at each clinical trial site
  - Contralateral ear plugged or masked, as needed
- Aided speech testing in quiet, soundfield
  - CNC Words in quiet at 60 dB SPL
  - One list of 50 words will be presented to the individual implant ear(s) alone

  - Lists will be randomized at each clinical trial site
  - Contralateral ear plugged or masked, as needed
- Aided audiogram, soundfield
  - Soundfield thresholds (500 – 4000 Hz) in the individual implant ear(s) alone
  - Contralateral ear plugged or masked, as needed
- Aided signal-to-noise ratio testing, soundfield
  - QuickSIN at 60 dB SPL in the individual implant ear(s) alone
  - Speech and noise will be presented at 0° azimuth
  - Lists will be randomized at each clinical trial site
  - Reported as a signal-to-noise ratio loss
  - Contralateral ear plugged or masked, as needed
- Subjective questionnaires
  - SSQ12 & HDSS

Programming should be completed according to the IFU for SYMFIT software.

7.2.7 SCHEDULE OF EVENTS TABLE

		Candidacy/ Pre-op	Surgery	Activation	2 weeks post-activation	1 month post-activation	3 months post-activation
	Informed Consent	X					
	Medical Assessment	X					
	Surgery		X				
	Unaided thresholds	X		X			
Implant Ear(s)	AzBio 60 dB SPL +5 dB SNR	Unaided				Aided	Aided
Implant ear(s)	CNC Words 60 dB SPL quiet	Unaided				Aided	Aided
Implant ear(s)	Soundfield thresholds	Unaided			Aided		Aided
Implant ear(s)	QuickSIN 60 dB SPL	Unaided				Aided	Aided
	SSQ12	X					X
	HDSS	X					X

(TABLE 1)

8 ASSESSMENT OF SAFETY

8.1 REPORTING OF KNOWN RISKS

The rate of occurrence of known risks will be reported and summarized for the duration of the study. Events will be reported as the number and proportion of subjects experiencing a risk.

8.1.1 LIST OF KNOWN RISKS

The list of known potential risks for BONEBRIDGE implantation are:

- Post-surgical displacement of the implant
- Post-surgical translocation of the BC-FMT
- Extrusion of the implant

- Skin-related issues
- Infection
- Tinnitus
- Vertigo
- Headache
- Dural erosion/compression
- CSF leak
- Meningitis
- Bleeding/hematoma or subdural hematoma
- Facial nerve injury
- Intra-operative complications, including from anesthesia
- Device failure

8.1.2 UNKNOWN RISKS

Any events related to the device or procedure that are not included in the list above occurring in the study population will also be summarized and reported.

8.2 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an event may be brought to the attention of the investigator during study visits, interim visits, or phone conferences over the duration of the study. All events will be reported on the Risk Occurrence case report form. Information to be collected on the CRF includes: event description, date of onset, time of onset, seriousness, and the date/time of resolution (if applicable).

Investigators should record all reportable events with start dates occurring any time after the IC is obtained. Any medical condition that is present at the enrollment/baseline evaluation will not be reported as an event. If the subject's condition deteriorates at any time during the study, however, the event will be reported.

9 CLINICAL MONITORING

Clinical site monitoring is conducted to ensure that the rights and well-being of subjects are protected, that the reported trial data are accurate, complete, and verifiable from source documents, and that the trial is being conducted in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirements.

Case report forms and other related study documentation will be reviewed as MED-EL receives the completed paperwork throughout the duration of the study. Completed study records will be reviewed 100% for missing data entries. Accuracy of study records will be monitored based on the investigator's history, accuracy of study records, the rate of occurrence of known risks, and the occurrence of protocol deviations.

10 STATISTICAL CONSIDERATIONS

10.1 STATISTICAL HYPOTHESES

The primary endpoint is change in the AzBio sentence score from pre-operative levels to 3 months. An increase of 10 percentage points in this score is considered clinically relevant. The hypotheses to be tested are:

Ho: $\mu\Delta < 10$
Ha: $\mu\Delta \geq 10$

where $\mu\Delta$ is the mean change in the AzBio sentence scores from pre-operative to 3 months post-operative. These scores are represented as a percentage of words accurately repeated during testing.

10.2 DESCRIPTION OF STATISTICAL METHODS

10.2.1 GENERAL APPROACH

Continuous variables will be summarized using mean, median, inter-quartile range, minimum, and maximum values. Categorical variables will be summarized using counts and percents. Testing of the primary endpoint will be done at the 0.025 level of significance.

10.2.2 ANALYSIS OF THE PRIMARY ENDPOINTS

The mean change in AzBio sentence score from baseline to 3 months post-activation will be summarized as a continuous variable using the descriptive statistics described in section 10.4.1. Additionally, a one-sided, paired t-test comparing the mean change in AzBio sentence score to the superiority margin of 10 will be performed and the corresponding p-value will be reported. A p-value less than 0.025 will result in rejection of the null hypothesis indicating that the mean change in AzBio sentence score was greater than 10 percentage points.

The rate of occurrence of known risks will be summarized and reported as the number and proportion of subjects experiencing an event.

10.2.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary endpoints will not be formally tested but will be summarized using appropriate descriptive statistics.

The number and percentage of subjects performing similarly or better on CNC words, soundfield thresholds, QuickSIN, and bone conduction thresholds at 3 months post-activation, compared to the pre-operative unaided condition, will be presented. The formal definitions of what is considered worse, similar, and better are presented in section 4.2.2.

10.2.4 ADHERENCE AND RETENTION ANALYSES

Subjects lost to follow-up or terminated early for other reasons will be tabulated and summarized. For those subjects without a 3-month follow-up visit, the 3-month AzBio score will be imputed using last observation carried forward. That is, the 1 month Azbio score will be used as the 3 month AzBio score for the purposes of analysis. Only a small number of subjects are expected to be lost to follow-up, and benefit from the implant should be immediate, making this imputation method reasonable.

10.2.5 BASELINE DESCRIPTIVE STATISTICS

Baseline descriptive statistics will be summarized and reported for all subjects with available baseline data. All demographic and medical history information will be tabulated and presented as described in section 10.3.1 above.

10.2.6 ADDITIONAL SUB-GROUP ANALYSES

The change in AzBio sentence score and any change in aided bone conduction thresholds will be summarized by hearing loss type. No formal statistical comparison will be done between these two groups nor will any testing be formally done against the 10 percentage point increase as was done for the total combined group.

10.2.7 EXPLORATORY ANALYSES

Subjective improvement, as measured by the SSQ12 and HDSS questionnaires at three months post-activation, will be summarized. Responses will be compared to the pre-operative “everyday listening condition.”

10.2.8 MULTIPLE COMPARISON/MULTIPLICITY

There is only one endpoint being formally tested in this study, therefore multiplicity is not an issue.

10.3 SAMPLE SIZE

A sample size of 30 subjects provides a power of 94.2% to detect a 10 percentage point increase in the AzBio sentence score from baseline to 3 months using an alpha level of 0.025. This assumes that an average increase of 30 percentage points with a standard deviation of 30. These initial estimates used for the sample size calculation came from the results for the Electric-Acoustic System (EAS) Investigational pivotal trial.

10.4 SITE POOLABILITY

Poolability of the data collected at the three centers will be established in the following manner. For each subject, the change from baseline to 3 months in the AzBio sentenc score will be

computed. The changes in AzBio sentence score will be analyzed using a one-way analysis of variance in which site forms the levels of the single factor. The overall F-test will be used to demonstrate poolability of the primary endpoint data. If the p-value for the overall F-test is greater than or equal to 0.10 then the data will be considered poolable. If the p-value is less than 0.10, then additional methods (e.g. stratified analysis) may need to be employed in the analysis of the primary endpoint.

11 ETHICS/PROTECTION OF HUMAN SUBJECTS

11.1 ETHICAL STANDARD

The investigator will ensure that the study is conducted in accordance with regulations for the protection of human subjects found in 21 CFR Part 50 and 21 CFR Part 56.

11.2 INSTITUTIONAL REVIEW BOARD

The protocol, IC form, and any recruitment or participant materials will be submitted to the IRB for review and approval. IRB approval of both the protocol and IC must be obtained prior to beginning enrollment. Any amendment to the study protocol must also receive IRB approval before those changes are implemented in the study. Changes to the consent form will also be submitted to the IRB; at that time, a determination as to whether or not previously consented subjects need to be re-consented will be made.

11.3 INFORMED CONSENT PROCESS

11.3.1 CONSENT DOCUMENTS PROVIDED TO PARTICIPANTS

A consent form with detailed descriptions of the study device, study procedures, and risks will be given to the participant. Written documentation of IC is required prior to initiating any study-related activities. The IC template included with this protocol will be provided to each investigative site.

11.3.2 CONSENT PROCEDURES AND DOCUMENTATION

The IC process will be initiated prior to the participant's involvement in any study-related activities. Potential participants must be informed as to the purpose of the study and the potential risks and benefits known, or that can be reasonably predicted or expected. These risks are described in the written consent form.

Consent forms will be IRB approved, and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and will answer any questions that may arise. All participants will receive a verbal explanation of the purpose, procedures, and potential risks of the study, as well as their rights as research participants.

The participant will sign the IC prior to being enrolled in the study. The investigator administering the IC will sign and date the form to indicate the document was sufficiently explained to the subject and their signature was witnessed. Consent may be withdrawn at any time during participation in the study. A copy of the signed IC will be provided to the subject, while the original will be retained by the investigator in the study file.

11.4 PARTICIPANT AND DATA CONFIDENTIALITY

The study protocol, documentation, data, and all other information generated will be kept in strict confidence. No information concerning the study or the data will be released to any unauthorized third party, without prior written approval of MED-EL. The investigator will guarantee that all persons involved will respect the confidentiality of any information concerning the study subjects.

All information provided to the investigator by MED-EL will be kept strictly confidential and confined to the personnel involved in conducting the study. Such personnel will be informed of the confidential nature of the information. It is recognized that this information may be communicated in confidence to the relevant IRB. In addition, no reports or information about the study or its progress will be provided to anyone not involved in the investigation, other than MED-EL or the relevant IRB, except if required by applicable law or regulation.

All data provided to MED-EL will be identified by a unique subject ID, thereby ensuring that the subject's identity remains unknown. The subjects should be informed in writing that their data will be stored and analyzed in a computer, with confidentiality maintained in accordance with applicable regulations.

The subjects should also be informed that authorized representatives of MED-EL and/or regulatory authorities may require access to parts of the site records (relevant to the study), including medical history, for data verification. The investigator is responsible for keeping a subject identification list of all subjects screened and enrolled.

12 DATA HANDLING AND RECORD KEEPING

12.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Prior to initiation of the study, investigators who may complete CRFs and are responsible for maintaining appropriate documentation will be identified. The investigator will be responsible for maintaining complete and accurate documentation of study procedures and medical records, including IC forms, for the duration of the study. Copies of correspondence with the IRB, Clinical Monitor, and MED-EL in general should also be maintained. Data on subjects will be collected in an anonymous manner, and any records sent to MED-EL should be de-identified.

The investigator is responsible for ensuring completeness, legibility, and accuracy of the recorded data. Source documentation should be completed in a neat, legible manner to ensure accurate interpretation of the data. When making changes or corrections, cross out the original

entry with a single line, and initial and date the change. Do not erase, write over, or use correction fluid or tape on the original document.

12.2 STUDY RECORDS RETENTION

Upon completion of the study, it is the investigator's responsibility to maintain all study records in a safe and secure location. Study-related documents should be kept for the duration of the study as required by 21 CFR Part 812.40 and the institution's IRB.

12.3 PROTOCOL DEVIATIONS

Any noncompliance with the protocol or with GCP requirements will be reported to MED-EL in the protocol deviation log as a protocol deviation. Protocol deviations may be on the part of the investigator, participant, or other study staff. Corrective actions will be implemented based on the type and frequency of protocol deviations from each site. It is the responsibility of the investigator to be familiar with the protocol and to be vigilant regarding potential protocol deviations. Deviations should be submitted to MED-EL and the IRB in a timely manner, as required.

12.4 PUBLICATION AND DATA SHARING POLICY

All results generated in this study will be considered strictly confidential. No investigator may submit the results for publication without prior written permission of MED-EL. Once the study has concluded, publication of the multi-center data will be sought.

Authorship will be determined based on the amount of contribution to the study. The lead site (as designated prior to study initiation) may choose up to two authors for the multi-center publication. Additionally, the site with the most implanted subjects may also choose up to two authors. In the event that the lead site also enrolls the most subjects, then the site with the second largest number of subjects may choose up to three authors. The authors selected will be at the discretion of the principal investigator (PI) at each of the aforementioned sites. MED-EL reserves the right to include additional authors who have made substantial contributions to the study. Investigators may submit the results for presentation at conferences, with written approval from MED-EL.

The lead author will be the PI from the lead site. Last author will be at the discretion of MED-EL and could include the original PI from the lead site, if that person has since moved, or the PI at the site implanting the most subjects.

Any investigator wishing to present center-specific data at a national or international forum must inform MED-EL of the presentation title, forum, and date prior to submission of the abstract.

13 CONFLICT OF INTEREST POLICY

Any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or other aspect of this trial will be disclosed and managed.

14 LITERATURE REFERENCES

Badran, K., Bunstone, D., Arya, A., Suryanarayanan, R., & Mackinnon, N. (2006). Patient Satisfaction with the Bone-Anchored Hearing Aid: A 14-Year Experience. *Otology & Neurotology, 27*, 659-666.

Cox, R., & Alexander, G. (1995). The abbreviated profile of hearing aid benefit. *Ear & Hearing, 16*(2), 176-186.

Luetje, C., Brackman, D., Balkany, T., Maw, J., Baker, R., Kelsall, D., . . . Arts, A. (2002). Phase III clinical trial results with the Vibrant Soundbridge implantable middle ear hearing device: A prospective controlled multicenter study. *Otolaryngology - Head and Neck Surgery, 126*(2), 97-107.

Noble, W., Jensen, N., Naylor, G., Bhullar, N., & Akeroyd, M. (2013). A short form of the Speech, Spatial and Qualities of Hearing scale suitable for clinical use: the SSQ12. *International Journal of Audiology, 52*(6), 409-412.

Riss, D., Arnolder, C., Baumgartner, W.-D., Blineder, M., Flak, S., Bachner, A., . . . Hamzavi, J.-S. (2014). Indication Criteria and Outcomes with the Bonebridge Transcutaneous Bone-Conduction Implant. *The Laryngoscope, 124*(12), 2802-2806.

Schmerber, S., Deguine, O., Marx, M., Van de Heyning, P., Sterkers, O., Mosnier, I., . . . Karkas, A. (2016). Safety and effectiveness of the Bonebridge transcutaneous activer direct-drive bone-conduction hearing implant at 1-year device use. *Eur Arch Otorhinolaryngol, 274*(4), 1835-1851.

Sprinzl, G., & Wolf-Magele, A. (2016). The Bonebridge Bone Conduction Hearing Implant: indication criteria, surgery and a systematic review of the literature. *Clin Otolaryngol, 41*, 131-143.

Sprinzl, G., Lenarz, T., Ernst, A., Hagen, R., Wolf-Magele, A., Mojallal, H., . . . Wolframm, M. (2013). First European Multicenter Results with a New Transcutaneous Bone Conduction Hearing Implant System: Short-Term Safety and Efficacy. *Otology & Neurotology, 34*(6), 1076-1083.

Weiss, R., Leinung, M., Baumann, U., Weissgerber, T., Rader, T., & Stover, T. (2016). Improvement of speech perception in quiet and in noise without decreasing localization

abilities with the bone conduction device Bonebridge. *Eur Arch Otorhinolaryngol, 274*(5), 2107-2115.

Zernotti, M., & Bravo Sarasty, A. (2015). Active Bone Conduction Prosthesis: Bonebridge. *Int Arch Otorhinolaryngol, 19*, 343-348.

APPENDICES

APPENDIX A – SURGICAL RECOMMENDATIONS

Surgical Steps	Main Tasks	Pay Attention to:
1. Preparation	• Shave hair • Mark BCI 601 or BCI 602 outline with C-Sizer and T-Sizer or Flat T-Sizer • Mark incision	• Position of BC-FMT and screws (depends on findings of CT scan) • Position of coil (consider use of eyeglasses, hats, etc.; transition of BCI can be bent ± 90 degrees in the horizontal plane
2. Incision	• Incise and prepare skin flap • Place C-Sizer and T-Sizer or Flat T-Sizer	• Skin flap integrity (incision may impair blood supply of skin flap) • Position of incision (not over implant body, further posterior if auricular reconstruction is planned at later stage)
3. Creation of bone bed for BC-FMT and periosteal pocket for coil	• Mark bone bed clearly • Drill bone bed • Check size with T-Sizer or Depth-Gauge Assembly • Elevate periosteum for coil section of implant • Estimate skin flap thickness to be ≤ 7 mm over coil section of BCI	• Correct position (depends on findings of CT scan) • Avoid exposing sigmoid sinus or dura (use diamond burr when drilling close to them) • Use BCI Lifts if required
4. Preparing BCI 601 or 602 fixation	• Drill fixation points with drill bit provided, using T-Sizer or Depth-Gauge Assembly as a guide	• Orientation/distance of fixation points (depends on CT scan) • Don't change position of T-Sizer or Depth-Gauge Assembly between drilling fixation holes one and two
5. Fixation of the BCI 601 or 602	• Remove BCI from sterile package • Add appropriate BCI Lifts onto fixation wings if required • Arrange BCI over site • Place appropriate screws in anchor holes of BC-FMT • Tighten screws with torque wrench	• Only use bipolar electrocautery once the implant is in the surgical field • The BCI can be damaged by excessive bending • Don't use torque > 32 Ncm (otherwise bone can be damaged)
6. Closure	• Verify fixation of BC-FMT • Verify position of coil • Close skin flap in layers • Apply pressure dressing over the wound	• BC-FMT must be installed tightly

Version	Date	Significant Revisions

Version	Date	Significant Revisions
1.0	12/28/2018	Original version
2.0	11/20/2019	Study protocol updated to include BCI 602 implant and minor clarification to inclusion criteria wording