STATISTICAL ANALYSIS PLAN

for

Investigation of the FAST Sound Coding Strategy in Newly Implanted Adult Cochlear Implant Recipients

April 6, 2016

Version 2.1

Study Sponsor:

Cochlear Americas
13059 East Peakview Avenue
Centennial, CO 80111

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1.0 Data Analyses

1.1 Study Population

The study population will include up to 20 adults (18 years of age or older) who are audiological and medical candidates to receive a Nucleus® cochlear implant and are capable of completing the study evaluation.

1.2 Sample Size

Based on the variability observed in the FAST take-home trial in experienced ACE recipients, it was determined using G*Power (Faul et al. 2007) that a minimum of 11 subjects would provide at least 90% power for hypothesis testing of the two co-primary endpoints at the 0.025 alpha level. More subjects will provide additional power or a similar degree of power for more conservative assumptions. Because the non-inferiority sample size calculation assumes a true difference of 0 between ACE and FAST, we propose a sample size of 20 subjects to allow for:

1. the possibility that variability will be greater than expected,
2. the possibility of a clinically insignificant difference between the two strategies,
3. the possibility of subject attrition.

The planned sample size of 20 subjects will provide adequate power for the primary efficacy endpoints. The following general assumptions have been made:

- Non-inferiority tests with M_2 margins of 10 rationalized arcsine units (rau, Studebaker 1985) for CNC word recognition and −2 dB for average BKB sentence recognition across two types of noise (babble and speech-shaped noise)
- One-sided 0.025 alpha levels
- Assumed distribution for population (standard deviation) based on the FAST take-home trial in experienced ACE recipients
- Desire for 90% power

The power analyses for the primary test metrics are provided below.

Sample size calculation for CNC word recognition:

Scenario (Non-inferiority)	Minimum Evaluable Sample Size Required
One-sided 0.025 alpha, 90% power, SD = 7.20 rau, M_2 = 10 rau, true difference = 0	8

Sample size calculation for BKB sentence reception (using previous data from testing in babble only):

Scenario (Non-inferiority)	Minimum Evaluable Sample Size Required
One-sided 0.025 alpha, 90% power, SD = 1.84, M_2 = -2dB, true difference = 0	11

1.3 Safety

1.3.1 Primary Safety Objective

An adverse event (AE) is any undesirable clinical or medical occurrence associated with the use of the device, procedure, or participation in the study, which does not result in serious injury or illness related to the surgical procedure or the device.

Adverse events that occur during this study may be associated with the implant procedure, including those from general anesthesia, or specifically associated with the use of the device. An adverse event will be considered to be device-related when, in the judgment of the Primary Investigator, there is a logical connection between the use of the device and the occurrence of the event, above and beyond the study procedure itself. Adverse events associated with cochlear implantation in previous investigations include tinnitus, dizziness, swelling, facial nerve stimulation, and open and/or short circuit electrodes, among others.

Adverse events will be counted regardless of severity, seriousness, onset, duration, or relation to study treatment.

A serious adverse event (SAE) is any untoward medical occurrence that

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- requires medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
- leads to fetal distress, death, or congenital abnormality or birth defect
- is a medically important event or reaction

For any SAE, if the Primary Investigator judges that there is a logical connection (caused or contributed to) between the use of the device and the occurrence, the SAE will be noted as device-related.

1.3.1.1 *Analysis of Primary Safety Objective*

All Adverse Events will be tabulated according to the study interval, the number of procedure-related events, and the number of device-related events. Procedure- and device-related Adverse Events will be summarized as rates, where the numerator for each rate will be the number of subjects with at least one procedure- or device-related event, and the denominator will be the total number of subjects. No formal statistical comparisons will be conducted.

1.4 Efficacy

Efficacy of the FAST strategy will be determined by a comparison of outcome measures with subjects using ACE versus FAST. The test metrics for this purpose will include CNC word recognition, BKB sentence reception in babble and in speech-shaped noise, battery life duration, and SSQ ratings.

1.4.1 Primary Efficacy Objectives

The two co-primary efficacy endpoints will be based on analyses of CNC word recognition and BKB sentence reception in babble and speech-shaped noise after 3 months of experience with each strategy (collected at 3-months and 6-months post initial activation). The objective of the two co-primary efficacy endpoints is to test for non-inferiority of FAST compared to ACE. Study success will be defined by rejection of the null hypotheses for both of the two co-primary endpoints.

1.4.1.1 *First Co-Primary Efficacy Endpoint: CNC Word Recognition*

The objective of the first co-primary efficacy analysis is to demonstrate non-inferiority of FAST compared to ACE for word recognition in quiet as evaluated with the CNC test. Success for the first co-primary endpoint will be based on rejection of the null hypothesis of inferiority, with a non-inferiority margin of 10 rau based on clinical judgment and variability observed in previous studies ($M_2 = 10$). The treatment effect will be estimated using a LMM adjusted for period and sequence and a random effect for subject. If the upper 97.5% confidence bound is less than 10 rau, statistical significance will be met at the 0.025 alpha level. The first co-primary endpoint is represented by the following hypotheses:

H_0: $CNC_{diff} \geq 10\, rau,$

H_a: $CNC_{diff} < 10\, rau,$

where:

CNC_{diff} = ACE – FAST treatment difference, controlling for period and sequence effects, for CNC word recognition in rationalized arcsine units (rau).

1.4.1.2 *Second Co-Primary Efficacy Endpoint: BKB Sentence Reception in Noise*

The objective of the second co-primary efficacy analysis is to demonstrate non-inferiority of FAST compared to ACE for sentence reception in babble and speech-shaped noise as evaluated with the BKB test. The average speech reception threshold (SRT) across the two noise types will be taken for each subject. For the speech reception threshold procedure employed in this study, results are presented as the signal-to-noise ratio (SNR) at which 50% recognition is achieved. Therefore, a lower SRT in dB indicates better performance. Success for the second co-primary endpoint will be based on rejection of the null hypothesis of inferiority, with a non-inferiority margin of −2dB based on clinical judgment and variability observed in previous studies ($M_2 = -2$dB). The treatment effect will be estimated using a LMM adjusted for period and sequence and a random effect for subject. If the lower 97.5% confidence bound is greater than −2 dB, statistical significance will be met at the 0.025 alpha level. The second co-primary endpoint is represented by the following hypotheses:

H_0: $SRT_{diff} \leq -2dB,$

H_a: $SRT_{diff} > -2dB,$

where:

SRT_{diff} = ACE – FAST treatment difference, controlling for period and sequence effects, for SRT averaged across two noise types.

1.4.2 Secondary Efficacy Objectives

1.4.2.1 *Battery Life*

The secondary efficacy endpoint for battery life will be based on battery logs as recorded by the subject during the take-home period with each strategy. The objective of this secondary endpoint is to demonstrate superiority of FAST compared to ACE for battery life. Success for this secondary endpoint will be based on rejection of the null hypothesis that battery life with FAST is less than or equal to battery life with ACE. The estimated within-subject mean difference in battery life between FAST and ACE will be reported with a 95% confidence interval. A one-sided t-test will be conducted at the 0.025 significance level. The secondary endpoint for difference in battery life is represented by the following hypotheses:

H_0: $BLD \leq 0$,

H_a: $BLD > 0$,

where:

BLD = within-subject battery life difference for FAST – ACE.

1.4.2.2 *Speech, Spatial, and Qualities of Hearing Scale (SSQ12-C)*

The secondary efficacy endpoint for the quality and speech understanding questionnaire will be based on subjects' responses on the SSQ12-C as recorded one month after crossover from the first strategy to the second strategy. The SSQ12-C is a comparative, closed-ended questionnaire composed of 12 items assessing speech perception, spatial hearing, sound quality, and listening effort. A response of 0 on the questionnaire indicates equivalent performance between FAST and ACE, while positive or negative responses indicate a preference for one strategy over the other.

The difference between the two study groups will be evaluated with a two-sided t-test using average responses on the SSQ12-C across the 12 questions within each group. Success for this secondary endpoint will be based on a non-significant result, indicating no difference between the two groups in terms of crossing over from one strategy to the other (i.e., not rejecting the null hypothesis that responses from the two groups are equivalent). The mathematical expressions are:

H_0: $\mu_{G1} = \mu_{G2}$,

H_a: $\mu_{G1} \neq \mu_{G2}$,

where:

μ_{G1} = mean response value on the SSQ12-C for Group 1;

μ_{G2} = mean response value on the SSQ12-C for Group 2.

1.5 Type I Error Control

Study success will be defined by rejection of the null hypotheses of inferiority of FAST compared to ACE for both of the two co-primary endpoints. Because study success depends on the two endpoints together, type I error will be maintained at an overall one-sided alpha level of 0.025.

Secondary efficacy analyses will be conducted using two additional variables: battery life duration and the SSQ12-C. Success for the battery life endpoint will be based on rejection of the null hypothesis that FAST is not superior to ACE at a one-sided alpha level of 0.025. However, success for the SSQ12-C analysis will be based on a non-significant result at the 0.05 level for a two-sided test, indicating no significant difference. Therefore, adjustments for multiplicity will not be made for the secondary efficacy analyses, as such adjustments would actually increase the chance of finding no significant difference and thus increase the possibility for incorrectly passing the SSQ endpoint.

1.6 Additional Statistical Analyses

1.6.1 Analysis of Baseline Characteristics

The baseline characteristics of the study group will be presented descriptively. The effects of baseline covariates on the co-primary efficacy measures will be analyzed with univariable and multivariable regression models. Baseline covariates to be explored include (but are not limited to) working memory score from the Reading Span Test, age at implantation, duration of hearing loss, degree of contralateral hearing loss, and gender. Quantitative variables such as age will be presented with mean, standard deviation, median, minimum, and maximum.

1.6.2 Supportive Efficacy Analyses

Additional supportive analyses may also be conducted. These may include, but are not limited to, acute sound quality ratings conducted at the crossover appointment and clinical audiological testing including sound field thresholds and AzBio sentences. All supportive analyses will be clearly described as such.

1.7 Justification of Pooling Across Study Sites

Pooling data from study sites will be done based on the following: all sites will have the same protocol, the sponsor will monitor the sites to assure protocol compliance, and the data gathering mechanism (case report forms and data acquisition) will be the same across all study sites.

Consistency of the primary efficacy endpoints will be assessed by testing for a difference between sites in the difference between FAST and ACE for CNC word recognition and BKB sentence reception in noise. Testing will be conducted via an analysis of variance model, with difference between FAST and ACE as the outcome and site as the factor. A p-value for the site factor of less than 0.15 will be considered evidence of differences between sites for one of the primary efficacy endpoints. If there is evidence of a difference, additional analyses will be performed to explore the possible role of baseline characteristics to explain the results. Results for the primary efficacy endpoint will also be presented separately by site, irrespective of the test of differences between sites, to help understand both qualitative and non-significant differences between sites.

1.8 Justification of Pooling Across Devices

Pooling data from subjects with different internal devices (CI24RE, CI512, and CI532) will be done based on the following: all devices included in this study use a perimodiolar electrode and are similar in function, and the co-primary efficacy endpoints are based on within-subject comparisons for which the device remains constant.

Consistency of the primary efficacy endpoints will be assessed by testing for a difference across devices in the difference between FAST and ACE for CNC word recognition and BKB sentence reception in noise. Testing will be conducted via an analysis of variance model, with difference between FAST and ACE as the outcome and device as the factor. A p-value for the device factor of less than 0.15 will be considered evidence of differences across devices for one of the primary efficacy endpoints. If there is evidence of a difference, additional analyses will be performed to explore the possible role of baseline characteristics to explain the results. Results for the primary efficacy endpoints will also be presented separately by device, irrespective of the test of differences across devices, to help understand both qualitative and non-significant differences across devices.

1.9 Missing Data

All efforts will be put forth to ensure near complete follow-up, with particular focus on the assessment of the primary outcomes and occurrence of adverse events. A reminder of subject follow-up due dates will be provided to participating centers to facilitate scheduling of the follow-up visits.

Sensitivity analysis will be conducted to address the potential impact of missing endpoint data using a multiple imputation analysis with 10 imputed datasets. A separate imputation model will be performed for each primary outcome variable (CNC score and average SRT). The predictor variables in the model will include, but are not limited to, the three target variables in the primary endpoint analysis (treatment, period, and sequence), and five auxiliary variables to improve the estimation of missing datapoints (Reading Span score, age, duration of hearing loss, pre-operative sentence score, and duration of hearing aid use). The imputed datasets will then be combined for inference using standard methods such as those available in SAS PROC MIANALYZE or other valid statistical software.

2.0 References

Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*, *39*, 175-191.

Studebaker, G. A. (1985). A “rationalized” arcsine transform. *Journal of Speech and Hearing Research*, *28*, 455–62.

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PROTOCOL

Investigation of the FAST Sound Coding Strategy in Newly Implanted Adult Cochlear Implant Recipients

IDE #G150140

Version 2.4

September 28, 2017

Study Sponsor:

Cochlear Americas
13059 E. Peakview Avenue,
Centennial, CO 80111

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Investigator Responsibilities

I, the undersigned, am responsible for the conduct of the study at the site below and by my signature below, I confirm that I have read, understand and will strictly adhere to the study protocol, "**Investigation of the FAST Sound Coding Strategy in Newly Implanted Adult Cochlear Implant Recipients**."

Clinical Investigational Site

Primary Investigator's Name (print)

Title

Signature

Sponsor Representative

Title

Signature

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Clinical Investigational Synopsis

Title	Investigation of the FAST Sound Coding Strategy in Newly Implanted Adult Cochlear Implant Recipients
Study Sites	Up to 7 study sites
Study Duration	6 months post-activation (per subject)
Study Population	20 newly implanted unilateral cochlear-implant recipients
Design Overview	The design is a within-subject, repeated-measures take-home study. Adult cochlear-implant recipients will be given two different sound coding strategies, FAST and ACE, for take-home use in a crossover design. The period of time with each strategy will be 3 months, for a total of 6 months of participation post initial activation. Study procedures will include mapping, speech perception, sound quality judgments, a questionnaire, cognitive testing, and battery logs.
Primary Objective	1. To determine if FAST is non-inferior to ACE for word recognition in quiet in newly-implanted cochlear-implant recipients. 2. To determine if FAST is non-inferior to ACE for sentence perception in noise in newly-implanted cochlear-implant recipients.
Primary Endpoint	1. Word recognition in quiet will be non-inferior for FAST compared to ACE. 2. Sentence perception in noise will be non-inferior for FAST compared to ACE.
Secondary Objectives	1. To quantify the battery life benefit for FAST compared to ACE. 2. To obtain insight into sound quality differences between the strategies and the relative difficulty of conversion for the cochlear-implant recipient from ACE to FAST versus FAST to ACE.
Secondary Endpoints	1. Duration of battery life will be superior for FAST compared to ACE. 2. Comparative ratings on a hearing questionnaire will not be significantly different between the two experimental groups.
Study Intervals	Primary data points are at 3 months and 6 months post-activation.

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Abbreviations

Term	Definition
ACE	Advanced Combination Encoder strategy
ADRO	Adaptive Dynamic Range Optimization
AE	Adverse Event
ASC	Automatic Sensitivity Control
BTE	Behind-the-ear
CP810	Behind-the Ear Cochlear Processor 800 series
CP900	Behind-the Ear Cochlear Processor 900 series
CP1000	Behind-the Ear Cochlear Processor 1000 series
CRF	Case Report Form
FAST	Fundamental Asynchronous Stimulus Timing strategy
IA	Initial Activation
IRB	Institutional Review Board
ITD	Interaural timing difference
SAE	Serious Adverse Event
SNR	Signal to noise ratio
S0N0	Speech and background noise presented at 0 degrees azimuth
SRT	Speech Reception Threshold

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1.0 Introduction

The Fundamental Asynchronous Stimulus Timing (FAST) strategy offers excellent potential as a low power alternative coding strategy to the current default strategy in Nucleus® cochlear implants, Advanced Combination Encoder (ACE). Additionally, FAST offers potential bilateral benefits – localization and listening in spatially separated noise – because it has been shown in acute, controlled studies to provide more access to interaural timing difference (ITD) cues (Smith, 2010). FAST outputs a pulse at a time and level that corresponds with the exact time and amplitude of the peak of each envelope cycle. In contrast, ACE uses a fixed pulse rate (default of 900 pulses per second per channel) that bears no relationship to the coded acoustic stimulus.

Previous research with experienced cochlear-implant recipients has shown issues with conversion from ACE to FAST. The FAST strategy typically sounds very different in quality, and acclimatization can be lengthy. This extended adaptation time makes it difficult to show conclusively that FAST is non-inferior to ACE for speech understanding. A potential barrier to evaluating performance with FAST in current cochlear-implant recipients is the extensive amount of prior experience that many recipients have using ACE. Hence, there is a distinct need to evaluate FAST in newly implanted recipients.

The present study will compare speech intelligibility and sound quality with FAST and ACE in a group of 20 newly implanted subjects. There will be a 3-month period of take-home experience with each strategy in a crossover design. The battery life benefit of FAST compared to ACE will also be quantified.

2.0 Study Objectives

Primary Objectives:

1. To determine if FAST is non-inferior to ACE for word recognition in quiet in newly-implanted cochlear-implant recipients.
2. To determine if FAST is non-inferior to ACE for sentence perception in noise in newly-implanted cochlear-implant recipients.

Primary Endpoints:

1. Word recognition in quiet will be non-inferior for FAST compared to ACE.
2. Sentence perception in noise will be non-inferior for FAST compared to ACE.

Secondary Objectives:

1. To quantify the battery life benefit for FAST compared to ACE.

2. To obtain insight into sound quality differences between the strategies and the relative difficulty of conversion for the cochlear-implant recipient from ACE to FAST versus FAST to ACE.

Secondary Endpoints:

1. Duration of battery life will be superior for FAST compared to ACE.
2. Comparative ratings on a hearing questionnaire will not be significantly different between the two experimental groups.

2.1 Study Design

The design is a within-subject, repeated-measures clinical investigation.

2.2 Study Procedures

Adult cochlear-implant subjects will be given two different sound coding strategies, FAST and ACE, for take-home use in a crossover design. The period of time with each strategy will be 3 months, for a total of 6 months of participation post initial activation. Study procedures will include mapping, speech perception, sound quality judgments, a questionnaire, and battery logs for both strategies as well as a brief cognitive test. Procedures are described in detail in section 5.0 of this protocol.

2.3 Study Length

The anticipated recruitment time is 6 months. The duration of the study for each subject is 6 months post-activation. The total study duration is expected to be 12 months.

3.0 Device Description

The cochlear implant system that will be used in this IDE study comprises:

- Nucleus® Cochlear Implant
- Nucleus 5 (CP810) Sound Processor, and
- Nucleus Custom Sound™ programming software.

3.1 Implant Description

FDA-approved Cochlear Nucleus CI24RE, CI512, or CI532 cochlear implants will be used in this IDE. There have been no changes to this internal system component.

3.2 Sound Processor Description

Commercially available Nucleus 5 (CP810) sound processors will be used in this IDE. There have been no changes to the hardware of the CP810 processor. The CP810 is a behind-the-ear (BTE) sound processor. It is functionally similar to the newer generation Nucleus 6 (CP900 series) and Nucleus 7 (CP1000) processors, but without some of the advanced features (i.e. SmartSound iQ, Wireless Accessories, Data Logging, and iPhone compatibility).The CP810 processor will be loaded with different firmware for the ACE and FAST portions of the crossover study.

3.3 Programming Software Description

The default coding strategy (ACE) and the experimental coding strategy (FAST) will be programmed in the CP810 processor for take-home use with Custom Sound software.

4.0 Subject Population

Adult cochlear-implant candidates capable of completing the study evaluation will be recruited to participate in the IDE. Vulnerable populations will not be eligible for study participation per 45 CFR part 46, subparts A through D as reported by the Investigator.

4.1 Inclusion Criteria

- Medical and audiological candidate for a unilateral CI24RE, CI512, or CI532 series implant
- Post-linguistically deafened
- Native speaker of American English
- Eighteen years of age or older

4.2 Exclusion Criteria

- Previous or existing cochlear-implant recipient
- Pre-linguistically deafened (onset of severe-to-profound hearing loss at less than two years of age)
- Ossification or any other cochlear anomaly that might prevent complete insertion of the electrode array
- Diagnosis of retro-cochlear pathology
- Diagnosis of auditory neuropathy

- Unrealistic expectations on the part of the subject regarding the possible benefits, risks, and limitations that are inherent to the surgical procedure and use of the prosthetic device
- Unwillingness or inability to comply with all investigational requirements
- Additional cognitive handicaps that would delay rate of improvement with the cochlear implant

4.3 Release of Medical Information

Subjects will be required to release the exchange of medical information between the Investigator(s) and the Sponsor. This requirement will be clearly identified in the Informed Consent form.

5.0 Investigational Procedures

5.1 Design Overview

This study will implement a within-subject crossover design with 20 subjects. All subjects will receive each of the treatments – the ACE and FAST strategies. In this repeated measures design, half of the subjects, Group 1, will be mapped with FAST first and the other subjects, Group 2, with ACE first, using formalized mapping procedures. Endpoint speech perception testing, additional to standard clinical testing, will be conducted after 3 months of use with the initial strategy. At the 3-month post initial activation (IA) session, each recipient will be programmed with the crossover strategy. The crossover strategy will then be assessed after 3 months of take-home use at 6 months post IA (refer to Table 1). As indicated in Table 1, fine-tuning of the cochlear implant stimulation levels (i.e. MAP) will occur at 1 week and 1 month after receiving each strategy. Standard clinical testing will also occur at 3 months and 6 months post activation.

The order in which the subjects are programmed with the ACE and FAST strategies will be counterbalanced according to group; Group 1 will start with FAST and Group 2 with ACE. Subjects will be randomly assigned to either Group 1 or 2. Standardized programming procedures will be used to program the FAST and ACE strategies. Subjects will be blinded as to the identity of the strategies.

The study design strikes a balance between providing a reasonable amount of take-home experience with each of the strategies and obtaining outcome comparison data for the strategies within the required timeframe. It is acknowledged that maturational effects are not eliminated with crossover to the alternative strategy at 3 months post IA. The exclusion criteria for enrollment will provide control over some of these variables. To further address maturational effects, subjects' scores from the Reading Span Test (a cognitive test of working

memory) will be included as a statistical covariate to understand differences in adaptation that might be associated with working memory.

Depending on the Clinical Site, endpoint speech perception evaluations will be conducted either at the Clinical Site or at the Denver Research & Technology Labs (Cochlear Americas). These evaluations will include sentence in noise testing in dynamic four-talker babble and speech-shaped noise. The test setup will be with the target speech and competing noise both presented from a speaker in front of the recipient (S0N0). A speech reception threshold (SRT) will be obtained, which represents the signal-to-noise ratio (SNR) at which the recipient scores 50% intelligibility. Word recognition in quiet will also be conducted.

All subjects will be implanted with a CI24RE, CI512, or CI532 implant and will be given the latest commercially available sound processor. However, recipients will be fit with a CP810 sound processor with no advanced features for the duration of the study (adaptive directionality, wireless accessories, and SmartSound iQ will not be used during study participation).

At the crossover appointment (3 months post IA), endpoint speech perception testing will be conducted with the first strategy. The second strategy will then be programmed for take-home use. Subjects will be asked to acutely rate sound quality with this second strategy in direct comparison to the first strategy. One month after take-home use with the second strategy, subjects will be asked to complete a questionnaire again rating sound quality and speech understanding with the second strategy compared to the first strategy. Comparing the quality of strategy 2 to strategy 1 after a longer period of take-home use with strategy 2 is likely to be less reliable, given reliance on the memory of strategy 1.

Evaluating the sound quality of FAST versus ACE is complex. To minimize memory effects and increase statistical power, a direct comparison of strategies would be ideal. The comparative quality ratings of ACE and FAST at the crossover appointment will provide some insight into sound quality with the two strategies. If the conversion from the initial strategy to the crossover strategy shows larger quality differences for one of the two groups, this may indicate underlying disparities between the two strategies. However, based on previous research with existing recipients, it is known that the sound quality of FAST differs from ACE. The quality and speech understanding questionnaire conducted one month after the crossover appointment will provide further understanding of quality differences after some degree of acclimatization.

Subjects in Group 2 who are initially programmed with ACE and then reprogrammed with FAST at the crossover 3 months post IA will need to be re-programmed with the default ACE program at the final visit 6 months post IA. The ACE map will be fine-tuned at this final visit and will be loaded onto the patient's

personal sound processor for take-home use. Instruction will be provided on the use of the processor controls.

The FAST strategy is not currently approved by the FDA as a commercial speech processing strategy that recipients may choose as their clinical strategy for ongoing use. Subjects will be informed prior to enrolling that they will not have the option of continuing to use FAST after the completion of this study. However, this study may provide data for a future submission to seek FDA approval for FAST. In the event that the FAST strategy becomes clinically approved in the future, the current subjects will have access to FAST through their clinical audiologists. At the conclusion of the study, subjects will be provided with the option to upgrade to a compatible sound processor. This option must be redeemed within 5 years from completion of the study.

5.2 Description of Test Measures

5.2.1 Clinical Audiological Testing

Subjects will undergo a standard battery of audiological tests. The clinical data gathered for this study will include frequency-specific thresholds at standard audiometric frequencies (250 – 8000 Hz) and aided speech recognition with AzBio sentences (Spahr et al., 2012) at 60 dBA in the sound field. Audiological data will be gathered pre-operatively and at 3-months and 6-months post IA. CNC word recognition (Peterson & Lehiste, 1962) will also be conducted at the pre-operative candidacy visit.

5.2.2 Device Fitting

Mapping will be conducted using standard clinical procedures. For the CP810 processor that will be used for the duration of this study, the programming clinician will include an Everyday program with ADRO+ASC using standard microphone directionality. The Everyday program will be used for testing throughout the trial. Clinicians may provide other individualized programs as needed for take-home use (e.g., with fixed directional microphones for noisy situations); however, the adaptive directionality mode will not be available. The same feature settings will be used for FAST and ACE. At the conclusion of the study, the subject's personal sound processor will be loaded for take-home use with the range of features that are available at that time.

5.2.3 Sound Quality Ratings

At the crossover visit, acute sound quality ratings will be conducted to compare perceived quality with FAST and ACE at the time of switchover. Immediately after mapping the second strategy, the clinician will read the "Rainbow Passage" and ask the subject to rate his or her perception of the intelligibility, loudness, naturalness, and overall sound quality of the second strategy in comparison to

the first strategy. The rating scale will range from unchanged (0) to much better (+5) or much worse (-5).

5.2.4 Speech Perception (Endpoint Testing)

All speech perception tests will be conducted with recorded materials in a unilateral, implant-only configuration using the subject's Everyday program. The following endpoint speech perception tests will be performed at Cochlear Americas' Research & Technology Labs or at the Clinical Site. The clinician who conducts endpoint speech testing will not be the same clinician who conducts programming for an individual subject, and the testing clinician will be blinded from the subject's group assignment. Thus, the endpoint speech testing will be double-blinded.

5.2.4.1 Monosyllabic Word Recognition

Monosyllabic word recognition will be conducted using CNC words (Peterson & Lehiste, 1962). The test will be performed in the sound field at 0° azimuth at a level of 60 dBA. Two paired 50-word lists will be administered at each evaluation session, for a total of 100 words. The order of lists will be counterbalanced.

5.2.4.2 Sentence Recognition in Four-Talker Babble

The first speech-in-noise task will be conducted using BKB sentences with a male target talker (Bench et al., 1979). A four-talker babble background will be presented. The level of the babble will be adapted to find the SRT, defined as the SNR in dB providing 50% intelligibility. Sentences will be presented at 65 dBA at 0° azimuth in the sound field, with babble presented from the same spatial location (S0N0). The order of lists will be counterbalanced.

5.2.4.3 Sentence Recognition in Speech-Shaped Noise

A second speech-in-noise test will be completed using untested BKB sentences with a speech-shaped noise background. Sentences will be presented at 65 dBA at 0° azimuth in the sound field, with the competing noise presented from the same spatial location (S0N0). The competing noise will be adapted to find the SRT as described previously. The order of lists will be counterbalanced.

5.2.5 Reading Span Test

The Reading Span Test is a working memory task that measures the ability to simultaneously store and process information (Daneman & Carpenter, 1980). Subjects will be asked to read a sequence of sentences and judge whether each sentence is sense or nonsense. At the end of the sequence, the subject's task is to recall the first word or the last word of each of the preceding sentences.

5.2.6 Battery Life Questionnaire

Subjects will be asked to complete two battery questionnaires, one for FAST and one for ACE. Each questionnaire will contain four logs. Subjects will start each battery log with a fully charged battery. Subjects will track what time the processor was turned on with a fully charged battery and what time the processor was turned off (or, if the battery ran out of power, what time this occurred). They will complete this process until they have gone through four cycles of fully charged batteries.

5.2.7 Quality and Speech Understanding Questionnaire

The comparative version of the Speech, Spatial and Qualities of Hearing scale (short form), the SSQ12-C (Noble et al., 2013), will be administered at 4-months post IA (1 month post-crossover). This scale is a 12-item questionnaire that records a subject's experiences in the areas of speech perception, spatial hearing, sound quality, and listening effort.

5.3 Preoperative Procedures

5.3.1 Visit 1

Visit 1 will take place at the Clinical Sites. A candidacy evaluation will be conducted to determine the subject's eligibility to enroll in the study. The candidacy evaluation will include a hearing history, air conduction and bone conduction audiogram, a CNC word test, and an AzBio sentence test.

5.4 Surgical Procedure

There are no modifications to the standard surgical procedure for this study.

5.5 Postoperative Procedures

5.5.1 Visit 2

Visit 2 will be conducted at the Clinical Sites. Procedures will include initial activation and mapping of the first strategy (Group 1 will receive FAST, and Group 2 will receive ACE). Subjects will be oriented to use of the CP810 processor.

5.5.2 Visit 3

Visit 3 will be conducted at the Clinical Sites. Procedures will include fine-tuning of the initial strategy.

5.5.3 Visit 4

Visit 4 will be conducted at the Clinical Sites. The first battery life questionnaire will be handed out to the subject, and instructions for completing and returning

the questionnaire will be provided. Mapping will be conducted for fine-tuning of the initial strategy.

5.5.4 Visit 5

Visit 5 will include endpoint speech perception tests, the Reading Span Test, clinical audiological testing, and programming of the crossover strategy. Depending on the Clinical Site, endpoint speech testing (CNC words and BKB sentences) and the Reading Span Test will be conducted either at the Clinical Site or at the Denver Research & Technology Labs (Cochlear Americas). All programming will be conducted at the Clinical Sites. Since endpoint speech testing will be administered by a clinician blinded to the current treatment, endpoint speech testing and programming will be performed by different clinicians. The crossover strategy will be programmed (Group 1 will receive ACE, and Group 2 will receive FAST), and the acute sound quality ratings will be conducted.

5.5.5 Visit 6

Visit 6 will be conducted at the Clinical Sites. Procedures will include fine-tuning of the crossover strategy.

5.5.6 Visit 7

Visit 7 will be conducted at the Clinical Sites. The SSQ12-C will be completed, and the second battery life questionnaire will be handed out to the subject. Mapping will be conducted for fine-tuning of the crossover strategy.

5.5.7 Visit 8

Visit 8 will include endpoint speech perception tests, clinical audiological testing, final programming, and fitting with the patient's personal sound processor. Depending on the Clinical Site, endpoint speech testing will be conducted either at the Clinical Site or at the Denver Research & Technology Labs (Cochlear Americas). All programming will be conducted at the Clinical Sites. Since endpoint speech testing will be administered by a clinician blinded to the current treatment, endpoint speech testing and programming will be performed by different clinicians. The subject will be fitted with his or her personal sound processor and the ACE strategy (both groups). Counseling on use of the personal sound processor will be provided.

5.6 Summary of Data Collection Visits

Testing at Clinical Sites								
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**
Test	**Candidacy**	**Initial Activation (IA)**	**1 week (post IA)**	**1M (post IA)**	**3M (post IA)**	**3M plus 1 week (post IA)**	**4M (post IA)**	**6M (post IA)**
Strategy Programming		Program initial strategy Group 1 - FAST Group 2 - ACE	Fine-tuning of initial strategy	Fine-tuning of initial strategy	Program crossover strategy Group 1 - ACE Group 2 - FAST	Fine-tuning of crossover strategy	Fine-tuning of crossover strategy	Program ACE; counsel use of personal processor (both groups)
Clinical Audiological Testing	X				X			X
Sound Quality Ratings					X			
Battery Life Questionnaire				X			X	
Quality and Speech Understanding Questionnaire							X	
Testing either at Clinical Sites or at Denver Research & Technology Labs (Cochlear Americas)								
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**
Test	**Candidacy**	**Initial Activation (IA)**	**1 week (post IA)**	**1M (post IA)**	**3M (post IA)**	**3M plus 1 week (post IA)**	**4M (post IA)**	**6M (post IA)**
Speech Perception					X			X
Reading Span Test					X			

Table 1. Summary of data collection visits.

6.0 Adverse Events

An adverse event (AE) is any undesirable clinical or medical occurrence associated with the use of the device, procedure, or participation in the study, which does not result in serious injury or illness related to the surgical procedure or the device.

A serious adverse event (SAE) is any untoward medical occurrence that

- results in death
- is life-threatening

- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- requires medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
- leads to fetal distress, death, or congenital abnormality or birth defect
- is a medically important event or reaction

6.1 Assessment and Reporting of Adverse Events

To monitor subject safety throughout this IDE study, any procedure or device related adverse events will be recorded. Information on all adverse events will be maintained by event type. The investigator will complete an Adverse Event form if any adverse event is reported or observed for a subject during this IDE, even if the event was acknowledged as a risk factor in the Informed Consent form.

Adverse device effects refer to any undesirable clinical or medical occurrence associated with use of the device or participation in the study. Any/all adverse device effects are to be recorded via the Adverse Event form. Adverse device effects will be reported if observed, even if they were acknowledged as risk factors in the Informed Consent form.

6.2 Unanticipated Adverse Device Effects

Unanticipated adverse device effects refer to any event not identified above that represents a “serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.” [FDA 21 CFR 812.3(s)]

Investigators are to inform their respective Institutional Review Boards (IRBs) and Cochlear Americas immediately if an unanticipated adverse device effect is suspected (no more than 10 working days after the investigator learns of the effect). If the case is determined to be an unanticipated adverse device effect, the investigator will fill out an “Unanticipated Adverse Device Effect Form.” Cochlear Americas will report the results of an evaluation of the unanticipated adverse device effect to the FDA and all other reviewing IRBs and investigators within 10 working days after first receiving notice of the event.

7.0 Study Completion

7.1 Completed Subjects

Subjects who complete the 6-month crossover study will be provided with the option to upgrade to a compatible sound processor. This option must be redeemed within 5 years from completion of the study. At the end of their participation, all subjects will return to the ACE strategy and will be fitted with their personal sound processor. Because subjects will not use their personal sound processors for the first 6 months after surgery, the device warranty for the personal sound processor will be extended by 6 months, and the trial period will be 90 days from the fitting of the personal sound processor. During the 90-day trial period, subjects will have the option to exchange their personal sound processor for another commercially available device. Subjects will also receive an expanded 5-year warranty on all parts and pieces included in their personal sound processor kit. Subjects will continue to receive standard clinical follow-up care after the completion of the study.

7.2 Discontinued Subjects

Subjects who withdraw or are discontinued prior to the completion of the 6-month visit will receive compensation of $12.50/ hour for the cumulative period of time spent on study procedures. This payment will be in lieu of the option for a processor upgrade. This is outlined clearly in the patient informed consent form. All subjects will return to the ACE strategy and will be fitted with their personal sound processor.

7.3 Premature Study Termination

The Sponsor may terminate the study early in the case of major non-adherence to the protocol, or if it is anticipated that recruitment will not be met for the required number of subjects to complete the study objectives. In the event of premature study termination, the subjects who are already enrolled will be sponsored through study completion.

8.0 Data Analysis

8.1 Statistical Analysis

Endpoint speech perception data will be analyzed using linear mixed models (LMM) in order to test for treatment effects while controlling for period and sequence effects. Non-inferiority will be tested with the confidence intervals of the treatment effects from the statistical models. If the one-sided limit of the 97.5% confidence bound does not exceed the non-inferiority margin, statistical

significance will be met at the 0.025 alpha level. The non-inferiority margin for word recognition is 10 rationalized arcsine units (rau). The non-inferiority margin for the sentence in noise tests with an adaptive SNR is −2dB. The non-inferiority margins are based on clinical judgment and variability observed in previous studies testing FAST and ACE.

8.2 Sample Size

Sample size calculations were conducted using G*Power 3.1 under the following general assumptions:

- Non-inferiority tests with margins of 10 rau for CNC word recognition and −2 dB for sentence reception in noise
- One-sided 0.025 alpha level
- Assumed distribution for population (standard deviation) based on a previous FAST take-home trial in experienced ACE recipients
- Desire for 90% power

To reject the null hypothesis of inferior CNC word recognition for FAST compared to ACE (using a standard deviation of 7.20 rau), a sample size of 8 subjects is required.

To reject the null hypothesis of inferior sentence reception in noise for FAST compared to ACE (using a standard deviation of difference scores of 1.84 dB), a sample size of 11 subjects is required.

An increased sample size of 20 subjects will be enrolled, which will allow for the possibility of subject attrition as well as providing a similar degree of power under more conservative assumptions.

8.3 Additional Statistical Analyses

Statistical analysis for this study is addressed in detail in the document entitled “Statistical Analysis Plan for Investigation of the FAST Sound Coding Strategy in Newly Implanted Adult Cochlear Implant Recipients.”

9.0 Risk Benefit Statement

9.1 Benefits

It is possible but not guaranteed that advances to cochlear implant technology will improve performance or usability of devices for future recipients. This investigation will help to inform the future development of the FAST strategy and

the planning of future studies of FAST in the newly implanted population. There are no direct benefits anticipated for subjects participating in this study.

9.2 Risks

With any cochlear implant program, there is a very small risk of unintentional over-stimulation. Subjects may experience sounds in mapping that are uncomfortably loud.

There is a risk that recipients may experience difficulty converting from the initial strategy to the crossover strategy. It is known from previous studies with experienced cochlear implant recipients that the experimental FAST strategy can sound very different in quality to the default ACE strategy. Some experienced ACE recipients have struggled to adapt to the FAST strategy over an 18-week period. The conversion risk is clearly identified in the patient informed consent form. The consent form also clearly indicates the option to withdraw from the study at any time.

Subjects will not be able to use their personal sound processor until the completion of the study. Instead, they will be loaned the CP810 sound processor for the duration of their participation. The CP810 processor has been shown to have similar general performance outcomes to the Nucleus 6, Kanso, and Nucleus 7 sound processors. However, during study participation, subjects will not have access to some advanced features (adaptive directionality, SmartSound iQ, wireless accessories, and iPhone compatibility). These differences are clearly explained in the patient informed consent form. At the end of the trial, subjects will be fit with their personal sound processor and will have access to the full range of features that are commercially available at that time.

10.0 Good Clinical Practices Statement

The study obligations for the Investigator(s) are outlined in guidelines for Good Clinical Practice (GCP), ISO14155:2011 (Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice), and the Declaration of Helsinki.

11.0 Access to Study Documents and Study Monitoring

Investigator(s) will provide access to study documentation including source data for the purposes of monitoring, audits, IRB review, and regulatory inspections.

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12.0 Quality Control and Assurance

Study sites may be subject to Quality audits at any point during the study. Regulatory agencies may conduct inspections during the course of the clinical investigation and after study completion.

13.0 Institutional Review Board

The final version of the IDE protocol will be submitted to the Western Institutional Review Board (WIRB®), and written approval obtained, before patients are recruited and subjects are enrolled. Each site will obtain approval from its designated IRB prior to commencing any study-related activities. A copy of the IRB approval will be kept in the Investigator file(s). Any additional requirements imposed by the IRB and/or regulatory authority shall be followed. The Investigator(s) will submit the appropriate documentation if any necessary extension or renewal of the IRB approval must be obtained.

14.0 Informed Consent Process

Written informed consent shall be obtained from each subject after explaining the rationale for and the details, aims, and objectives of the study, the risks and benefits of the trial treatment (and alternative treatments), and the extent of the patient's involvement. The Investigator is responsible for ensuring that all patients give written informed consent prior to any study-related examination or activity. All patients shall sign and date the Informed Consent Form, and a copy of the Informed Consent Form shall be given to the patient.

The Sponsor and the Investigator(s) shall avoid improper influence on or inducement of the subject, monitor, the Investigator(s) or other parties participating in or contributing to the clinical investigation.

15.0 Confidentiality

A Case Report Form (CRF) will be completed for each study subject, summarizing all clinical and study data. The CRF contains confidential material. Subjects will only be referred to in the CRF by their subject numbers in order to retain subject confidentiality. Specific instructions to complete the CRF shall be provided to the clinical investigation team as appropriate.

Copies of the completed CRFs are to be provided to the Sponsor as soon as practical after completion and review. The original CRFs are to be retained by the Investigator for a period of time as determined by local regulations.

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16.0 Protocol Deviations and Amendments

The Investigator must receive prior approval from the Sponsor, and the IRB when necessary, to deviate from the IDE protocol except in cases of emergency to protect the rights, safety, and well-being of the subjects. Emergency protocol deviations must be documented and reported to the Sponsor and the IRB.

Study procedures will not be changed without mutual agreement between the Sponsor and the Investigator(s). Changes will be implemented in a signed protocol amendment, and for significant changes, approval will be obtained from the IRB and the FDA as necessary.

17.0 Data Management

Data will be recorded on electronic CRFs within the electronic data capture system DataLabs™ or Medidata. DataLabs or Medidata will produce a report of the summary data per subject. Source data for study evaluations may include paper worksheets or electronic spreadsheets. All source data will be stored in subject binders or on password-protected computers. In the event that the site requests assistance with data entry from the Sponsor, the Sponsor may assign a non-study related team member to assist the site with data entry. The study monitor will compare the DataLabs CRFs with the source data.

18.0 Record Keeping and Retention

All source documents, CRFs, and trial documentation will be kept by the Investigator(s) for the appropriate retention period as stipulated by local regulations and ICH-GCP.

19.0 Study Report and Publication

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law.

The aggregate data resulting from this study will be the proprietary information of the Sponsor and may be made public after all data have been analyzed and the study results are available. None of the data resulting from this study will be allowed to be presented or published in any form, by the Investigator(s) or any other person, without the prior written approval of the Sponsor. At the end of the study, a clinical study report will be written by the Sponsor.

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20.0 References

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