Interventional Trial

The Neuro Zti Cochlear Implant System Efficacy and Safety in Adults (PIC-07)

Statistical Analysis Plan Version 3.0

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Signature page

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Record of modifications

Version	Date	Comment
1.0	07/03/2018	First version
2.0	10/12/2019	Remove of ECAP analysis
3.0	27/01/2020	Revision of the document: - Correction of section 1.2, bullet points secondary objectives for consistency with PIC_07 version G, add "to evaluate the trend…speaking patients. - Addition in section 1.4 tables references for better understanding of study plan - Addition of section 5.7.3 "sustainability of the effect at 12 months" for consistency with PIC_07 version G section 3.6.2.4 "secondary analyses". - Addition of PPS for all analysis performed on FAS - Addition of descriptive analysis on major complication related to device - Addition of descriptive analysis for impedance and explanted patients

Table of Content

List of abbreviations and definition of terms

Abbreviation	Definition
AAMI	Association for the Advancement of Medical Instrumentation
AE	Adverse Event
CI	Confident Interval
CIS	Cochlear Implant System
CT	Computed Tomography
dB SPL	Decibel Sound Pressure level
ECAP	Electrically-evoked Compound Action Potential
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FDA	Food and Drug Administration
FU	Follow-Up visit
HINT-Q/N	Hearing In Noise Test-Quiet/Noise
HLT	High Level Term
Hz	Hertz
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
PPS	Per Protocol Set
PT	Preferred Term
SAE	Serious Adverse Event
SAS	Safety analysis Set
SOC	System Organ Term

1. Overview and study plan

1.1. Study Design

This pivotal study is designed as a prospective multi-center, one arm, non-randomized, open label, repeated measures clinical study. The subjects are their own control.

For this pivotal study, 55 patients will be enrolled by 5 centers in Canada and 1 in Denmark.

The Neuro cochlear implant system (CIS) is indicated in individuals with severe-to-profound hearing loss who do not obtain benefit from appropriately fitted hearing aid(s). Cochlear implant surgery is safe, but as with any surgery, possible issues or device related issues may occur. The risk-benefit balance is well known in cochlear implantation.

The aim of this study is to assess the efficacy and the safety of this new CIS in adults.

Device efficacy is defined as an improvement in the speech recognition battery presented at conversational speech levels (60 dB SPL) in quiet after 6 months of use compared to the preoperative condition (best-aided preoperative condition).

Speech perception tests will be conducted

- Preoperatively, on both ear with the best fitted hearing aid(s), and
- Postoperatively, on ipsilateral ear with activated CIS and an occluded contralateral ear with ear-plug.

1.2. Study Objectives

The primary objectives are:

- To demonstrate the improvement in the speech recognition, in quiet condition, after implantation of the Neuro CIS with respect to preoperative conditions.
- To evaluate the device safety profile and in particular the risk of complication.

Evaluation at 6 months compared to baseline will be used to determine the efficacy of the device.

The incidence rate of major complications at 12 months of device use will be estimated to evaluate the safety. Data from literature on similar devices FDA-approved will be used as state of the art.

The primary population will be composed of English-speaking subjects. In the efficacy assessment, a sub-population will be used as a primary set of patients because different languages is expected to influence the magnitude of the effect of the device. The objective is to assess in English speaking subjects the device performance at month 6 in quiet conditions compared to baseline (best-aided condition) using HINT-Q test-sentences presented at conversational level.

Hypothesis: the mean HINT-Q score obtained with the Neuro CIS after 6 months of device use in English speaking subjects is greater than the score at baseline.

H0: $\mu_{M6} - \mu_0 \leq 0$ points
H1: $\mu_{M6} - \mu_0 > 0$ points

An improvement of approximately 50 points with respect to baseline is expected and an improvement of 20 points is considered clinically pertinent.

Occurrence of major complications in all participants suffering from severe to profound bilateral sensorineural hearing loss and for whom an implantation of the device was initiated will be the co-primary objective. All surgical and device-related events will be reported, and the number and proportion of major complications will be estimated.

Adverse events or complications will be classified as medical/surgical or device related. Complications will be classified as major if they require surgical intervention and minor if they resolve spontaneously or with non-invasive medical treatment categories. Any device failure will be investigated and classified according to AAMI CI86:2017 guideline for Cochlear Implants.

Occurrence of major complications will be a co-primary endpoint and the presentation of the safety profile (all adverse events reported) will be a secondary objective, mainly descriptive. Incidence rate of minor and major complications will be estimated globally and per categories in order to describe the device safety profile.

Secondary objectives are:

- To establish the time course of the change from baseline of HINT-Q score in English speaking patients and in all patients to assess the efficacy of the device in a dynamic perspective.
- To test the sustainability of the device effect in Quiet conditions (HINT-Q) through the comparison of the scores at month 6 and month 12 in English speaking patients and in all patients in case of absence of significant language effect in the improvement from baseline.
- To assess the performance of the device in noise using HINT-N test in English speaking and in all patients at 3, 6 and 12 months compared to baseline (best-aided condition). The comparison of the score at 6 and 12 months will indicate the sustainability of the effect.
- To evaluate the trend of device efficacy in quiet and noise conditions across English speaking, French speaking and Danish speaking patients. In other words; To verify the homogeneity of the observed device effect across the three languages in quiet and noisy conditions through the comparison of the time course of the response of English speaking, French speaking and Danish speaking patients. The purpose is to know whether the results on the overall population reflect correctly the three sub-populations (languages).

Technical functionalities assessment:

- To assess the time course from baseline of impedance values to check device technical functionality. Mixed model will be used to assess in a dynamic perspective the objective measures evolution.

1.3. Determination of sample size

Sample size determination is based on the two co-primary endpoints: change from baseline to 6 months of the HINT-Q (efficacy assessment), and major complication incidence rate during the 12-month follow-up (safety assessment).

The expected efficacy is an improvement of 50 points at 6 months of device use.

Data on the change from baseline to 6 months are not available in literature, but 2 studies describe the HINT-Q magnitude after 12 months of device use. Waltzman et al. [1] described an increase of 47.7% (SD=26.6%) from pre- to 3 months post-implantation, similar results are reported by Lin et al. [2] with a magnitude of 60% (SD=24.1%) at 12 months. Considering an observed performance plateau around 6 months, we can consider that standard deviation obtained at 3 and 12 months can be used for 6 months of device use in this study. In addition, in the main studies conducted at 6 months, the standard deviation are ranged from 22% to 28%, which is consistent with other results on the change from baseline. Data from literature using the same efficacy assessment criterion provided a weighted average ± weighted standard deviation change from baseline of 57.43% ± 25.05%. Such estimation has been rounded conservatively to 50% ± 25%.

The sample size required to have 95% chance to get a significant efficacy result assuming a true mean improvement of 50%, a standard deviation of change from baseline of 25% and a type I error of 0.025 (one-sided) is 7 patients. It means that the expected improvement is so large with respect to the variability that the sample size calculation is not driven by efficacy considerations.

As requested by the FDA, the sample size will be set at a total of at least 50 subjects to support the safety. If the incidence rate of major complications is 2% then the chance to observe at least one event is 63.5%. The exact upper limit of the 95% CI will be 10.6% for an observed rate of 2%.

Regarding any complication the expected rate 35%. If the observed rate is 36% then the precision is around 13% in points.

In order to ensure that at least 50 subjects will be implanted with the device, starting with the anesthesia followed by surgery procedure, 55 subjects will be included.

An arbitrary minimum of 39 English speaking patients and 16 non-English-speaking patients will be recruited to meet the FDA requirement. It is possible that the recruitment in a given language be smaller than expected. In this case patients from other languages may replace the shortage provided that a minimum of 5 French speaking patients and 5 Danish speaking patients be recruited to justify the class of language.

[1] Waltzman SB, Cohen NL, Roland JT Jr. A comparison of the growth of open-set speech perception between the nucleus 22 and nucleus 24 cochlear implant systems. Am J Otol. 1999 Jul;20(4):435-41.

[2] Lin FR, Chien WW, Li L, Clarrett DM, Niparko JK, Francis HW. Cochlear implantation in older adults. Medicine (Baltimore). 2012 Sep;91(5):229-41.

1.4. Study plan

Protocol activity	V1	V2	V3	V4	V5	V6	V7	V8	Unscheduled visit(s) #
	8 weeks pre-surgery	4 weeks pre-surgery	Baseline	2 weeks post-surgery	1 month post-surgery	3 months post-activation	6 months post-activation	12 months post-activation	
	Screening	Inclusion	Surgery	Follow-up	Activation	Follow up	Follow up	End of study	NA
	Week (-8)	Week (-4)	Week (0)	Week (+2) post-surgery	Month (+1) post-surgery	Month (+4) post-surgery	Month (+7) post-surgery	Month (+13) post-surgery	NA
Eligibility									
Informed consent	X*	X**							
Eligibility criteria		X							
Demographic data		X							
Medical and Hearing History		X							
Evaluations									
HINT-Q		X				X	X	X	
HINT-N		X				X	X	X	
Study device									
Surgery			X						
Implant activation					X				
Patient Diary									
Diary issued					X	X	X		
Diary returned						X	X	X	
Safety									
Adverse event reporting			X	X	X	X	X	X	X
Electrodes Impedance			X		X	X	X	X	(X)
ECAP			X		X	X	X	X	(X)
Concomitant medications		X	X	X	X	X	X	X	X

*Informed consent given

**Informed consent obtained

visits may occur in addition to the predefined protocol specific visits. Unscheduled consultations must be related to CI complications/adverse events and/or additional speech processor fittings. The PI may plan any unscheduled consultations as needed. Impedance and ECAP measurements are optional and depend on the nature of patient visit.

Visit	Visit interval (defined as number of weeks relative to visit 3, baseline)	Visit window (defined as number of days from previous visit indicated plus and/or minus day stated)	Visit window (defined as a range in days from previous visit indicated)
1	-8	NA	NA
2	-4	28 days from visit 1 (-25 to +14 days)	3-42 days from visit 1
3	0	28 days from visit 2 (+/- 14 days)	14-42 days from visit 2
4	+2	14 days from visit 3 (-7 to +6 days)	7-20 days from visit 3
5	+4	28 days from visit 3 (-3 to +6 days)	25-34 days from visit 3
6	+16	112 days from visit 3 (-7 to +6 days)	105-118 days from visit 3
7	+28	196 days from visit 3 (-7 to +6 days)	189-202 days from visit 3
8	+52	364 days from visit 3 (-7 to +6 days)	357-370 days from visit 3

2. Collected Data

Data will be obtained through 2 types of document: an electronic Case Report Form (eCRF) and a paper Patient Diary. The eCRF will be completed by the investigator at each of 7 visits planned by the protocol (no collected data at the first screening visit V1).

2.1. Electronic Case report Form

Visit 1 (screening, Week -8 pre-surgery): no data collected, informed consent form given to the patient

Visit 2 (inclusion, Week -4 pre-surgery)

- Date of visit
- Date of written informed consent
- Inclusion/exclusion criteria
- Demographic data: birthday, gender, language, vital signs (weight/height)
- Medical history: allergies and significant medical history
- Concomitant medications
- Etiology: age at onset of hearing loss, age of first used hearing aid, age at onset of severe to profound hearing loss (for each ear), vertigo, tinnitus
- Diagnostic imaging: CT scan, MRI exam and exam
- Audiometric evaluations: HINT-Q, HINT-N
- Audiometric evaluations in routine care shall be recorded, if available
- Cochlear implantation scheduling date

Visit 3 (implantation, Week 0 surgery)

- Date of surgery
- Type and time of surgery, surgical approach
- Objective measures: impedance and ECAP test
- Presence of adverse events
- Modification of concomitant medications

- Adverse events

Visit 4 (follow-up, Week +2 post-surgery)

- Date of visit
- Clinical examination: general state, scarring, skin-flap assessment
- Presence of adverse events
- Modification of concomitant medications

Visit 5 (activation, Month +1 post-surgery)

- Date of activation
- Objective measures: impedance and ECAP test
- Delivery of Patient Diary with instructions to use it
- Presence of adverse events
- Modification of concomitant medications

Visit 6 and 7 (follow-up, Month+3 and Month+6-surgery)

- Date of visit
- Audiometric evaluation: results of HINT-Q and HINT-N tests
- Audiometric evaluations in routine care, if available
- Objective measures: impedance and ECAP test
- Respect of stimulation duration assessed through the patient diary
- Presence of adverse events
- Modification of concomitant medications

Visit 8 (end of study, Month +12 surgery)

- Date of visit
- Completion of study and reason of discontinuation
- Audiometric evaluation: results of HINT-Q and HINT-N tests
- Audiometric evaluations in routine care, if available
- Objective measures: impedance and ECAP test
- Respect of stimulation duration assessed through the patient diary
- Presence of adverse events
- Modification of concomitant medications

Unscheduled visit

- Date of visit
- Reason of visit
- Objective measures: impedance and ECAP test
- Modification of concomitant medications
- Presence of adverse events

2.2. Patient Diary

Patient must indicate in the Patient Diary for each day the duration of the stimulation (in hours) and the reason why the duration has not been respected (battery, sound issues, other reason).

At visits 6, 7 and 8, the investigator will review this Patient Diary and indicate in the eCRF all days without respected stimulation duration (less than 8 hours/day).

3. General statistical approach

The quantitative variables will be summarized using the following parameters:

- Number of missing and non-missing data,
- Mean and Standard deviation,
- 2-sided 95% Confidence Interval (CI) of the mean,
- Median, minimum and maximum.

The qualitative variables will be summarized using the following parameters:

- Number of missing and non-missing data,
- Counts and percentages with 2-sided 95% CI.

Statistical analysis will be performed at the 5% global significance level using 2-sided tests.

Statistical tests will be chosen according the type of variable:

By default, missing data or unknown responses will not be counted in the denominator of percentages but will be presented in the results tables.

Handling of missing data:

- Rule 1: If the assessment at M6 is missing but a further assessment is available, the missing assessment will be replaced by the next available data.
- Rule 2: If the assessment at M6 and M12 are missing but the assessment at M3 is available then M3 score will be carried forward.
- Rule 3: If the assessment at M6 and M12 is not available in quiet conditions but available in noise then the score at M6 in noise will be used.
- Rule 4: In case of lost to follow-up or withdrawal of the inform consent for unknown reason a stochastic regression imputation will be used. This technique computes a regression equation that generates predicted values for the missing data. After a random error term generated from a normal distribution (with a mean of zero and a variance equal to the residual variance from the preceding regression analysis) is added to each predicted score and the resulting sum is used in place of missing values.
- Rule 5: In case of withdrawal not due to a failure of the implantation or complications the baseline will be imputed at month 6.
- Rule 6: In case of withdrawal due to major complications requiring new implantation, the worst observed score will be imputed.

Sensitivity analyses

The best-case scenario will consist in deleting patients without data at M6 and M12 (if M12 is available then M12 will be imputed at M6).

- The worst-case scenario will consist in imputing a total loss of hearing (score = 0%)
- Tipping point analysis approach will be applied to assess the rules which overturn the conclusion. The steps going from the best scenario to the worst one (all missing scores are 0) and including rules of the primary analysis.

4. Analysis population

4.1. Full Analysis Set (FAS)

The Full Analysis Set will include all subjects implanted with the device, regardless whether any post-operative data are available.

The primary analysis will be performed on a subgroup of this set. This subgroup will be composed of English-speaking patients to avoid the probable effect of language on the response.

4.2. Per Protocol Set (PPS)

The Per Protocol Set will include all patients of the FAS and who will complete the clinical trial according to the protocol.

It consists of subjects who will satisfy the following criteria:

- Completion of the pivotal study
- Protocol compliance during the pivotal study
- No violation of any eligibility criteria that could influence the primary efficacy endpoint
- No violation of the protocol or deviation from the protocol which could influence the outcome of efficacy endpoints

The English-speaking subgroup in the PPS will be used in a sensitivity analysis of the primary analysis.

4.3. Safety Analysis Set (SAS)

The Safety Analysis Set will include all patients for whom the surgery of implantation started.

5. Data analysis

All statistical analysis will be generated using SAS version 9.4.

5.1. Follow-up of the study

- Number of patients in each analysis data sets according to the decisions made during the Data Review meeting to determine major/minor protocol deviations (refer to table 1).

- Number of patients present at each visit and listing of patients not present at one visit (refer to table 1).

- Time between visits (refer to table 6):
    - Date of surgery (V3) – Date of inclusion (V2) (days)
    - Date of activation (V5) – Date of surgery (V3) (days)
    - Date of follow-up visits (V4, V6, V7 and V8) – Date of surgery (months)
    - Date of unscheduled visit – Date of surgery (V3) (months)
    - Date of end of visit (V8) – Date of surgery (V3) (months)

- Discontinuation: Yes / No (refer to table 2)
  Patient will be considered as withdrawn:
    - If the question "did the patient complete the study" is answer "NO"

  OR
    - if the end of study visit is not performed
    - If YES, reasons of discontinuation: Screen failure / Adverse event / Death / Patient request / Investigator decision / Loss to follow-up / Protocol violation / Study terminated by the sponsor / Other

- The patient disposition will be provided as described in the figure 1. It will include the following information:
    - Number of subjects screened; included
    - Withdrawals and reasons
    - Protocol violations/deviations and exclusions from each data sets
    - Number of patients in each analysis data sets

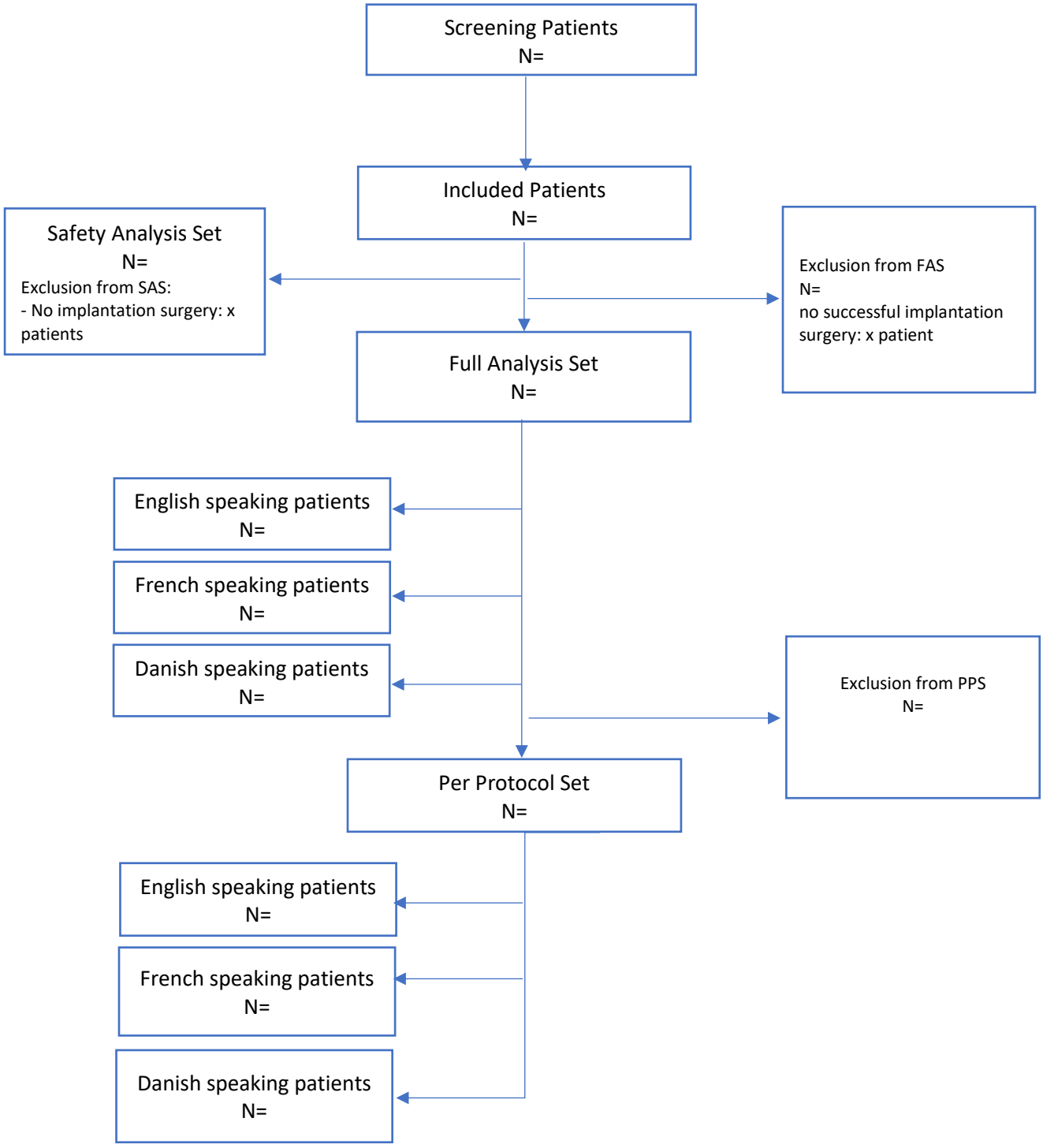

FIGURE 1 : PATIENT DISPOSITION DIAGRAM

5.2. Baseline characteristics

(refer to table 3)

- Age: Calculation (years) = (date of visit V2 – date of birth)/365.25
  Classes (years): [18 – 35[; [35 – 50[; [50 – 70[; ≥ 70

- Gender: Male / Female

- BMI: Calculation (kg/m²) = weight (kg) / height (m)²
  Classes (kg/m²): [18 – 25[; [25 – 30[; [30 – 35[; ≥ 35

- Language speaking: English / French / Danish

5.3. Medical history

(refer to table 4)

- Allergies: Yes / No
  If Yes, cause and type of reaction (will be presented through a listing classified by allergy and patient)

- Significant medical history: Yes / No
  Calculation: YES is defined as at least, one disease/syndrome ticked Past

- Significant concomitant disease: Yes / No
  Calculation: YES is defined as at least, one disease/syndrome ticked Present

- Concomitant medication: Yes / No
  Calculation: YES is defined as patient with at least one concomitant treatment
  Frequency of treatment classified according to the ATC classes

5.4. Hearing history

(refer to table 5)

- Etiology:
  Frequency of primary cause by ear (right / left): Aging / Auto immune / Genetics / Noise exposure / Otosclerosis / Meniere's disease / Acoustic neuroma / Meningitis / Mondini / Head trauma /Viral / Ototoxic drugs / Unknown / Other cause

- Hearing history:
  - Duration of hearing loss for each ear (right / left) (years):

Calculation: Age of first used hearing aid – Age at onset of hearing loss, or
Calculation: Age at cochlear implantation - Age of onset of hearing loss

- Duration of hearing sensorial hearing loss for each ear (right / left) (years)
  Calculation: Age at cochlear implantation – Age at onset of severe to profound hearing loss

- Vertigo: Yes / No
- Tinnitus: Yes / No
- Diagnostic imaging:
  - CT imaging: Yes / No
    If Yes, results: bony labyrinth anomaly, cochlear malformation, ossification
  - MRI: Yes / No
    If Yes, results: auditory nerve lesions, cochlear malformation, ossification/fibrosis, central lesions of the auditory pathway
- Audiological assessment:
  - Pure tone audiometry:
    Duration = Date of visit 2 – Date of audiometry assessment
    For each ear (right / left), values of dB for each tested frequency: 250 Hz / 500 Hz / 1 kHz / 2 kHz / 4 kHz / 8kHz
  - Performance of Tympanometry: Yes / No
    if YES, results by ear (right / left):
  - Speech perception test: percentage of correct words for HINT-Q and HINT-N tests
  - Performance-of Speech audiometry routine test: Yes / No
    if YES, results by patient will be presented through a listing

5.5. Surgery

(refer to table 7)

- Ear implanted: Right / Left
- Cochlear implant type: Neuro Zti CLA / Neuro Zti EVO
- Full electrode array insertion : yes/no
- Number of electrodes out of cochlea,
- Time of surgery (min)

- Objective measures: Yes / No
    - If YES, performance of impedance and ECAP testings: Done / Not done / Meet an issue
    - If Impedance DONE: value (kilo ohms) for the 20 channels
    - If ECAP DONE: Download the results into the eCRF

5.6. Primary end point

5.6.1. HINT in Quiet at Month 6

Change from baseline to month 6 (refer to table 8).

Calculation = HINT-Q at Month 6 - HINT-Q at Inclusion visit

The primary efficacy endpoint of the Neuro CIS is assessed with the HINT score in quiet, on the ipsilateral ear.

The mean HINT scores in quiet will be used as the primary outcome measures for assessing the primary benefit.

The primary analysis will be performed on a subgroup of the FAS which consists of all English-speaking patients (Exclusion of Danish and French-Canadian speaking patients). The analysis will be replicated in PPS.

5.6.2. Major complication incidence rate

The occurrence of major complications within the first year of follow-up will be the co-primary endpoint for assessing the primary risk of device implantation.

Safety data shall be collected through the duration of the study and reflect the type and duration of any adverse event(s) and classified as major or minor complications. An AE is any adverse change from the subject's baseline condition, symptoms or disease which is considered to be clinically relevant by the investigator that occurs whether or not it is considered to be related to the medical device. A complication is any adverse change symptoms or disease related to the surgery or the medical device. Complications will be classified as major if they require surgical intervention or not recovered spontaneously and minor if they resolve spontaneously or with non-invasive medical treatment categories (according to Cohen and Hoffman criteria).

Three incidence rates will be calculated and provided (refer to tables 9 and 16.1):

- Major complications rate which will be considered as a co-primary estimate of device side-effects
- Minor complications rate which will be considered as a secondary evaluation of side-effects
- Incidence rate of any complications

5.7. Secondary efficacy endpoints

5.7.1. Time course of the change of HINT-Q

Calculation of change from baseline =
Percent of correct words of HINT-$Q_{\text{Month 3/6/12}}$ – Percent of correct words of HINT-$Q_{\text{Inclusion visit}}$ (Refer to tables 8,10 and 11)

5.7.2. Homogeneity of HINT-Q results across languages

Calculation of change HINT-$Q_{\text{Month 3/6/12}}$ =
Percent of correct words of HINT-$Q_{\text{Month 3/6/12}}$ – Percent of correct words of HINT-$Q_{\text{Inclusion visit}}$ (refer to tables 12)

5.7.3. Sustainability of the effect at 12 months

Calculation of change HINT-Q at Month 6/12 = Percent of correct words of HINT-Q at Month 6/12 – Percent of correct words of HINT-Q at 3/6 months

Calculation of change HINT-Q at Month 12-3 = Percent of correct words of HINT-Q at Month 12 – Percent of correct words of HINT-Q at 3 months in case of the change between Month 12 and Month 6 is not significant.
Applicable across language if no effect on language (refer table 12), otherwise applicable only on English-speaking subjects (11.1).

5.7.4. HINT-N

Calculations described for HINT-Q in sections 5.7.1, 5.7.2, 5.7.3, will have to be performed on the HINT-N (refer to tables 13 and 14).

5.8. Technical functionalities - Impedance

Average of each electrode impedance at each time points and description of localization and number of electrode deactivation (refer to table 15 and related figure).

5.9.Safety data

According to the Protocol, safety data are collected from the pre-operative visit (during surgical procedure) to the end of patient participation.

The number and the percentage of patients who experienced:

- at least one Adverse Event (AE)

- at least one Serious Adverse Event (SAE)
- at least one Adverse Event that led to discontinuation (DisAE): action taken of the AE ticked Discontinued permanently
- at least one Fatal Adverse Event: outcome of the AE ticked Death
- at least one complication
- at least one minor complication

will be calculated (table 16.1).

The total number of events, the mean number of events in patients experiencing the event and the percentage of patients experiencing the event will be reported (table 16.2).

An AE is any adverse change from the subject's baseline condition, symptoms or disease which is considered to be clinically relevant by the investigator that occurs whether or not it is considered to be related to the medical device. A complication is any adverse change symptoms or disease related to the surgery or the medical device

Complications will be classified as major or minor according to the Cohen & Hoffman criteria by the investigator.

Then, MedDRA classification will be performed on all adverse events, during the review of data (refer to table 16.3).

A presentation of all AEs (refer to table 16.4) will be made according to System Organ Class (SOC) and Preferred Term (PT) from MedDRA classification. Incidence rates will be summarized for each PT and SOC terms.

6. Statistical analysis

6.1. Analysis of efficacy endpoint

The primary analysis of the primary efficacy endpoint will be performed on a subgroup of the FAS which consists of all English-speaking subjects.

Additional analysis with a replicate PPS will be performed on this subset of English-speaking patients.

The primary test is a one sample T-test performed on the change from baseline to 6 months after activation of the device. The value of the mean improvement under the null hypothesis is zero. The type I error (α) is set to 0.025 (one-sided).

The one sample Wilcoxon rank test will be applied in a sensitivity analysis. In case the normality assumption is strongly violated or in the presence of several outliers, the result of this sensitivity analysis will have a particular importance.

To further describe the benefit of the Neuro CIS in the studied population, the number of patients (as well as rate among the total population) showing a benefit of at least 20 percentage points in HINT-Q score after 6 months of device use when compared to baseline will be computed (table 8 with the related figure and table 16.6).

6.2. Co-primary analysis of safety endpoint

No formal hypothesis testing of safety data will be performed.

The incidence rate of major complications will be presented as well as its 95% exact confidence interval (CI). A forest plot will present this rate with its 95% CI and the rates with the 95% CI of major complications obtained in previous generation and in the scientific literature (refer to the tables 9.1, 9.2 and the related figure).

6.3. Analysis of secondary endpoints

6.3.1. Time course of the HINT-Q response in FAS and PPS

The analysis will be done on the FAS sub-group of English-speaking patients and replicated in PPS.

The time course of the change from baseline in the HINT-Q will be estimated with a mixed model for repeated measures using the change from baseline as the response, the patients (random effect) and the visit (fixed effect) as covariates.

The time (visit) effect will be tested (H1: at least two visits differ on average) and if a significant effect of visits is observed then visits responsible for the significant difference will be searched.

The intercept and its 95% confidence interval will be interpreted as the coverage effect of the implant over a period of one year. This will be an approximation due to the absence of an assessment at 9 months.

The 95% Confidence Interval of the mean at each visit will be provided.

(refer to table 10)

6.3.2. Sustainability of the effect at 12 months in FAS and PPS

HINT-Q performed at Month 6 in the FAS and PPS sub-group of English speaking patients will be compared to the result at Month 3, and the result at month 12 will also be compared to those obtained at Month 3 and 6 to assess the sustainability of the effect over time.

A one-sided ($\alpha = 0.025$) t-test for paired samples will be used. (refer to tables 11.1 and table 11.2).

6.3.3. Homogeneity of HINT-Q results across languages and estimates of effects in the FAS and PPS

(Refer to table 12)

This analysis will be done on the FAS and replicated in PPS.

A mixed model for repeated measures will be fitted using the change from baseline to Month 3, Month 6 and Month 12 in the HINT-Q score as the responses and the following covariates or terms: the visit (M3, M6 and M12, fixed effect), the patient (random effect), the language (fixed effect) and the interaction between visit and language. The variance covariance matrix will be unstructured.

If the p value of the interaction is below 0.15 then a signal of potential interaction will be detected and the time course of the change from baseline will be possibly dependent upon the language.

If the p value of interaction is above 0.15, an interaction will be still possible due to the poor power of the interaction test, but the magnitude of the difference should be limited. Findings obtained on the three languages combined will provide a better external validity than those obtained on English speaking only. Consequently, the interaction will be interpreted as a measure of the generalizability of the effect across languages.

Regardless the p value of interaction a graph will present the time course of the response for each language and for all languages combined.

A series of contrasts will be performed to estimate and test (table 12):

- The difference between languages in the magnitude of the change from baseline at each time point. The contrast at Month 6 will be of major importance.
- The magnitude of the change from baseline to each time point for the 3 languages combined. The estimate at Month 6 will be the most supportive result.
- The significance (difference from zero) of overall (all languages) change at each time point.
- The overall difference between Month 6 and Month 12 of the change from baseline (all languages combined).
- The visit effect (is there a difference between visits in the change from baseline?)
- In the presence of potential interaction between languages and time then the mean effect of languages will be investigated.

6.3.4. Analysis of HINT-N in FAS and PPS

All analyses performed on the HINT-Q will be replicated on the HINT-N, with the score at post-implantation visits considered as the response. (refer to tables 13 and 14).

6.3.5. Measures of impedance in FAS and PPS

The time course of electrodes impedance performed at each time points will be analyzed through a mixed model for repeated measures and contrasts of interest. (refer to table 15).

6.3.6. ECAP

Measures will be performed over time from Baseline to Month 12 and results downloaded into the eCRF. Due to the differences format of ECAP files downloaded (pdf, Excel file, pictures), it will not be possible to perform ECAP analysis. Nevertheless, all the downloaded files will be provided.

6.4. Safety analysis

Every tables will be presented on Safety Analysis Set.

The total number of events, the mean number of events per patient and the percentage of patients experiencing events will be presented per preferred term (table 16.2).

In addition, a table will provide the number and the percentage of patients with (table 16.1):

- at least one Adverse Event (AE)
- at least one Serious Adverse Event (SAE)
- at least one Adverse Event that led to discontinuation (DisAE): action taken of the AE ticked Discontinued permanently
- at least one Fatal Adverse Event: outcome of the AE ticked Death
- at least one complication
- at least one minor complication

A presentation of all AEs will be made according to System Organ Class (SOC) and Preferred Term (PT) from MedDRA classification.

A table should describe of device related vs not device related AEs, as well as study vs not study related AEs. (Table 16.2 and related figure)

Incidence rates will be summarized for each PT and SOC terms (refer to table 16.3) AEs will be presented in terms of patients (number and percentage) and in terms of events (number and mean number per patient experiencing the event at least once). For the latter, an event occurring at 2 distinct times during the treatment period will be counted twice for calculating the mean number of events per patient. For one patient, if two events are both coded to the same PT, the patient will be counted only once at the PT level.

The time to the first minor or major complications will be investigated through Kaplan Meier survival (event free) analysis and the graph of the estimated event free probability by the time will be presented.

Listing of SAEs and deaths (age, gender, time to AE, description of AE, outcome, discontinuation, relationship, severity, PT and SOC terms) will be presented (refer to table 16.4).

6.5.Site effects analysis

The site effect is partly confounded with the language effect. Consequently, the site effect will be investigated in English speaking patients. An analysis of variance using the change from baseline to M6 as the response and the site as covariate will be performed. If the site effect is significant, then the mean change from baseline to M6 is dependent upon the site. Regardless the p value of ANOVA a Forest plot presenting the mean change from baseline to M6 of each site along with the 95% confidence interval will be presented to verify whether there is just a quantitative difference across sites or a qualitative one (refer to table 12 and the related figure). In case of significant site effect and qualitative difference the site with the largest mean deviation from the overall mean change from baseline will be removed from the sample to estimate the overall mean change from baseline in the remaining sites.

7. Mock of tables

Table 1 : Disposition of patient

	English speaking patients N=	French speaking patients N=	Danish speaking patients N=	Global population N=
Screening patients	xx	xx	xx	xx
Included patients	xx (xx.xx%)	xx (xx.xx%)	xx (xx.xx%)	xx (xx.xx%)
Surgery	xx (xx.xx%)	xx (xx.xx%)	xx (xx.xx%)	xx (xx.xx%)
Activation	xx (xx.xx%)	xx (xx.xx%)	xx (xx.xx%)	xx (xx.xx%)
Visit at M3	xx (xx.xx%)	xx (xx.xx%)	xx (xx.xx%)	xx (xx.xx%)
Visit at M6	xx (xx.xx%)	xx (xx.xx%)	xx (xx.xx%)	xx (xx.xx%)
Visit at M12	xx (xx.xx%)	xx (xx.xx%)	xx (xx.xx%)	xx (xx.xx%)
Full Analysis Set Exclusion reason 1 Exclusion reason 2 …	xx (xx.xx%) xx (xx.xx%) xx (xx.xx%)	xx (xx.xx%) xx (xx.xx%) xx (xx.xx%)	xx (xx.xx%) xx (xx.xx%) xx (xx.xx%)	xx (xx.xx%) xx (xx.xx%) xx (xx.xx%)
Per Protocol Set Exclusion reason 1 Exclusion reason 2 …	xx (xx.xx%) xx (xx.xx%) xx (xx.xx%)	xx (xx.xx%) xx (xx.xx%) xx (xx.xx%)	xx (xx.xx%) xx (xx.xx%) xx (xx.xx%)	xx (xx.xx%) xx (xx.xx%) xx (xx.xx%)
Safety Analysis Set Exclusion reason 1 Exclusion reason 2 …	xx (xx.xx%) xx (xx.xx%) xx (xx.xx%)	xx (xx.xx%) xx (xx.xx%) xx (xx.xx%)	xx (xx.xx%) xx (xx.xx%) xx (xx.xx%)	xx (xx.xx%) xx (xx.xx%) xx (xx.xx%)

Table 2 : Discontinuation

	English speaking patients N=	French speaking patients N=	Danish speaking patients N=	Global population N=
Discontinuation of study	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
Screen failure	x	x	x	x
Adverse event	x	x	x	x
Death	x	x	x	x
Patient request	x	x	x	x
Investigator decision	x	x	x	x
Loss to follow up	x	x	x	x
Protocol deviation	x	x	x	x
Study terminated by the sponsor	x	x	x	x
Other	x	x	x	x

Table 3 : Demographics – SAS, FAS and PPS population

	English speaking patients N=	**French speaking patients N=**	**Danish speaking patients N=**	**Global population N=**
Age (years)	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x
[18; 40 [	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
[40; 50 [	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
[50; 60 [	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
>= 60	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
Gender				
Male	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
Female	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
BMI (kg/m²)	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x
[18; 25 [	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
[25; 30 [	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
[30; 35 [	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
>= 35	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)

Table 4 : Medical history – SAS, FAS and PPS population

	English speaking patients N=	French speaking patients N=	Danish speaking patients N=	Global population N=
Allergies				
Yes	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
No	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
Significant medical history				
Yes	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
No	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
Significant concomitant disease				
Yes	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
No	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
Concomitant medication				
Yes	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
No	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)

Table 5 : Hearing history – SAS, FAS and PPS population

	English speaking patients N=	French speaking patients N=	Danish speaking patients N=	Global population N=
Etiology				
For right ear				
Aging	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
Auto immune	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
Genetics	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
Noise exposure	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
Ostosclerosis	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
Meniere's disease	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
Acoustic neuroma	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
Meningitis	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
…				
For left ear				
Aging	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
Auto immune	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
Genetics	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
Noise exposure	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
Ostosclerosis	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
Meniere's disease	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
Acoustic neuroma	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
Meningitis	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
…				
Duration of hearing loss (years)				
Right ear	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x
Left ear	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x
Duration of first used hearing aid (years)				
Right ear	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x
Left ear	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x

	English speaking patients N=	French speaking patients N=	Danish speaking patients N=	Global population N=
Duration of severe to profound hearing loss (years) Right ear	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x
Left ear	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x
Vertigo Yes No	 x (xx.xx%) x (xx.xx%)	 x (xx.xx%) x (xx.xx%)	 x (xx.xx%) x (xx.xx%)	 x (xx.xx%) x (xx.xx%)
Tinnitus Yes No	 x (xx.xx%) x (xx.xx%)	 x (xx.xx%) x (xx.xx%)	 x (xx.xx%) x (xx.xx%)	 x (xx.xx%) x (xx.xx%)
CT imaging bony labyrinth cochlear malformation ossification	x (xx.xx%) x (xx.xx%) x (xx.xx%) x (xx.xx%)	x (xx.xx%) x (xx.xx%) x (xx.xx%) x (xx.xx%)	x (xx.xx%) x (xx.xx%) x (xx.xx%) x (xx.xx%)	x (xx.xx%) x (xx.xx%) x (xx.xx%) x (xx.xx%)
MRI auditory nerve lesions cochlear malformation ossification, bibrosis central lesions of the auditory pathway	x (xx.xx%) x (xx.xx%) x (xx.xx%) x (xx.xx%) x (xx.xx%)	x (xx.xx%) x (xx.xx%) x (xx.xx%) x (xx.xx%) x (xx.xx%)	x (xx.xx%) x (xx.xx%) x (xx.xx%) x (xx.xx%) x (xx.xx%)	x (xx.xx%) x (xx.xx%) x (xx.xx%) x (xx.xx%) x (xx.xx%)
Audiological assessment Pure tone audiometry (days)	x.xx±x.x	x.xx±x.x	x.xx±x.x	x.xx±x.x
right 250Hz	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x
500Hz	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x
1kHz	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x
2kHz	x.xx±x.x	x.xx±x.x	x.xx±x.x	x.xx±x.x

	CI= [x.x;x.x] [xx ; xx] Med=x	CI= [x.x;x.x] [xx ; xx] Med=x	CI= [x.x;x.x] [xx ; xx] Med=x	CI= [x.x;x.x] [xx ; xx] Med=x
4kHz	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x
8kHz	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x
left 250Hz	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x
500Hz	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x
1kHz	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x
2kHz	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x
4kHz	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x
8kHz	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x
Performance of Tympanometry				
Yes*	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
No	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
*If yes, results for right ear				

Ear Canal Volume	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x
daPa	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x
Compliance	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x
*If yes, results for left ear Ear Canal Volume	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x
daPa	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x
Compliance	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x
Speech perception test				
Yes	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
No	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
Performance of Speech audiometry routine test				
Yes**	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
No	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)

**if yes, results by patient will be presented through a listing.

Table 6 : Time between visits – SAS, FAS and PPS population

Time between visits	English speaking patients N=	French speaking patients N=	Danish speaking patients N=	Global population N=
Time between surgery and inclusion (days)	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x
Time between activation and surgery (days)	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x
Time between Fu V4 and surgery (months)	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x
Time between Fu V6 and surgery (months)	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x
Time between Fu V7 and surgery (months)	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x
Time between Fu V8 and surgery (months)	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x
Time between End of study and surgery (months)	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x
Time between unscheduled visit and surgery (months)	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x

Table 7 : Surgery description – FAS and PPS population

	English speaking patients N=	French speaking patients N=	Danish speaking patients N=	Global population N=
Ear implanted				
Right	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
Left	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
Cochlear implant				
Neuro Zti CLA	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
Neuro Zti EVO	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
Time of surgery (min)	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x
Electrode array full insertion				
Yes	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
No	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
Electrode out of cochlea	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x
Objective measurements				
Yes	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
No	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
If YES, Impedance				
Done	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
Not done	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
Meet an issue	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
If YES, ECAP				
Done	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
Not done	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)
Meet an issue	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)	x (xx.xx%)

Table 8: Assessment of primary endpoint - HINT in Quiet at Month 6 – FAS and PPS English Speaking patients sub-group

	English speakingpatients FAS N=	English speakingpatients PPS N=
HINT-Q at Baseline – Percent of correct words	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x
HINT-Q at Month 6 – Percent of correct words	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x
Change at Month 6	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x
P value	x.xxx	x.xxx

Figure N (to be done with data in the SAR) : Histogram of HINT-Q change (<20, 20 – 50, >50)

Table 9.1 : Assessment of primary endpoint - Major complication incidence rate – SAS population

SAS population	Patients N=
Major complications	
Yes	x (xx.xx%)
No	x (xx.xx%)
CI	[x.x;x.x]

Table 9.2 : Major complication related to device – SAS population

SAS population	Major complications N=
Related to device	
Yes	x (xx.xx%)
No	x (xx.xx%)

Figure N (to be done with data in the SAR) : Forest plot of major complications incidence rate

Table 10: Assessment of secondary endpoints – Time course of the HINT-Q response – FAS and PPS English speaking patients' sub-group

Source	Model parameter	df	Sum of squares	Mean Ssquare	F Value	Pr > F	R-Square
Model Error Corrected Total	Change HINT-Q Patient Visit						

Table 11.1 : Assessment of secondary endpoints – Sustainability of the effect of HINT-Q at Month 12 – FAS and PPS English speaking patients sub-group

	English speaking patients (FAS) N=	English speaking patients (PPS) N=
HINT-Q at baseline – Percent of correct words	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI=[x.x;x.x] [xx ; xx] Med=x Missing=x
HINT-Q at Month 3 – Percent of correct words	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI=[x.x;x.x] [xx ; xx] Med=x Missing=x
HINT-Q at Month 6 – Percent of correct words	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI=[x.x;x.x] [xx ; xx] Med=x Missing=x
HINT-Q at Month 12 – Percent of correct words	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI=[x.x;x.x] [xx ; xx] Med=x Missing=
Change at Month 3 (vs baseline) – Percent of correct words P value	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x x.xxx	x.xx±x.x CI=[x.x;x.x] [xx ; xx] Med=x Missing=x x.xxx
Change at Month 12 (vs baseline) – Percent of correct words	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI=[x.x;x.x] [xx ; xx] Med=x Missing=x

P value	x.xxx	x.xxx
Change from M3 to M6 – Percent of correct words P value	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x x.xxx	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x x.xxx
Change from M3 to M12 – Percent of correct words P value	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x x.xxx	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x- x.xxx
Change from M6 to M12 – Percent of correct words P value	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x x.xxx	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x x.xxx

Table 11.2 : Assessment of secondary endpoints – Time course of HINT-Q – FAS and PPS English speaking patient sub-group

Source	df	Sum of squares	Mean Square	F Value	Pr > F	R-Square
Model Error Corrected Total						

Table 12 : Assessment of secondary endpoints – Homogeneity of HINT-Q across languages – FAS and PPS population

	English speaking patients N=	**French speaking patients N=**	**Danish speaking patients N=**
HINT-Q at Baseline – Percent of correct words	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x
HINT-Q at Month 3 – Percent of correct words	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x
HINT-Q at Month 6 – Percent of correct words	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x
HINT-Q at Month 12 – Percent of correct words	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x
Change in HINT-Q at Month 3 – Percent of correct words P.value	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x X.XXX	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x X.XXX	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x X.XXX
Change in HINT-Q at Month 6 – Percent of correct words P.value	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x X.XXX	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x X.XXX	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x X.XXX
Change in HINT-Q at Month 12 – Percent of correct words P.value	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x X.XXX	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x X.XXX	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x X.XXX

Source	Model parameter	df	Sum of squares	Mean Ssquare	F Value	Pr > F	R-Square
Model Error Corrected Total	Patient Visit Language						

Figure N (to be done with data on the SAR) : Forest plot for HINT-Q average by site

Table 13: Assessment of secondary endpoints –HINT-N – FAS and PPS English speaking patients sub-group

	English speaking patients (FAS) N=	English speaking patients (PPS) N=
HINT-N at Month 3 – Percent of correct words	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI=[x.x;x.x] [xx ; xx] Med=x Missing=x
HINT-N at Month 6 – Percent of correct words	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI=[x.x;x.x] [xx ; xx] Med=x Missing=x
HINT-N at Month 12 – Percent of correct words	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI=[x.x;x.x] [xx ; xx] Med=x Missing=x
Change at Month 3 (vs baseline) P value	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x x.xxx	x.xx±x.x CI=[x.x;x.x] [xx ; xx] Med=x Missing=x x.xxx
Change at Month 6 (vs baseline) P value	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x x.xxx	x.xx±x.x CI=[x.x;x.x] [xx ; xx] Med=x Missing=x x.xxx
Change at Month 12 (vs baseline) P value	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x x.xxx	x.xx±x.x CI=[x.x;x.x] [xx ; xx] Med=x Missing=x x.xxx
Change from M3 to M6 – Percent of correct words P value	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x x.xxx	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x x.xxx
Change from M3 to M12 – Percent of correct words	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x

P value	x.xxx	x.xxx
Change from M6to M12 – Percent of correct words P value	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x x.xxx	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x x.xxx

Table 14: Descriptive assessment–HINT-N – FAS and PPS Homogeneity of HINT-N across languages

	English speaking patients N=	French speaking patients N=	Danish speaking patients N=
HINT-N at Baseline – Percent of correct words	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x
HINT-N at Month 3 – Percent of correct words	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x
HINT-N at Month 6 – Percent of correct words	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x
HINT-N at Month 12 – Percent of correct words	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x
Change in HINT-N at Month 3 – Percent of correct words P value	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x x.xxx	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x x.xxx	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x x.xxx
Change in HINT-N at Month 6 – Percent of correct words P value	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x x.xxx	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x x.xxx	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x x.xxx
Change in HINT-N at Month 12 – Percent of correct words P value	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x x.xxx	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x x.xxx	x.xx±x.x CI= [x.x;x.x] [xx ; xx] Med=x Missing=x x.xxx

Source	Model parameter	df	Sum of squares	Mean Ssquare	F Value	Pr > F	R-Square
Model Error Corrected Total	Patient Visit Language						

Table 15 : Assessment of secondary endpoints – Impedance – FAS and PPS population

	Impedance e1 patients N=	…	Impedance e20 patients N=
Electrode impedance at Activation Patients deactivated/out of range	x.xx±x.x CI= [x.x;x.x] Missing=x x	…	x.xx±x.x CI= [x.x;x.x] Missing=x x
Electrode impedance at Month 3 Patients deactivated/out of range	x.xx±x.x CI= [x.x;x.x] Missing=x x	…	x.xx±x.x CI= [x.x;x.x] Missing=x x
Electrode impedance at Month 6 Patients deactivated/out of range	x.xx±x.x CI= [x.x;x.x] Missing=x x	…	x.xx±x.x CI= [x.x;x.x] Missing=x x
Electrode impedance at Month 12 Patients deactivated/out of range	x.xx±x.x CI= [x.x;x.x] Missing=x x	…	x.xx±x.x CI= [x.x;x.x] Missing=x x

Source	Model parameter	df	Sum of squares	Mean Ssquare	F Value	Pr > F	R-Square
Model Error Corrected Total	channel Visit						

Figure N (to be done with data on the SAR) : Curve graph of patient number with deactivated and/or out of ranges electrodes –Impedance in function of electrode position– FAS and PPS population

Table 16.1 : Summary of patient by AE on SAS population

SAS	Global population N=
At least one AE	
Yes	x (xx.xx%)
No	x (xx.xx%)
At least one serious AE	
Yes	x (xx.xx%)
No	x (xx.xx%)
At least one AE that led to discontinuation	
Yes	x (xx.xx%)
No	x (xx.xx%)
At least one Fatal Adverse Event	
Yes	x (xx.xx%)
No	x (xx.xx%)
At least one complication	(xx.xx%)
Yes	x (xx.xx%)
No	x (xx.xx%)
At least one minor complication	(xx.xx%)
Yes	x (xx.xx%)
No	x (xx.xx%)
At least one AE related to device	
Yes	x (xx.xx%)
No	x (xx.xx%)

Table 16.2 Summary of AE – SAS population

	Global population
Number of AE	x
Severity	
Mild	x (xx.xx%)
Moderate	x (xx.xx%)
Severe	x (xx.xx%)
ND	x (xx.xx%)
Relation to device	
Definitely related	x (xx.xx%)
Possible related	x (xx.xx%)
Not related	x (xx.xx%)
Unknown	x (xx.xx%)
Relationship to trial procedure	
Improbable	x (xx.xx%)
Possible	x (xx.xx%)
Probable	x (xx.xx%)
Certainly	x (xx.xx%)
Unknown	x (xx.xx%)
Action taken	
None	x (xx.xx%)
Discontinued permanently	x (xx.xx%)
Discontinued temporarily	x (xx.xx%)
Unknown	x (xx.xx%)
Treatment/therapy	
Yes	x (xx.xx%)
No	x (xx.xx%)
ND	x (xx.xx%)
Outcome of AE	
Death	x (xx.xx%)
Not Recovered	x (xx.xx%)
Recovered	x (xx.xx%)
Recovered with sequelae	x (xx.xx%)
Recovering	x (xx.xx%)
Unknown	x (xx.xx%)
Anticipated AE	
Yes	x (xx.xx%)
No	x (xx.xx%)
ND	x (xx.xx%)
Serious Adverse Event	
Yes	x (xx.xx%)
No	x (xx.xx%)
ND	x (xx.xx%)

Figure N (to be done with data on the SAR) : Safety analysis – relation to device and relation to trial procedure

Table 16.3: AE by SOC and PT (coding by MedDRA)

System Organ Term	Preferred Term	Number of AE.	Number of patient
At least one AE		x (xx.xx%)	x (xx.xx%)
Gastrointestinal disorders	** Total **	x (xx.xx%)	x (xx.xx%)
	Abdominal discomfort	x (xx.xx%)	x (xx.xx%)
	…	x (xx.xx%)	x (xx.xx%)
Infections and infestations	** Total **	x (xx.xx%)	x (xx.xx%)
	Influenza	x (xx.xx%)	x (xx.xx%)
	…	x (xx.xx%)	x (xx.xx%)
Injury, poisoning and procedural complications	** Total **	x (xx.xx%)	x (xx.xx%)
	Ligament sprain	x (xx.xx%)	x (xx.xx%)
	…	x (xx.xx%)	x (xx.xx%)
Respiratory, thoracic and mediastinal disorders	** Total **	x (xx.xx%)	x (xx.xx%)
	Bronchitis	x (xx.xx%)	x (xx.xx%)
	…	x (xx.xx%)	x (xx.xx%)
Vascular disorders	** Total **	x (xx.xx%)	x (xx.xx%)
	Hypertension	x (xx.xx%)	x (xx.xx%)
	…	x (xx.xx%)	x (xx.xx%)

Table 16.4 : List of AE

Patient number	Language	Age	Gender	Time of onset	Description	SOC Term	PT Term	Outcome	Relationship	Seriousness	Severity

Table 16.5 : Concomitant treatment coding by ATC

Level 1	**therapeutic subgroup**	**X**
Level 2		X
Level 3	Medical name	X

Level 1 is the anatomical main group and therapeutic subgroup.

Level 2 is the therapeutic/pharmacological subgroup and chemical/therapeutic/pharmacological subgroup.

Level 3 is the chemical substance.

Table 16.6: List of patients with explantations

Patient ID	**Date of implantation**	**Date of explantation**	**Explantation reason**	**Device replaced (Yes/No)**