Statistical Analysis Plan

InSightec

A Pivotal Study to Evaluate the Efficacy and Safety of ExAblate Transcranial MRgFUS Thalamotomy Treatment of Medication Refractory Essential Tremor Subjects

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Final

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List of Abbreviations

AE	Adverse Events
BMI	Body Mass Index
CRF	Case Report Form
CRST	Clinical Rating Scale for Tremor
CT	Computer Tomography
DVT	Deep Vein Thrombosis
ET	Essential Tremor
ITT	Intent to Treat
LOCF	Last Observation Carried Forward
MRI	Magnetic Resonance Imaging
PHQ	Patient Health Questionnaire
PP	Per Protocol
QUEST	Quality of Life in Essential Tremor
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SF	Screen Failure

1 Introduction

The current document describes a full statistical analysis plan (SAP) for the ET-002 Study. ET-002 is a prospective, multi-center, randomized, double-blind (to subjects and Tremor Core Lab assessor), two-arm study. The design of this study includes two stages: Main and Crossover. In the Main stage subjects are randomized in a 3:1 ratio to either ExAblate or Sham Control (henceforth "ExAblate" and "Sham," respectively). The Crossover stage of the study is designed for subjects randomized to the Sham group in the Main stage to receive an unblinded ExAblate treatment, if eligible, at 3-months follow-up post Sham treatment, and to be followed in a similar fashion as the Main stage of ExAblate subjects in terms of planned follow-up visits and assessments.

2 Study Objectives

The objectives of this trial are to evaluate the efficacy and safety of ExAblate system in treatment of medication-refractory tremor in subjects with essential tremor.

The Main stage of the study relates to subjects randomized to either ExAblate or Sham, while the Crossover stage of the study examines outcomes for subjects randomized to Sham who eventually received active treatment with ExAblate. Both Main and Crossover stages of the study provide information on the safety and efficacy of the procedure up to twelve months post-treatment. However, only the Main stage will be used to test device safety and efficacy for the purpose of regulatory approval. The Crossover stage will serve to follow-up safety and efficacy to 12 months.

3 Treatment Groups

Each subject in the Main stage of the study will be randomly assigned to either of the following treatment groups:

- ExAblate – Active treatment with ExAblate
- Sham – Sham Control treatment

The randomization scheme will be 3:1 ExAblate-to-Sham.

Subjects in the Crossover stage of the study will undergo active treatment with ExAblate following their initial Sham treatment.

4 Study Schedule

The following table summarizes the sequence of procedures that a subject in this study will follow.

Summary of Study Schedules and Measurements									
	Screening	**Baseline Assessment**	**Treatment**	**1 Day**	**1 Week**	**1 Month**	**3 Month**	**6 Month**	**12 Month**
Consent	X								
Eligibility Evaluation with Labs	X	X							
Medications	X	X	X	X	X	X	X	X	X
30 Day Medication Stabilization		X							
Medical History	X								
Physical Exam	X			X	X	X	X	X	X
Neurological Status	X		X	X	X	X	X	X	X
CRST (Unblinded Site Assessor)	X							X	X
CRST (Blinded Site Assessor)		X				X	X		
CRST (Blinded Tremor Core Lab)		X				X	X	X	X
QUEST	X	X				X	X	X	X
PHQ-9	X					X	X	X	X
CT		X							
MRI		X							X
Treatment			X						
Adverse Events			X	X	X	X	X	X	X
Exit Form									X

5 Analysis Populations

5.1 Safety Analysis Population

The Safety analysis population will include all randomized subjects who received at least one sonication – ExAblate or Sham – in the Main stage of the study, as indicated by the following:

- CRF field "Number of Performed Sonications" on the ExAblate Treatment Form has a value of at least one

  or
- At least one CRF field “Sonication Duration [sec]” on Sonication Form has a value greater than zero.

5.2 Efficacy Analysis Populations

5.2.1 Intent to Treat (ITT)

The ITT analysis population will include all Safety subjects for whom there exist valid baseline measurement and at least one post-baseline measurement on the primary efficacy data.

5.2.2 Per Protocol (PP)

The PP analysis population will include all ITT subjects who have observed primary efficacy data at three months and have no major protocol violations likely to affect outcome.

5.3 Crossover Analysis Population

The Crossover analysis population will include all subjects who received at least one sonication in the Crossover stage of the study.

6 Definition of Endpoints

6.1 Safety Endpoints

The safety endpoints are:

- Adverse Events (AE's)
- Serious Adverse Events (SAE's)

6.2 Efficacy Endpoints

6.2.1 Confirmatory Primary Endpoint

The confirmatory primary efficacy endpoint in this study is Percent Improvement from Baseline at three months post-treatment in the treated (contralateral) upper extremity CRST sub score. For each subject the primary endpoint will be calculated as follows:

1. Identify which side of the brain was treated, as indicated by CRF field "Side of Brain being treated" on the ExAblate Treatment Form
2. If the RIGHT side of brain was treated, then the Tremor Core LAB variables from the LEFT side of the CRST assessment (contralateral side) will be used:
    - Part A = item #6 (LUE tremor): Rest + Posture + Action/Intention

      Note:
        - ➔ If only two individual rates are obtained, the sum will be calculated over the two available rates.
        - ➔ If a single individual rate is obtained, Part A will be considered as missing and should be imputed as described in Section 7.1.
    - Part B = item #11 Left* + item #12 Left + item #13 Left + item #14 Left + item #15 Left

      *Item #11 will be taken into account only for left-handed subjects. For right-handed subjects Part B will be the sum of 4 items only, without item #11.

      Note:
        - ➔ If a single item is missing, the sum will be calculated over the available items – four items for left-handed subjects and three items for right-handed subjects.

➔ If more than one item is missing, Part B will be considered as missing and should be imputed as described in Section 7.1.

3. If the LEFT side of brain was treated, then the Tremor Core LAB variables from the RIGHT side of the CRST assessment (contralateral side) will be used:
   - Part A = item #5 (RUE tremor): Rest + Posture + Action/Intention

     Note:
     - ➔ If only two individual rates are obtained, the sum will be calculated over the two available rates.
     - ➔ If a single individual rate is obtained, Part A will be considered as missing and should be imputed as described in Section 7.1.
   - Part B = item #11 Right* + item #12 Right + item #13 Right + item #14 Right + item #15 Right

     *Item #11 will be taken into account only for right-handed subjects. For left-handed subjects Part B will be the sum of 4 items only, without item #11.

     Note:
     - ➔ If a single item is missing, the sum will be calculated over the available items – four items for right-handed subjects and three items for left-handed subjects.
     - ➔ If more than one item is missing, Part B will be considered as missing and should be imputed as described in Section 7.1.
4. Denote the treated (contralateral) upper extremity CRST sub score at visit [k] as $\text{CRST}_{[\text{contralateral, k}]}$, then:

$$\text{CRST}_{[\text{contralateral, k}]} = \frac{Part\ A + Part\ B}{Total}$$

   Where, *Total* is the maximal sum that could be achieved in Part A and Part B, based on the available items (obtained and imputed). Note that Total should be re-adjusted for each patient based on his/her available information.

   For example, if the following conditions for a subject hold
   - The treated side of the body is ipsilateral to handedness,
   - One item in Part A is missing
   - All five items in Part B are obtained

then the Total = 8 (Maximum that could be achieved in Part A) + 20 (Maximum that could be achieved in Part B) = 28

Note: Lower $CRST_{[contralateral,\ k]}$ scores are better than higher scores.

5. The confirmatory primary efficacy endpoint (denoted as PE) – Percent Improvement from Baseline at three months post-treatment in the treated (contralateral) upper extremity CRST sub score – will be calculated as follows:

$$PE = \frac{CRST_{[contralateral,\ Baseline]} - CRST_{[contralateral,\ 3\ months\ FU]}}{CRST_{[contralateral,\ Baseline]}} \times 100$$

Note: higher PE values represent improvement.

For both stages (Main and Crossover) the primary efficacy endpoint will be calculated using Baseline score, measured before Main stage treatment initiation.

6.2.2 Confirmatory Secondary Endpoints

The confirmatory secondary efficacy endpoints in this study are the following:

- SE1=Improvement from Baseline at three months in Quality of Life in Essential Tremor (QUEST). SE1 will be calculated as follows:
    - Categorize the 30 questions into 5 dimensions as follows:
        - Communication: #1 – #3
        - Work and Finances: #4 – #9
        - Hobbies and Leisure: #10 – #12
        - Physical: #13 – #21
        - Psychosocial: #22 – #30
    - Score all applicable questionnaire answers as follows:
        - Never = 0
        - Rarely = 1
        - Sometimes = 2
        - Frequently = 3
        - Always = 4

      Note:
        - ✓ All questions answered "N/A" will be excluded from the calculation (only questions 4, 5, 7, 8 and 14 can be answered "N/A")

- ✓ Questions 6, 7, 11 and 12 can only be scored at two values – either a 0 or a 4

- For each subject, calculate dimension score as a percentage of total possible score for each dimension separately. Denote dimension score for dimension [i] at visit [k] as $DS_{[i,\,k]}$, then:

$$DS_{[i,k]} = \frac{Total\ \boldsymbol{applicable}\ points_{[i,k]}}{Total\ possible\ points\ (\#\ of\ \boldsymbol{applicable}\ questions\ \times 4)_{[i,k]}} \times 100$$

Note: missing data should be imputed as described in Section 7.2.1.

- For each subject, calculate QUEST summary of dimensions total score as a mean of the five dimension scores. Denote QUEST summary of dimensions total score at visit [k] as $QUEST_{[k]}$, then:

$$QUEST_{[k]} = \frac{\sum_{i=1}^{5} DS_{[i,k]}}{5}$$

Note: lower $QUEST_{[k]}$ scores are better than higher scores.

- For each subject, calculate SE1 as follows:

$$SE1 = \frac{QUEST_{[Baseline]} - QUEST_{[3\ months\ FU]}}{QUEST_{[Baseline]}}$$

Note: higher SE1 values represent improvement.

- SE2=Percent Improvement from Baseline at twelve months post-treatment in the treated (contralateral) upper extremity CRST sub score. SE2 will be calculated similarly to PE from the previous section, based on 12 months FU data.

- SE3=Percent Improvement from Baseline at three months post-treatment in functional disabilities CRST total score, as measured by CRST Part C. Note, that Part C is performed by Site Assessor only. SE3 will be calculated for each subject as follows:
  - Denote functional disabilities CRST Part C total score at visit [k] as $CRST\_C_{[k]}$, then:

$CRST\_C_{[k]}$ = average of answers to items #16-#23 at visit [k]

Note: if no more than two items are missing, the average will be calculated over the available items; otherwise, CRST Part C total score will be considered missing and should be imputed as described in Section 7.2.3.

- Calculate SE3 as follows:

$$SE3 = \frac{CRST\_C_{[Baseline]} - CRST\_C_{[3\ months\ FU]}}{CRST\_C_{[Baseline]}} \times 100$$

Note: higher SE3 values represent improvement.

6.2.3 Additional Secondary Endpoints

The additional secondary endpoints in this trial include, for each subject:

- Clinical Rating Scale for Tremor (CRST) Parameters:
  - Part A and B CRST Score, as assessed by Core LAB Reviewer:
    - For treated side of the body = $CRST_{[contralateral,\ k]}$, as defined in Section 6.2.1
    - For non-treated side of the body = $CRST_{[ipsilateral,\ k]}$, which is defined similar to $CRST_{[contralateral,\ k]}$ when using values obtained from upper extremity ipsilateral to the side of brain being treated
  - Part B Score for treated side of the body, as assessed by Core LAB Reviewer, for each motor task
  - Part C Score, as assessed by Site Assessor:
    - For each item separately
    - Overall, defined as a sum of all individual items
  - Overall CRST Score, defined as "Total A + Total B + Total C", where:

    Total A = sum of all severity scores of Part A items (1-10 at rest, posture and action/intention), as assessed by Core Lab Reviewer, excluding Head Tremor at Rest

    Total B = sum of all severity scores of Part B items (11-15, right and left), as assessed by Core Lab Reviewer

    Total C = sum of all severity scores of Part C items (16-23), as assessed by Site Assessor

- Quality of Life in Essential Tremor Parameters, as assessed by QUEST questionnaire:
    - Overall Quality of Life Score, as defined by CRF field "Overall, how would you rate your quality of life?"
    - Waking Hours with Tremor in Any Body Part, as defined by CRF field "On a typical day, how many of your waking hours do you have tremor in ANY body part?"
    - Tremor Severity Score, separately for the following categories:
        - Head
        - Voice
        - Treated arm/hand
        - Non-treated arm/hand
        - Treated leg/foot
        - Non-treated leg/foot
    - QUEST Parameters (based on questions 1-30), as defined in Section 6.2.2:
        - Dimension Score ($DS_{[i, k]}$), separately for each dimension
        - Summary of Dimensions Total Score ($QUEST_{[k]}$)

7 Handling of Missing Data

ITT analysis population: missing confirmatory primary and secondary efficacy data will be imputed using the last observation carried forward (LOCF) method, as described in Sections 7.1 and 7.2 below. Other missing data will not be imputed; only observed data will be used.

Safety, PP and Crossover analysis populations: all missing data will not be imputed; only observed data will be used.

7.1 Imputation of Confirmatory Primary Efficacy Data

Confirmatory primary efficacy endpoint (PE) is considered missing if either Part A or Part B at 3 Months FU is missing.

Imputation of Part A

Part A is considered missing if at least two out of the three individual rates within item #5 (or #6) are missing. Missing rates at 3 Months FU will be imputed using LOCF method, i.e. rates from 1 Month FU will be carried forward. If a single individual rate is obtained and two other rates are missing, the non-missing rate will be taken as is and will not be imputed.

Imputation of Part B

Part B is considered missing if more than one required items is missing. Missing items at 3 Months FU will be imputed using LOCF method, i.e. items from 1 Month FU will be carried forward. The obtained items will be taken as is and will not be imputed.

7.2 Imputation of Confirmatory Secondary Efficacy Data

7.2.1 Imputation of Confirmatory Secondary Endpoint 1 (SE1)

SE1 is defined as average over five QUEST dimension scores. Thus, SE1 is considered missing if at least one dimension score is missing. Below we define when and how each of these dimension scores should be imputed.

Communication, Work and Finances, Hobbies and Leisure Dimensions

The dimension score is considered missing if at least one of applicable items (within a specific dimension) is missing. Missing applicable items will be imputed using LOCF method.

Physical and Psychosocial Dimensions

The dimension score is considered missing if more than two applicable items (within a specific dimension) are missing. Missing applicable items will be imputed using LOCF method.

7.2.2 Imputation of Confirmatory Secondary Endpoint 2 (SE2)

The imputation of SE2 will be done similarly to PE, as described in Section 7.1.

7.2.3 Imputation of Confirmatory Secondary Endpoint 3 (SE3)

CRST Part C total score is considered missing if more than two items are missing. Missing items at 3 Months FU will be imputed using LOCF method (where applicable). The obtained (non-missing) items will be taken as is and will not be imputed.

8 Data Derivation and Transformation

Data not originally part of the CRF will be derived as follows:

- Age [years] = (Date of Informed Consent – Date of Birth + 1) / 365.25
- BMI [kg/m^2] = Weight (kg) / Height (m)^2
- Time from Initial ET Symptoms [years] = (Date of Informed Consent – Approximate Date of Initial ET Symptoms[1] + 1) / 365.25
- Time from Initial ET Diagnosis [years] = (Date of Informed Consent – Date of Initial ET Diagnosis[1] + 1) / 365.25
- Time from First ET Medical Therapy [years] = (Date of Informed Consent – Date of First ET Medical Therapy [1] + 1) / 365.25
- Handedness (Right / Left) is indicated by CRF field “Right or Left Handed” on Baseline CRST Form, as assessed by Site Assessor
- Treated Side of the Body (Right / Left) is defined as the opposite side of the brain being treated, indicated by CRF field “Side of Brain being treated” on the ExAblate Treatment Form
- Time Inside Scanner [min] = Time Out of Scanner – Time In Scanner
- Sonication Treatment Time [min] = Sonication End Time – Sonication Start Time
- Target Size [cm^3] = $\frac{4}{3}\pi(\frac{1}{2}\times SI[cm]\times RL[cm]\times AP[cm])$, where SI, RL and AP are the target dimensions Superoinferior, Right-Left and Anteroposterior respectively, as collected on the ExAblate Treatment Form
- The following will be provided by InSightec:

[1] If only Day is missing then the 15th of the Month will be imputed; if both Day and Month are missing then the 1st of July will be imputed.

- By-subject listing of all protocol deviations
- Coding of all Adverse Events

9 Interim Analysis

No interim analysis is planned for the ET-002 study.

10 Statistical Analysis

All statistical analyses will be carried out using SAS® Version 9.2 or higher under Windows® Server 2008 Terminal.

The data will be summarized in tables listing the mean, standard deviation, minimum, median, maximum and number of subjects for continuous data, or in tables listing count and percentage for categorical data where appropriate.

10.1 Subject Disposition

The following will be provided based on all recruited subjects:

- Subject disposition flow chart (Figure 1)
- Frequency distribution of answers (Yes / No) to inclusion / exclusion criteria (**Error! Reference source not found.**, **Error! Reference source not found.**)
- Frequency distribution of overall eligibility for the study (Yes / No) based on inclusion / exclusion answers (**Error! Reference source not found.**)
- Listing of screen failures along with the reason for not entering the study (**Error! Reference source not found.**)
- Subject accountability by visit and treatment group (**Error! Reference source not found.**)
- By-subject listing of all protocol deviations (**Error! Reference source not found.**)

The following will be provided using Safety analysis population:

- Number and percentage of subjects in each of the analysis populations by treatment group (**Error! Reference source not found.**)
- Listing of subjects excluded from each of the analysis populations along with the reason for exclusion (**Error! Reference source not found.**)

The following will be provided using ITT analysis population:

- Number and percentage of subjects by center and treatment group (**Error! Reference source not found.**)
- Termination of the Study Main Stage:
    - Number and percentage of subjects who completed / prematurely discontinued the first 3 months FU of the study Main stage by treatment group (**Error! Reference source not found.**)
    - Number and percentage of subjects who completed / prematurely discontinued the follow up period (from 3 up to 12 months) of the study Main stage for ExAblate group only (**Error! Reference source not found.**)
    - Listing of all dropouts along with reason for termination, treatment group and last available visit (**Error! Reference source not found.**)

The following will be provided using Crossover analysis population:

- Number and percentage of subjects by center (**Error! Reference source not found.**)
- Termination of the Study Crossover Stage:
    - Number and percentage of subjects who completed / prematurely discontinued the study crossover stage (**Error! Reference source not found.**)
    - Listing of all dropouts along with reason for termination and last available visit (**Error! Reference source not found.**)
- Subject accountability by visit (**Error! Reference source not found.**)

10.2 Baseline Characteristics

Baseline characteristics will be analyzed using the Safety analysis population.

Descriptive statistics or frequency distribution, as appropriate, by treatment group will be provided for the following:

- Demographic Characteristics and Vital Signs:
  - Age, BMI, Height, Weight (**Error! Reference source not found.**)
  - Gender, Race (**Error! Reference source not found.**)
- Medical History:
  - Significant medical conditions (other than the present disease) (**Error! Reference source not found.**)
  - Other significant medical conditions (protocol specific) (**Error! Reference source not found.**)
- Essential Tremors History:
  - Time from Initial ET Symptoms (**Error! Reference source not found.**)
  - Time from Initial ET Diagnosis (**Error! Reference source not found.**)
  - Time from First ET Medical Therapy (**Error! Reference source not found.**)
  - Family History of ET (**Error! Reference source not found.**)
    - Listing of subjects having family history of ET along with specification of relationship degree and the number of relatives (**Error! Reference source not found.**)
  - Indication of etiology due to neuroleptic drug exposure (**Error! Reference source not found.**)
  - Is subject considered medication refractory? (**Error! Reference source not found.**)
- MRI Examination (**Error! Reference source not found.**):
  - Any arteriovenous malformations that require treatment
  - Any aneurysms that require treatment
  - Evidence of a recent hemorrhage
- CT Examination (**Error! Reference source not found.**):
  - Any calcifications present within the treated area
  - Any implants within the skull or brain
  - Is the skull suitable for treatment?
  - History of DVT or systemic thrombosis

        - Evidence of acute thrombosis in lower extremities for subjects who had a history of DVT or systemic thrombosis
- CRST and QUEST questionnaire parameters at Baseline, as defined in Sections 6.2.1 and 6.2.2 (**Error! Reference source not found.**):
    - The Treated (Contralateral) Upper Extremity CRST Sub Score ($CRST_{[contralateral,\ Baseline]}$)
    - QUEST Summary of Dimensions Total Score ($QUEST_{[Baseline]}$)
    - Functional Disabilities CRST Part C Total Score ($CRST\_C_{[Baseline]}$)

Where applicable, baseline characteristics will be compared between treatment groups using two-sided t-test for continuous normal variables, Wilcoxon rank-sum test for continuous variables with distribution deviating from normal and Fisher's Exact test for categorical variables (**Error! Reference source not found.**).

10.3 Treatment Procedure

Treatment procedure characteristics will be analyzed using the Safety analysis population.

Descriptive statistics or frequency distribution, as appropriate, by treatment group will be provided for the following:

- Pre-Treatment Characteristics (**Error! Reference source not found.**):
    - Head Condition
    - Scars or Lesions on Head
    - Was the subject "off" medication for at least 12 hours prior to the treatment?
- Vital Signs per Time Point (**Error! Reference source not found.**):
    - Systolic Blood Pressure
    - Diastolic Blood Pressure
    - Heart Rate
    - O_2 Saturation
- Treatment Characteristics (**Error! Reference source not found.**):
    - Time Inside Scanner
    - Sonication Treatment Time

  - Target Size
  - Minimal Energy
  - Maximal Energy
  - Number of Performed Sonications
  - Treated Side of the Body (Right / Left) (**Error! Reference source not found.**)
- Procedure Interruption / Early Termination:
  - Interruption:
    - Procedure interrupted for more than 30 minutes due to MR system problems (**Error! Reference source not found.**)
    - Procedure interrupted for more than 30 minutes due to ExAblate system problems (**Error! Reference source not found.**)
    - Listing of all device malfunctions (**Error! Reference source not found.**)
  - Early Termination:
    - Procedure terminated prior to completion (**Error! Reference source not found.**)
    - Listing of all termination reasons (**Error! Reference source not found.**)

10.4 Blinding Assessment

Blinding assessment will be analyzed using the Safety and Crossover analysis populations separately. Frequency distribution of subjective perception of treatment received by visit and treatment group will be provided (**Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**) for the following blinding assessments:

- Subject Perception
- Site Assessor Perception
- Core Lab Reviewer Perception

Where appropriate, Fisher's exact test will be conducted to compare subjective perception between treatment groups.

10.5 Safety

All safety analyses will be performed on the Safety and Crossover analysis populations – separately and combined, and will be descriptive and narrative in nature. Note that mock tables are presented for Safety population only. For Crossover and combined (Safety and Crossover) populations the tables will be prepared in the similar manner, presenting ExAblate group only. The following will be provided by treatment group:

- Adverse Events:
    - Descriptive statistics of Number of Adverse Events per Subject (**Error! Reference source not found.**)
    - Frequency distribution of Experience of at Least One Adverse Event (**Error! Reference source not found.**)
    - All Adverse Events (AEs) will be tabulated using Frequency tables with – Number of Incidents, Number of Subjects and Percentage of Subjects by:
        - Body System, Preferred Term and Resolution Time (within 30 days, within 31-90 days, more than 90 days), separately for Adverse Events started within 30 days post treatment, 31-90 days post treatment and more than 90 days post treatment (**Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**). Note that in case resolution date is missing, AE will be assigned to "Unresolved" category.
        - Body System, Preferred Term and Severity (**Error! Reference source not found.**)
        - Body System, Preferred Term and Relation to Treatment (**Error! Reference source not found.**)
    - Serious Adverse Events (SAEs):
        - Listing of all SAEs (**Error! Reference source not found.**)
        - In case the number of SAEs is greater than 12, all AE tables will be repeated, presenting SAEs only

- The Kaplan-Meier curve of AE's free percentage of subjects by time will be presented by treatment group. The groups will be compared using a Log-Rank test.

10.6 Efficacy

10.6.1 Adjustment for Multiple Comparisons

This study has one primary and three secondary efficacy confirmatory endpoints. In order to control for multiplicity across the confirmatory endpoints, we will employ a hierarchical testing design. The primary efficacy analysis will be performed with a significance level of alpha = 0.05. Dependent on the successful confirmatory testing of the primary efficacy analysis, we will proceed with testing each of the three secondary efficacy confirmatory endpoints in the order listed in Section 6.2.2, proceeding with each test with alpha = 0.05 if all previous tests were successful. No confirmatory statements will be made about endpoints that are listed lower on the hierarchy after an endpoint fails testing. This way we will control the Type 1 error across all endpoints tested in this study.

10.6.2 Confirmatory Primary Efficacy

Primary efficacy analyses will be conducted on the ITT analysis population and will test the following hypothesis:

H_0: $M3_{ExAblate} \leq M3_{Sham}$

H_1: $M3_{ExAblate} > M3_{Sham}$

Where, $M3_{ExAblate}$ and $M3_{Sham}$ are means of Primary Endpoint (PE), as defined in Section 6.2.1, in the ExAblate and Sham groups, respectively.

This hypothesis will be analyzed using independent groups t-test with two-sided alpha=0.05, should the data not differ appreciably from normal theory. Otherwise, the Wilcoxon rank-sum test will be applied.

We will have succeeded if the Null is rejected and mean PE is higher in ExAblate than Sham. Descriptive statistics of the primary endpoint and comparison p-value will be provided (**Error! Reference source not found.**).

10.6.3 Confirmatory Secondary Efficacy

As indicated in Section 6.2.2, this study has three confirmatory secondary endpoints (SE1, SE2 and SE3). Hierarchical testing design will be applied to control for multiple statistical testing (as explained in Section 10.6.1).

SE1 Analysis:

The first confirmatory secondary efficacy analysis will be conducted on the ITT analysis population. The following hypothesis will be tested for SE1:

H_0: $Q3_{ExAblate} \leq Q3_{Sham}$

H_1: $Q3_{ExAblate} > Q3_{Sham}$

Where, $Q3_{ExAblate}$ and $Q3_{Sham}$ are means of the first Secondary Endpoint (SE1), as defined in Section 6.2.2, in the ExAblate and Sham groups, respectively.

This hypothesis will be analyzed using independent groups t-test with two-sided alpha=0.05, should the data not differ appreciably from normal theory. Otherwise, the Wilcoxon rank-sum test will be applied. Descriptive statistics and comparison p-value will be provided (**Error! Reference source not found.**).

SE2 Analysis:

The second confirmatory secondary efficacy analysis will be conducted on the ITT (subjects from ExAblate group only) population. The following hypothesis will be tested for SE2:

H_0: $M12_{ExAblate} \leq 0$

H_1: $M12_{ExAblate} > 0$

Where, $M12_{ExAblate}$ is the mean of the second Secondary Endpoint (SE2), as defined in Section 6.2.2, in the ExAblate group.

This hypothesis will be analyzed using one-sample t-test with two-sided Alpha = 0.05, should the data not differ appreciably from normal theory. Otherwise, the one-sample Wilcoxon signed rank test will be applied. Descriptive statistics and comparison p-value will be provided (**Error! Reference source not found.**).

SE3 Analysis:

The third confirmatory secondary efficacy analysis will be conducted on the ITT analysis population. The following hypothesis will be tested for SE3:

H_0: $C3_{ExAblate} \leq C3_{Sham}$

H_1: $C3_{ExAblate} > C3_{Sham}$

Where, $C3_{ExAblate}$ and $C3_{Sham}$ are means of the third Secondary Endpoint (SE3), as defined in Section 6.2.2, in the ExAblate and Sham groups, respectively.

This hypothesis will be analyzed using independent groups t-test with two-sided alpha=0.05, should the data not differ appreciably from normal theory. Otherwise, the Wilcoxon rank-sum test will be applied. Descriptive statistics and comparison p-value will be provided (**Error! Reference source not found.**).

10.6.4 Additional Secondary Efficacy

Additional secondary efficacy analyses will repeat those in the preceding sections (confirmatory primary and secondary efficacy analyses), when using PP analysis population instead of ITT (**Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**).

Analysis of additional secondary efficacy endpoints (defined in Section 6.2.3) will be conducted on both ITT and PP analysis populations.

Descriptive statistics of raw values and change or percent change from baseline, as appropriate, over time by treatment group will be provided for the following:

- Clinical Rating Scale for Tremor (CRST) Parameters:
    - Part A and B CRST, separately for treated and non-treated side of the body (**Error! Reference source not found.**, **Error! Reference source not found.**)
    - Part B Score for treated side of the body, for each motor task (**Error! Reference source not found.** – **Error! Reference source not found.**)
    - Part C Score for each item and Overall (**Error! Reference source not found.** – **Error! Reference source not found.**)
    - Overall CRST Score (**Error! Reference source not found.**)
- Quality of Life in Essential Tremor Questionnaire (QUEST) Parameters:
    - Overall Quality of Life Score (**Error! Reference source not found.**)

- Waking Hours with Tremor in Any Body Part (**Error! Reference source not found.**)
- Tremor Severity Score, separately for each category (**Error! Reference source not found.** – **Error! Reference source not found.**)
- QUEST Parameters (based on questions 1-30):
  - Dimension Score, separately for each dimension (**Error! Reference source not found.** – **Error! Reference source not found.**)
  - Summary of Dimensions Total Score (**Error! Reference source not found.**)

In addition, where appropriate, the following will be provided:

- Graphical presentation over time by treatment group
- Statistical testing to compare:
  - between treatment groups, by visit
  - within each treatment group, comparing Baseline to each follow-up visit
  - between treated and non-treated sides, within each treatment group, by visit

10.6.5 Covariate Analyses

The effects of covariates will be assessed for all confirmatory primary and secondary efficacy analyses.

The following covariates will be examined:

- Age
- Baseline CRST Score ($CRST_{[contralateral, Baseline]}$)
- Gender
- Center

Center is expected to have several categories. Keeping the number of categories as is will, in some cases, yield small subgroups and substantially reduce power. To address this issue, categories will be combined by grouping those with few observations into a

single category. Grouping of categories will be specified after category frequency have been produced but before statistical testing.

The following will be provided:

1. Analyses for PE, SE1 and SE3 will be conducted on ITT analysis population comparing ExAblate and Sham groups. The following model will be applied:

   *Y = Covariate + Treatment Group+ Covariate*Treatment Group*

   Where,

   Y = PE, SE1 or SE3, depending on the analysis

   Covariate = covariate of interest

   *Covariate*Treatment Group*= covariate by group interaction

   Models both with and without *Covariate*Treatment Group* interaction will be considered (**Error! Reference source not found.**).

   Statistical testing will be done by linear regression. In case the distribution of Y is extremely not normal, the non-parametric methods will be applied depending on the emerged distribution.

   Descriptive statistics of each endpoint will be presented by covariate levels and treatment group. For this purpose numerical covariates (Age and Baseline CRST Score) will be categorized into equal subgroups inside the emerged range of values (**Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**).

   Assessing the effect of a covariate on treatment will be done by examining the degree to which the significance of the Treatment Effect changes with the inclusion of the covariate (**Error! Reference source not found.**). Weakening or strengthening of the Treatment Effect in the presence of a covariate will be interpreted using both clinical and statistical considerations.

2. Analyses for SE2 will be conducted on the ITT (subjects from ExAblate group only) population and will repeat the second confirmatory secondary efficacy analysis for each level of covariate separately. For this purpose numeric covariates (Age and Baseline CRST Score) will be categorized into equal subgroups inside the emerged range of values.

   Descriptive statistics of SE2 will be presented by covariate levels (**Error! Reference source not found.**). In addition, for numeric covariates a scatter

plot of SE2 versus covariate will be produced (**Error! Reference source not found.**, **Error! Reference source not found.**). If no trend is observed, as shown on mock figures, the conclusion would be that the covariate has no effect on SE2.

10.6.6 Sensitivity Analyses

The method for imputation of missing data for the confirmatory primary efficacy analysis is defined as Last Observation Carried Forward (LOCF). In the case that there is a large amount of missing data, additional methods of imputing missing data will be used to examine the robustness of the treatment effect.

All sensitivity analyses will be conducted on the ITT analysis population and will repeat the confirmatory primary efficacy analysis.

Worst Case

Worst Case analysis will be assessed by imputing missing values as follows:

- The 10th percentile PE value of ExAblate group will be imputed to subjects with missing data in ExAblate group
- The 90th percentile PE value of Sham group will be imputed to subjects with missing data in Sham group

Descriptive statistics with comparison p-value will be provided (**Error! Reference source not found.**).

Best Case

Best Case analysis will be assessed by imputing missing values as follows:

- The 90th percentile PE value of ExAblate group will be imputed to subjects with missing data in ExAblate group
- The 10th percentile PE value of Sham group will be imputed to subjects with missing data in Sham group

Descriptive statistics with comparison p-value will be provided (**Error! Reference source not found.**).

Multiple Imputations

Multiple Imputations analysis will be assessed by creating 10 imputed data sets using the multiple imputation procedure (PROC MI in SAS®). Various baseline characteristics will be considered for the purpose of imputation. Missing PE values will be imputed. The confirmatory primary efficacy analysis will be repeated on each of 10 imputed data sets (**Error! Reference source not found.**). The summarized result (using PROC MIANALYZE in SAS®) will be presented (**Error! Reference source not found.**).

10.7 Crossover Stage Analysis

The Crossover stage includes Sham subjects who terminated the Main stage of the study with the reason "Sham subject crossed over ExAblate Arm at Month 3". According to the protocol, these subjects undergo Active ExAblate treatment and subsequent follow-up assessments, just as defined for the ExAblate group in the Main stage of the study.

All analyses in this section will be presented based on the Crossover analysis population. Results from the Main stage under Sham treatment will be presented in parallel with results under ExAblate treatment during Crossover stage, similarly to presentation of the Main stage results.

Descriptive statistics over time by treatment group will be provided for the following:

- Confirmatory primary and secondary efficacy endpoints
- Additional secondary endpoints

In addition, where appropriate, the following will be provided:

- Graphical presentation over time by treatment group
- Statistical testing to compare:
    - between treatment groups, by visit
    - within each treatment group, comparing Baseline to each follow-up visit
    - between treated and non-treated sides, within each treatment group, by visit

11 Data Listings

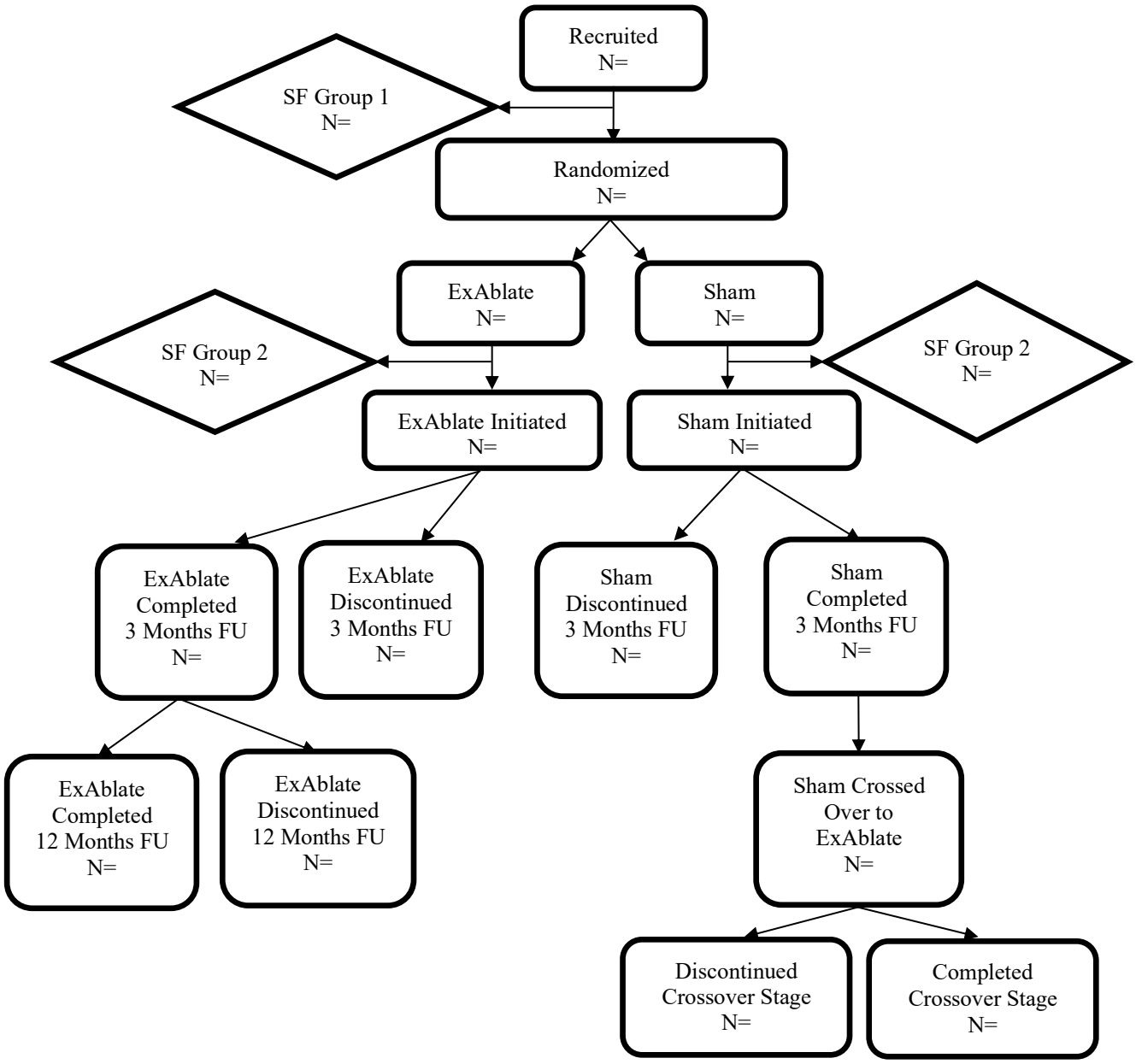
Data listings will be provided for all data available.

12 Appendix

The following section presents mock tables and figures for Section 10.

12.1 Subject Disposition

Figure 1 Subject Disposition Flow Chart



SF = Screen Failure