Summary of
STATISTICAL ANALYSIS PLAN

Clinical Investigation Plan number: QS-NIS-G-H-2101

POST MARKET FOLLOW-UP STUDY OF A ROBOTIC DEVICE FOR IMAGE-GUIDED PERCUTANEOUS NEEDLE PLACEMENT IN THE ABDOMEN

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1. INTRODUCTION

The purpose of the Statistical Analysis Plan (SAP) is to describe:

- The statistical methodology.
- The calculated/derived variables.
- The general rules and conventions.
- The tables, figures and listings (TFLs) to be included in the Clinical Study Report (CSR).

The SAP is based on the Clinical Investigation Plan version 2.0 dated 3rd October 2022 and the Case Report Form (CRF) version 2.0 dated 6th May 2022.

2. CLINICAL INVESTIGATION PLAN SUMMARY

2.1. Study objectives

Primary objective:

The primary objective of the study is to describe the performance related to the CT-guided procedure performed with the use of the Quantum Surgical EPIONE® device in the abdomen of the patient.
The primary endpoint is the technical success of each procedure. Technical success is defined in Section 9.1.1. The target is considered to have been reached when the needle(s) is(are) positioned accurately enough to allow the procedure to be carried out.

Secondary objectives:

The secondary performance objectives are as follows:

- Assessment of the needle placement accuracy through an estimation of the distance from the needle inserted and the predefined planning.
- Assessment of the number and the grading of needle readjustments to reach the target (minor, moderate, major).
- Assessment of post-intervention ablation success (ablation only).
- Assessment of the long-term performance of the procedure (local tumor progression rate).
- User satisfaction.
- Assessment of device's dysfunction.

The secondary safety objectives are as follows:

The safety objective is to assess the safety of the device, based on all adverse events (AEs) related to the device or the procedure, including Serious Adverse Events.

The investigator will describe the AE occurrence on a 2-point scale: "no major adverse event related to the CT-guided procedure" or "major adverse event related to the CT-guided procedure".

2.2. Study design

2.2.1. Study design and device

This is a prospective, non-comparative, non-interventional Post Market Clinical Follow-up (PMCF) study.

A total of 55 patients with indication for percutaneous CT-guided procedure in the abdomen will be included at one site in France (Gustave Roussy Institute, Paris) where the EPIONE® device is used routinely.

The operating principle of the investigational device is as follows:

- Pre-interventional CT-scan image acquisition.
- Planning with the device's software (choice of needle(s)' trajectory(ies) to reach the targeted point).
- Needle(s) insertion according to the pre-defined planning.
- Acquisition of a per-procedure CT-scan image to evaluate the needle(s) placement.

Four visits will be recorded in the CRF.

In case of several follow-up visits with the timeslots of Visits 3 and 4, only the last one will be reported in the CRF:

- **Visit 1** (within one month before treatment): the first visit is planned to screen the patient, present the study, and deliver the information notice and informed consent form.
- **Visit 2** (treatment): the second visit consists of recovery of the signed informed consent form, and the realization of the prescribed CT-guided intervention by the radiologist.
- **Visit 3**: Follow-up at 2 months (between 3 weeks to 3 months after treatment).
- **Visit 4**: Follow-up at 10 months (between 6 months to 15 months after treatment), end of study.

Patients who are scheduled for an EPIONE® CT-guided procedure in the abdomen will be enrolled in the study. Eligible patient from the investigator's site will be proposed to participate.
The inclusion period is estimated as 18 months for 55 patients. The study was initiated with the only one site for which the EPIONE® device is routinely used.

2.2.2. Study population

Inclusion criteria

The inclusion criteria are as follows:

- Patient is >18 years old.
- Patient for whom a CT-guided procedure in abdomen has been prescribed and agreed by a multidisciplinary team of radiologists, surgeons and clinicians.
- Patient with a confirmed non-opposition.

Exclusion criteria

The exclusion criteria are as follows:

- Patient unable to undergo general anesthesia.
- Pregnant or breast-feeding females.

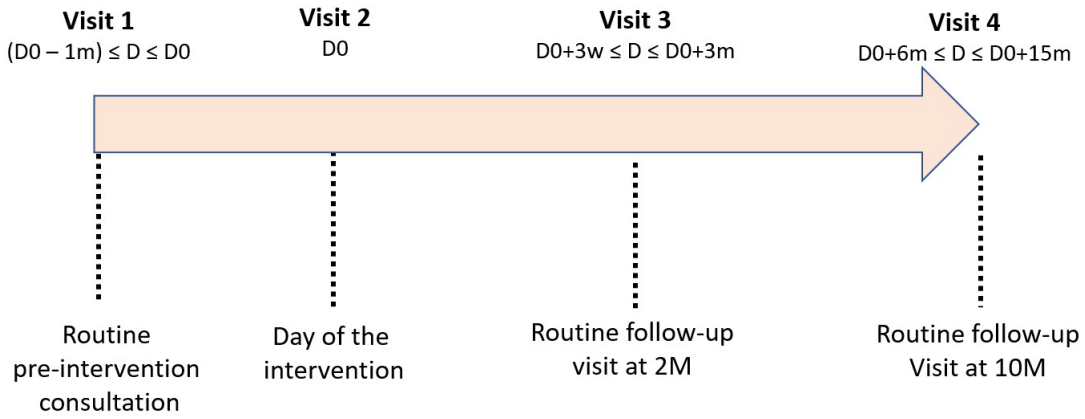
2.2.3. Study duration and flow chart

Study duration per patient

The study will last from patient's information and non-opposition form signature to Visit 4.

Duration can be 6 months to 16 months, depending on the day of patient's non-opposition confirmation and the day of Visit 4.

Flow chart of the study



2.3. Criteria for evaluation planned in the clinical investigation plan

2.3.1. Primary Variable

The primary objective of the study is the performance of the investigational device.

The performance variable is defined through the technical success of the procedure by the question: "Is/Are the needles positioned accurately enough with the robot to allow next step of the procedure to be carried out".

Frequency and percentage of patients with "Is/Are the needles positioned accurately enough with the robot to allow next step of the procedure to be carried out"= "Yes" reported by the investigator will be described by patient and by procedure.

2.3.2. Secondary Performance Variables

- Needle placement accuracy per needle after adjustments:
  - Estimated distance from the needle tip to expected target point and
  - Estimated distance from the ablation center to targeted ablation center by operators.
- The number of needle adjustments to reach the target and the grading of adjustment
- Post-intervention ablation success using Minimal Ablative Margin (MAM) evaluation.
- Long-term performance of the procedure using the local tumor progression (LTP) rate at around 2 months and 10 months.
- User satisfaction (5-points Likert scale) via 4 questions.
- Device dysfunction (Yes/No)

2.3.3. Secondary Safety Variables

All AEs related to the device or the procedure will be collected.

AEs are categorized in six classes defined below:

Minor complications

- A: No therapy, no consequences.
- B: Nominal therapy, no consequence; includes overnight admission for observation only.

Major complications

- C: Requires therapy, minor hospitalization (< 48 h).

- D: Requires major therapy, unplanned increase in level of care, prolonged hospitalization (> 48 h).
- E: Permanent
- F: Death

If answer is "Major adverse event related to the CT-guided procedure" to the question "Adverse events during procedure" (or AEs classes C, D, E or F in AEs form), the AE will be considered "major" as reported by the investigator.

2.4. Coding

Not applicable.

3. GENERAL ANALYSIS METHODOLOGY

3.1. Study periods

Planned first patient included: Q1 2022

Planned recruitment time: 18 months

Planned last patient completed: Q1 2024

3.2. Definition of protocol deviations

The protocol deviations will be listed by the statisticians when data collection ends. The deviations will then be categorized as major or minor during the interim/final Data Review Meeting (DRM) prior to locking database.

Patients with a major protocol deviation will be excluded from the Per Protocol (PP) population.

3.3. Analysis populations

Four different analysis populations are foreseen:

Screened Population
All patients who are proposed to enter in the study.

Intention-to-Treat (ITT) Population
All screened patients who have confirmed their non-opposition and are planned to be treated using the EPIONE® device.

Per Protocol (PP) Population
All patients in the ITT population treated by the EPIONE® device (including those for which the procedure was not completed with the EPIONE® device) without any major deviation.

Safety Population
All patients in the ITT population treated by the EPIONE® device (including those for which the procedure was not completed with the EPIONE® device).

3.4. Database lock

Interim and final database lock will be executed after resolution of all queries related to data and after the interim/final DRM is held. The interim/final database lock will be performed electronically using ENNOV Clinical V8.0 by the Delta Consultants data management team based on Delta Consultants' SOPs.

3.5. Statistical concerns

The statistical analysis will be performed by an external CRO (Contract Research Organization: Delta Consultants, Eybens, France). All statistical analyses will be produced using SAS® 9.4 software (Cary, NC, USA).
Results will be presented using tables, figures and listings in a Word document.

3.5.1. Summary statistics

Description of relevant study variables will be performed using n, number of missing data, mean, standard deviation, median, min and max for quantitative variables and using number of missing data, frequency and percentage of non-missing for qualitative variables.
Analyses will be presented by patient, by lesion (when relevant) and/or by needle (trajectory). The statistical analysis will take into account data clustering (*e.g*. several procedures for a given patient) in case of inferential statistics.

3.5.2. Level of significance

A 5% significance threshold will be used.

3.5.3. Adjustments for covariates

No adjustment for covariates is planned for this study.

3.5.4. Handling of dropouts and missing data

Missing data will not be imputed, except dates (missing day) if needed in order to calculate durations.

3.5.5. Multicentre studies

Not applicable since only one site will include patients.

3.5.6. Multiple comparisons/multiplicity

No handling of multiple comparisons will be performed.

3.6. Patient data listings

Individual data listings will be provided in Word format. Patient data listings are listed in Section 13 of this SAP.

4. STUDY PATIENTS

4.1. Disposition of patients

The disposition of patients according to populations of analysis (Screened, ITT, PP, Safety) and visits (Visit 1 – inclusion, Visit 2 – Procedure, Visit 3 – Follow up at 2 months and Visit 4 – Follow-up at 10 months, End of study) will be presented using frequency and percentages.
End of study information (study protocol completed as planned (visit 4), Adverse event, screen failure, patient's willing to withdraw from study, loss to follow-up, device malfunction, death, technical failure, non-feasibility and other) will be presented using frequency and percentages.

4.2. Protocol deviations

Validation of inclusion/exclusion criteria will be presented using frequency and percentages. All protocol deviations will be presented in patient data listings. Major deviations leading to exclusion from PP population will be described as frequency and percentage of patients in the ITT population.

5. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and tumor characteristics will be presented on ITT population using summary statistics for qualitative or quantitative parameters:

- Demographic data: age (years), gender, height (cm), weight (kg), Body Mass Index (kg/m^2).
- Tumor characteristics: treated organ (liver, kidney or other), type of CT-Guided percutaneous treatment to be planned.
- Planning with the EPIONE device (number of needles trajectories, needle identification information).

Medical history, comorbidities, concomitant treatments and planning with the EPIONE device at inclusion will be described in patient data listings.

6. MEASUREMENT OF TREATMENT COMPLIANCE

Not applicable.

7. PERFORMANCE ANALYSES

Performance analyses will be conducted on the ITT and PP populations.

7.1. Primary endpoint

7.1.1. Definition of the primary variable

The primary endpoint is the technical success of each procedure.
The parameter of the primary endpoint consists of the rate/percentage of robotically assisted needle placements that were accurate enough to allow the percutaneous procedure to be carried on.

The investigator will describe the technical success of the procedure on a 2-point scale:

- "Is/Are the needles positioned accurately enough with the robot to allow next step of the procedure to be carried out" ="Yes"
- "Is/Are the needles positioned accurately enough with the robot to allow next step of the procedure to be carried out" ="No"

The performance endpoint is defined by "Is/Are the needles positioned accurately enough with the robot to allow next step of the procedure to be carried out" ="Yes".

7.1.2. Statistical evaluation of the primary variable

Performance of the investigational device:
Frequency and percentage of patients with "Is/Are the needles positioned accurately enough with the robot to allow next step of the procedure to be carried out" ="Yes" reported by the investigator will be described by patient and by procedure. A 95% confidence interval will be provided for the percentage.

7.2. Secondary performance endpoints

7.2.1. Needle placement accuracy

<u>Accuracy per needle</u>

This secondary variable evaluates the deviation between the planned and actual needle position once inserted. Operator estimates:
- the 3D distance from the **needle tip** after adjustment(s) to the planned needle tip.
- the 3D distance between **the ablation center** after adjustment(s) and the planned ablation center (if applicable).

7.2.2. Number of needle adjustments to reach the target and grading of adjustment

This secondary variable records the number and the grading of iterations required to finally reach the target. The number of needle placement adjustments to reach the target will be presented using frequency and percentage per trajectory or per needle, per lesion and per patient.
In addition, grading of adjustment will be presented using frequency and percentage per needle, per lesion and per patient.

7.2.3. Post-intervention ablation success using Minimal Ablative Margin (MAM) evaluation

For each lesion ablation, minimal distance between the lesion margin and the ablated area margin (mm) will be collected and summary statistics for quantitative parameters will be provided.

7.2.4. Long-term performance of the procedure using the local tumor progression (LTP) rate

Patients treated with tumor ablation are evaluated for Local tumor progression (LTP) on follow-up imaging by physician during the routine follow-up visits.
Frequency and percentage of patients with any visible local tumor progression on control imaging will be presented at approximately 2 months and 10 months. A 95% confidence interval will be provided for the percentage.

7.2.5. User satisfaction (5-points Likert scale) via 4 questions

For each patient with a procedure, operator satisfaction will be evaluated using 5-points Likert scale (Very dissatisfied (0), Dissatisfied (1), Neutral (2), Satisfied (3) and Highly satisfied (4)) via four questions:

- Satisfaction level regarding the planning with EPIONE device®.
- Satisfaction level regarding the needle placement with EPIONE® device.
- Satisfaction level regarding the ergonomics of the EPIONE® device.
- Satisfaction level regarding the final result of the intervention.

Frequency and percentage of patients for each modality will be presented for each satisfaction question.

7.2.6. Device dysfunction

Frequency and percentage of patients with "Did a device dysfunction occur during the procedure for lesion?= "Yes"") will be presented using frequency and percentage per procedure.

8. SAFETY ANALYSES

The safety analysis will be conducted on the Safety population.

8.1. Adverse events

All detailed AEs will be listed by patient.

8.1.1. Summary of AEs

A summary of AE occurrence (number of AEs, number of patients, percentage of patients) will be presented overall, by intensity, by severity and by relationship with the device or procedure.

8.1.2. Major AEs

Frequency and percentage of patients with "major adverse event related to the CT-guided procedure" (vs "no major adverse event related to the CT-guided procedure") will be presented by lesion and by patient (at least one). A 95% confidence interval will be provided for the percentage.

8.1.3. Listing of AEs by patient

Individual listings of AEs will be presented by patient with all characteristics recorded from the CRF.

8.2. Deaths, other serious adverse events (SAEs) and other significant adverse events

Individual listings for SAEs, pregnancies (if any) and Device-related AEs (DRAEs) leading to withdrawal (or death) will be presented including all details recorded from the AE form in the CRF.

8.3. Clinical laboratory evaluation

Not applicable.