STATISTICAL ANALYSIS PLAN

WAVELIA BY MVG INDUSTRIES SAS – PILOT CLINICAL EVALUATION OF A MICROWAVE IMAGING SYSTEM FOR BREAST CANCER DETECTION – PROTOCOL NUMBER: TP.102.17.22.PAR

ClinicalTrials.gov ID: **NCT05757427**

JUNE 12TH 2025

FINAL

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TABLE OF CONTENTS

PAGE

LIST OF ABBREVIATIONS 3
1 Introduction 5
2 Study Design and Objective 6
2.1 Study Objective 6
2.2 Study Design 6
2.2.1 Experimental design 6
2.2.2 Study duration 7
2.2.3 Endpoint Measures 7
2.2.3.1 Primary Endpoints 7
2.2.3.2 Secondary Endpoints 8
2.2.3.3 Exploratory Endpoints 8
2.2.3.4 Safety Endpoints 8
2.2.4 Planned Sample Size and study hypothesis 8
3 Data Integrity 9
4 Statistical Software 10
5 SAS® Programs Validation 10
6 Blinding 10
This is an open-label, single site, pilot clinical investigation, assessors were not blinded to the Wavelia MBI output 10
7 Last Observed Value (LOV) 10
8 Missing Data handling 10
9 Baseline data 10
10 Interim Analysis 10
11 Significance levels and handling of type I error 11
11.1 Type I Error 11
12 Analysis Sets 11
12.1 Safety Analysis Set 11
12.2 Interim Analysis Set 11
12.3 Full analysis set 12
12.4 Statistical Analysis of Analysis Sets 13
13 Statistical Analyses 14
13.1 General Considerations 14
13.2 Demographic and Other Patient Characteristics 14
13.3 Disposition of Subjects and Tolerability 14
13.4 Primary Analyses 15
13.5 Secondary and Exploratory Analyses 15
13.6 Subgroup Analysis 16
13.7 Safety Assessment 17
13.8 Additional Exploratory Prognostic Factor Analysis 17
14 References 17

LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
BIRADS	Breast Imaging Reporting and Database System
CI	Confidence Interval
CIP	Clinical Investigation Plan
CRF	Case Report Form
DICOM	Digital Imaging and Communications in Medicine
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EU	European Union
FiH	First in Human
FPI	First Patient In
GCP	Good Clinical Practice
ID	Identifier
IDC	Invasive Ductal Carcinoma
ILC	Invasive Lobular Carcinoma
ISO	International Organization for Standardization
IVDR	In Vitro Diagnostic Regulation
MDCG	Medical Device Coordination Group
MDR	Medical Device Regulation
MRI	Magnetic Resonance Imaging
MVG	Microwave Vision Group
OBCD	Optical Breast Contour Detection
PI	Principal Investigator
ROI	Region-Of-Interest
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event

SAS	Statistical Analysis System
TL	Transition Liquid
USADE	Unanticipated Serious Adverse Device Effect
VDG	Volpara Density Grade

1 INTRODUCTION

This Statistical Analysis Plan (SAP) is a more detailed companion to the Statistical Methods section of the study protocol TP.102.17.22.PAR and provides a comprehensive description of the analysis sets, endpoints, methods and data analyses to be used. When differences exist in descriptions or explanations provided in the protocol and this SAP, the SAP prevails.

The investigational medical device Wavelia #2 was designed and manufactured by MVG Industries SAS located 13 rue du Zéphyr, 91140 Villejust, France. MVG Industries is a company founded in 1986 which has developed a proprietary ultra-fast multi-probe scanner technology in the microwave frequency spectrum. This technology has been adapted for use in the medical field, for the scanning of superficial organs which are composed of soft tissues. The Wavelia investigational medical device was designed to scan and image the human female breast, aiming to detect, localize and characterize breast lesions, which are dielectrically contrasted against the background healthy tissue, in the microwave frequency spectrum.

In the First-in-Human (FiH) study, conducted in 24 patients, the Wavelia #1 prototype system demonstrated the ability to detect and discriminate between palpable breast lumps, the imaging procedure had no safety issues and patients reported a favorable experience of the MWBI scan. The promising findings from the study, which provided initial data to support a valid clinical association in accordance with Stage 1 of the Guidance on Clinical Evaluation (MDR) / Performance Evaluation (IVDR) of Medical Device Software (MDCG 2020-1), warranted the preparation of further clinical investigations with an upgraded prototype version of the Wavelia system (Wavelia # 2).

The clinical data that was collected in this 2nd study with Wavelia was intended to build upon the outcomes of the First in Human (FiH) study (TN.32.1.17. SATF), as well as further address the current limitations of the state-of-the-art MWBI technology applied to clinical trials at this stage.

The intended purpose of the investigational device in this pilot clinical investigation is to assess the detectability and sizing of invasive breast cancers, the detectability of benign breast lesions, as well as the differentiation between malignant and benign breast lesions, using Wavelia #2. Female patients who present to the symptomatic clinics with a discrete breast abnormality larger than >1cm will be assessed for participation.

The patient is examined lying in prone position, firstly, on the examination table of the OBCD scanner and subsequently on the examination table of the MWBI scanner.

The total duration of the study was estimated to be 24 months. First patient included (FPI) was targeted for November 2022 with an overall recruitment timeline of 18 months. Database Lock was on 14 October 2024.

2 STUDY DESIGN AND OBJECTIVE

2.1 Study Objective

The study main objectives were to assess the detectability and sizing of invasive breast cancers, the detectability of benign breast lesions, as well as the differentiation between malignant and benign breast lesions using the Wavelia # 2 Microwave Breast Imaging System. This second study in patients is intended to progress to Stage 2 of MDCG 2020-1 in an adaptive manner, to build upon the clinical findings of the FiH study on a larger dataset of patients and with employment of the upgraded Wavelia prototype #2. Preliminary technical assessment of the new prototype was carried out initially, before continuing the clinical investigation on larger and more diverse patient datasets.

2.2 Study Design

2.2.1 Experimental design

The study was planned as a single arm pilot clinical investigation designed as a two-stage adaptive trial following Simon's two-stage minimax design [2], intended to stop for futility after the first stage (No-Go) or continue to the second stage (Go).

The study proceeded as follows:

Female patients who presented to the symptomatic clinics with a breast abnormality were reviewed for suitability and assessed for participation. The technical Go / No-Go assessment was carried out once 30 patients having a dominant discrete lesion from the Patient Aggregates 1 and 2 had been scanned (See Section 6.5 of the clinical trial protocol). If there were less than 18 detected lesions, then the trial was to be paused (No-Go) and a technical assessment made to determine the cause. After the technical adaptation, a second 30 patients could be scanned as noted above for a second and final technical Go/No-Go assessment. Once a technical "Go" was verified, a stage two analysis was implemented by including an additional 32 subjects. We reject the ability of the device to detect breast lesions with acceptable performance level at the end of the second stage if the dominant discrete breast lesions in fewer than or equal to 43 out of the 62 evaluable subjects is detected. If detection of the dominant discrete breast lesion is confirmed with Wavelia #2 MWBI in at least 44

out of the 62 evaluable subjects, then further clinical investigations on larger patient populations may be warranted with the Wavelia #2 MWBI prototype, towards identification of the potential clinical applications with added-value for the MWBI modality.

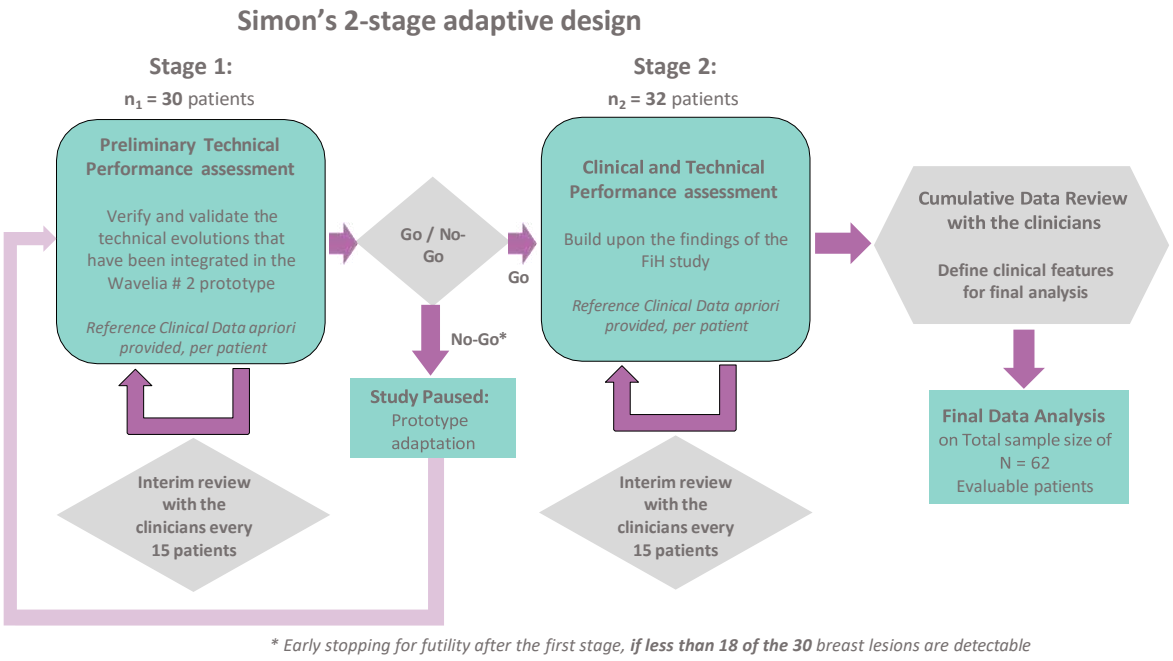

Figure 1: Schematic description of the adaptative study design

2.2.2 Study duration

Subjects were followed for approximately 3 weeks.

2.2.3 Endpoint Measures

2.2.3.1 Primary Endpoints:

- Detectability rate – defined as the percentage of breast lesions (benign or malignant) that were detected by the Wavelia # 2 Microwave Breast Imaging System and will be represented by a binary variable which will be assigned the value of 1 if the lesion, benign or malignant, was detected by the device and 0 (zero) otherwise.
- Discrimination between malignant and benign breast lesions measured by the proportion of malignant and proportion of benign breast lesions correctly

classified with Wavelia MWBI, in other words the sensitivity and specificity of malignancy.

2.2.3.2 Secondary Endpoints:

- Correct sizing of invasive breast cancers. The maximal linear size difference (in mm) between the MWBI lesion detection and the maximal size reported in the ultrasound lesion size estimates. This is measured as a continuous variable of difference in mm.
- Discrimination among different cancer-types: The proportion of cancers correctly classified per cancer type with Wavelia MWBI (e.g. ILC, IDC, other).- Note: No sufficient data for this analysis and it will not be presented.

2.2.3.3 Exploratory Endpoints:

- The proportion of malignant and the proportion of benign breast lesions correctly detected with Wavelia MWBI for patients who did not have a biopsy clip in their breast will be represented by a binary variable which will be assigned the value of 1 if the lesion (benign or malignant) was detected by the device and 0 (zero) otherwise.
- Correct sizing of invasive breast cancers in the subset of lesions with either MRI or post-surgery histology (Gold standard reference). The maximal linear size difference (in mm) between the MWBI lesion detection and the maximal size by the gold standard. This is measured as a continuous variable of difference in mm.
- Correct sizing of invasive breast cancers in the subset of lesions with either MRI or post-surgery histology (Gold standard reference). The maximal linear size difference (in mm) between **the ultrasound sizing** and the maximal size by the gold standard. This is measured as a continuous variable of difference in mm.

2.2.3.4 Safety Endpoints:

- Incidence of Serious Adverse Events and Serious Adverse Device Effects during the total duration of the trial as well as other adverse events reported.

2.2.4 Planned Sample Size and study hypothesis

The following hypothesis will be tested for the primary efficacy endpoints:

H_0: $P_0 \leq 60\%$
H_A: $P_1 \geq 75\%$

Where P is the percentage of malignant and benign breast lesions detected by the Wavelia device.

Rejection of the null hypothesis in this study design means that further testing is warranted since the product is promising.

The sample size is calculated solely for the first primary endpoint, no minimal number of benign nor malignant lesions was set.

The sample size is calculated for this trial design, assuming a $p_1 = 75\%$ and $p_0 = 60\%$ for power (1-beta) of 80%, and an alpha level of 5%.

Using the optimal minimax design, we calculate that in the first stage 30 patients are evaluated; if no more than 18 lesions are correctly detected, then terminate the trial for futility (No-Go). Otherwise, accrual continues to a total of 62 evaluable subjects. We will conclude that the Wavelia # 2 Microwave Breast Imaging system is effective in detecting breast lesions if more than 43 of the 62 subjects' lesions are detected. The probability of stopping the study after the first stage is 56.9%.

Note that in the case of an initial technical "No-Go" the first stage will be repeated in an additional 30 patients. Allowing a 10% loss to follow-up (patient drop-out/withdrawal) we may include up to 103 patients in the study.

3 DATA INTEGRITY

Throughout the duration of the study, regular quality management oversight activities and data reviews were performed remotely and at the study site to check for compliance with Good Clinical Practice (GCP) (ISO14155) and all applicable local regulations and guidelines. 100% source data verification was performed by the study Monitor to verify the accuracy of eCRF data against the source documents.

All required data in this trial was transcribed directly in the EDC (Electronic Data Capture) system and the relevant reference images and reports were verified for personally identifiable information (PII) and uploaded to the database in accordance with the approved Data Management Plan. The investigator and site team ensured the accuracy and completeness of the data. Sites were trained on

how to access and use the EDC system and were assigned a personal user login and password.

4 STATISTICAL SOFTWARE

All statistical analyses and data presentations, including tabulations and listings, will be performed using the SAS® version 9.4 (SAS Institute, Cary NC, USA) software.

5 SAS® PROGRAMS VALIDATION

All SAS® programs used for analyses described in this document will be validated by double programming, **or** by code review per BioStats SOP's.

6 BLINDING

This is an open-label, single site, pilot clinical investigation, assessors were not blinded to the Wavelia MBI output.

7 LAST OBSERVED VALUE (LOV)

The Last Observed Value (LOV) is defined as the last available post baseline visit data up to and including the termination visit.

8 MISSING DATA HANDLING

Missing data will not be imputed in this study.

9 BASELINE DATA

The data collected at the first visit will be considered as baseline data.

10 INTERIM ANALYSIS

One interim analysis (technical Go/No-Go assessment) is planned, after 30 subjects are enrolled to the study and the data for the primary endpoints is collected.

If, at the interim analysis, there are less than 18 detected lesions, then the trial will be paused (No-Go) and a technical assessment will be made to determine the cause. After the technical upgrade, a second 30 patients will be scanned for a second interim analysis (final technical Go/No-Go assessment).

If technical “Go” is verified, a stage two analysis is implemented by including an additional 32 subjects.

At the interim data review and Go / No-Go control point the Wavelia MWBI Region-Of-Interest (ROI) detection methodology (as employed first in the FiH study and patented for Wavelia MWBI) will be applied.

The constraint which was imposed in the FiH study data analysis, for detection of a single predominantly contrasted and persistent ROI in each breast, will be removed from this study, to ensure the analysis is more consistent with the real-world use. In this clinical investigation, more than a single ROI may be automatically detected (based on persistence and morphological properties) in each patient’s breast and further included in the clinical data analysis. A maximum of three (3) lesions will be evaluated in each breast.

11 SIGNIFICANCE LEVELS AND HANDLING OF TYPE I ERROR

11.1 Type I Error

This is a pilot study; no formal statistical inference will be performed except for the go-no go assessment. Nevertheless, where confidence limits are appropriate, unadjusted 95% confidence intervals will be presented.

12 ANALYSIS SETS

The following analysis sets are defined for this study:

12.1 Safety Analysis Set

The safety analysis set will consist of all patients enrolled in the study who completed an MWBI examination.

12.2 Interim Analysis Set

Interim data analysis will be performed in an initial cohort of 30 evaluable patients falling in any of the two (2) Aggregates defined below:

- Patient Aggregate #1: patients having biopsy confirmed invasive breast cancers of radiographic size >1cm (Imaging Score: M5/U5 or M4/U4 or M3/U3, Biopsy score: B5)

- Patient Aggregate #2: patients having biopsy-confirmed benign breast lesions (fibroadenoma, complex cysts etc.), of radiographic size >1cm (Imaging Score: M3/U3, Biopsy score; B2)

Note, we may have two such analysis sets, in the case of an initial technical No-Go. In this case a second Interim Analysis will be performed in 30 additional patients as illustrated in Figure 1 above.

12.3 Full analysis set

The full analysis set will consist of the *evaluable* patients from the interim analysis set plus an additional 32 patients. Once technical Go is confirmed, data will continue to be collected in a second cohort of 32 additional evaluable patients to build upon the clinical outcomes of the First in Human (FiH) study. Up to 103 patients may need to be enrolled in the study in order to reach 62 completed evaluable patients who have been scanned using technically validated MWBI. An ***evaluable*** patient must have met all inclusion and exclusion criteria, completed MWBI on both breasts with the technically validated MWBI and have collected relevant reference data for the primary and secondary endpoints. Patients who have a complete MWBI scan of at least one breast, will be included in the safety analysis, but will not be considered an evaluable patient for primary and secondary endpoint evaluation.

Following is the list of non-evaluable subjects excluded from the FA set with main reason:

Subject ID	Reason for Exclusion
008	All cysts aspirated before Wavelia scan (included due to residual lump)
019	Device deficiency (Wavelia scan with no transition liquid)
014	Patient coughing – no scan pause (low quality of scan due to movements)
069	Abandoned 1st breast scan due to pain / uncomfortable scanner-to-breast interface (silicon pad)

034	Single breast scan due to limited time of the patient (protocol constraint to require both breasts to be scanned)
052	Single breast scan due to limited time of the patient (protocol constraint to require both breasts to be scanned)
063	Single breast scan due to limited time of the patient (protocol constraint to require both breasts to be scanned)
055	Breasts too large (combined) factors resulting to non-evaluability: suboptimal positioning and lesion lying in the posterior half of the breast).
057	Breasts too large (combined) factors resulting to non-evaluability: suboptimal positioning and lesion lying in the posterior half of the breast).
062	Breasts too large (combined) factors resulting to non-evaluability: suboptimal positioning and lesion lying in the posterior half of the breast).
064	Breasts too large (combined) factors resulting to non-evaluability: suboptimal positioning and lesion lying in the posterior half of the breast).

12.4 Statistical Analysis of Analysis Sets

The safety analysis set will serve as the principal dataset for the safety assessments.

The interim analysis set will serve as the principal dataset for the technical Go/No-Go assessment.

The full analysis set (as noted above) will serve as the principal dataset for the primary, secondary and exploratory assessments.

13 STATISTICAL ANALYSES

13.1 General Considerations

Statistical analyses will be performed using SAS® V9.4 or higher (SAS Institute, Cary NC, USA). Statistical analyses and reporting will be performed in compliance with MDR 2017/745, FDA Guidance 21 CFR part 812 and E9 and ISO 14155. If any statistical tests are performed, they will be two-sided. The required significance level of findings will be equal to or lower than 5%. Where confidence limits are appropriate, the confidence level will be 95%.

If statistical tests are performed nominal p-values will be presented. Non-adjusted Confidence Interval (CI) will be presented.

All statistical analyses of safety and efficacy measures will be descriptive in nature. Continuous variables will be summarized by a mean, standard deviation, minimum, median and maximum, and categorical variables by a count and percentage. Confidence intervals will be provided where relevant. If multiple lesions are detected in a single patient's breast, statistics described below will be appropriately modified to accommodate the within patient correlation. A maximum of three (3) lesions is foreseen.

13.2 Demographic and Other Patient Characteristics

Demographic (Age) and other variables such as: breast density category, breast volume, lesion histological type, lesion size and presence (or not) of biopsy clip marking the lesion, will be tabulated. Continuous variables will be summarized by a mean, standard deviation, minimum, median and maximum, and categorical variables by a count and percentage.

A data listing of the subjects' demographic characteristics will be provided.

13.3 Disposition of Subjects and Tolerability

The numbers of subjects who were enrolled and completed each visit of the study will be provided, as well as the reasons for all enrolment discontinuations, grouped by major reason (e.g., lost to follow-up, adverse event, poor compliance). Termination reasons will be presented. Data listings of termination/withdrawal reasons will be provided.

13.4 Primary Analyses

- The primary analysis will be performed in an adaptive manner as follows:
  Clinical data collection on the first 30 patients with a dominant discrete lesion attributed to aggregates 1 and 2 (refer to definition of patient aggregates in Section 6.5 of the study protocol) for verification and approval of the technical evolutions that have been integrated in the Wavelia # 2 prototype with a decision on a Technical Go/No-Go. If there are less than 18 detected lesions, then pause the trial (No-Go) to assess and address the technical cause and adapt the Wavelia #2 prototype before conducing and second and final Technical G/No-Go in an additional 30 patients. Once technical "Go" is verified, stage two is implemented by including an additional 32 subjects.
  We reject the ability of the device to detect breast lesions with acceptable performance level at the end of the second stage if the dominant discrete breast lesion of fewer than 43 out of the 62 evaluable subjects is detected. If detection of the dominant discrete breast lesion is assured with technically validated Wavelia #2 MWBI in at least 44 out of the 62 evaluable subjects, then further clinical investigations on larger patient populations may be warranted with the Wavelia #2 MWBI prototype, towards identification of the potential clinical applications with added value for the MWBI modality.
  The final detection rate will be presented with 95% confidence interval considering 1 lesion per subject. A per lesion analysis will be performed as well.
- The proportion of benign and proportion of malignant breast lesions correctly classified with Wavelia MWBI will be calculated and presented with 95% confidence interval.

13.5 Secondary and Exploratory Analyses

- The maximal linear size difference (in mm) between the MWBI lesion detection and the maximal size by ultrasound will be summarized with descriptive statistics.
- The percentage of malignant and the percentage of benign breast lesions correctly detected by Wavelia MWBI on patients that did not have a biopsy clip marking the lesion position in the breast, will be presented with 95% confidence interval.

- The maximal linear size difference (in mm) between the MWBI lesion detection and the maximal size by the gold standard and between the ultrasound measured size and the gold standard will be summarized with descriptive statistics.

Note: If any unexpected atypical or abnormal findings are identified during this study that may incidentally indicate other diseases or other unknown conditions, these cases will be reported to and reviewed with the Principal Investigators (Clinical and Radiology). If the Principal Investigators determine that these findings are medically significant in their medical judgment, he or she will notify the subject and refer her for further follow-up according to the standard of care at the investigational site.

13.6 Subgroup Analysis

Subgroup analysis of the primary endpoints based on baseline factors may be assessed as exploratory analyses. This will be done by presenting the endpoints by parameter levels. The subgroups of interest include the following :

- **Age**:
  - Group 1 : Young patients < 40 years old
  - Group 2 : Pre-menopausal patients >=40 years old
  - Group 3: Post-menopausal patients
- **Breast density category (4 groups)**:
  - Group 1: Fatty breasts - Breast Density Category A or B
  - Group 2: Dense breasts - Breast Density Category C
  - Group 3: Extremely dense breasts: Breast Density Category D
  - Group 4: young patients with no mammogram available
- **Breast density category (3 groups)**:
  - Group 1: Fatty breasts - Breast Density Category A or B
  - Group 2: Dense breasts - Breast Density Category C or D
  - Group 3: young patients with no mammogram available
- **Breast density category and small lesions**
  - Group 1: Breast Density Category A or B and Reference Radiological Lesion Size <=15mm
  - Group 2: Breast Density Category C or D and Reference Radiological Lesion Size <=15mm

- Group 3: young patients with no mammogram available and Reference Radiological Lesion Size <=15mm

- **Breast volume**:
  - Group 1: Small breasts : Volume <600mL
  - Group 2: Large breasts : Volume >1200mL
  - Group 3: Medium -sized breasts: all the other

13.7 Safety Assessment

Device tolerability will be presented, the number and percentage of subjects who fail to complete the study and the number and percentage of subjects who fail to complete the study because of adverse events will be presented.

Adverse events will be presented in tabular format in general and by seriousness, severity and relation to study device.

Other safety measures will be presented in tabular format as well.

13.8 Additional Exploratory Prognostic Factor Analysis

A prognostic factor analysis is proposed to identify potential factors that may play a role in the differentiation between malignant and benign cases. Logistic regression modeling will be performed to assess potential factors that are predictors of the detection of a malignant finding. Variables identified will be entered into a multivariate model, the variables designated to remain in the model will be those factors which remain statistically significant when entered together in the models and maximize the predictive power (AUC of the ROC curve) of the model.

14 REFERENCES

The following documents were used to prepare the Statistical Analysis Plan:

1. TP.102.17.22.PAR - Clinical Investigation Plan 04 June 2024 Version E
2. Optimal Two-Stage Designs for Phase II Clinical Trials, Richard Simon, PhD, Controlled Clinical Trials Volume 10, Issue 1, March 1989, Pages 1-10.