# A PROSPECTIVE STUDY TO EVALUATE THE PERFORMANCE AND OPERATION OF THE BREVERA™ BREAST BIOPSY SYSTEM

**Hologic:** Hologic, Inc.
250 Campus Drive
Marlborough, MA 01752 USA

**Study Product:** Brevera Biopsy System with CorLumina™

**Protocol Number:** #16-05A

**Date:** 28FEB2017 – Version 4.0

This clinical study is performed in accordance with applicable guidelines, standards and regulations. This protocol template is based on ISO 14155:2011 Clinical Investigation Plan (Annex A).



## HOLOGIC SIGNATURE PAGE

The present study has been reviewed and approved.

Hologic representative (print) Title

Date

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**TABLES**

## 1. SYNOPSIS

| | |
|---|---|
| **Title:** | A Prospective Study to Evaluate the Performance and Operation of the Brevera Breast Biopsy System |
| **Device(s):** | The Hologic Brevera Breast Biopsy System with CorLumina Imaging Technology |
| **Objective:** | To obtain clinical, operational, and performance data and feedback on the Brevera Breast Biopsy System |
| **Design:** | Prospective, multi-center, controlled data collection study |
| **Primary Outcome:** | To obtain data on the operation and feedback from the perspective of the clinician(s), patients, and technologist(s) using the system. |
| **Planned Enrollment:** | Up to 500 subjects |
| **Population:** | Women with suspicious findings on previous imaging (e.g. mammographic, Magnetic Resonance Imaging or Conventional Diagnostic Ultrasound imaging (screening or Diagnostic)) who are sent for biopsy. |
| **Follow-up Schedule:** | No follow-up is required of subjects after the procedure and associated data collection. |
| **Number of Sites:** | Up to 10 across The Netherlands, Italy, France, Germany, Spain and the United Kingdom |
| **Study Duration (Estimated):** | **Study Start:** Q1/2017<br>**Enrollment Completion:** Q3/2017<br>**Last Patient, Last Visit:** Q3/2017<br>**Final Report:** Q4/2017 |
| **Inclusion Criteria:** | 1) Female aged 18 years of age or older<br>2) Subject has at least one breast imaging finding requiring biopsy for which images are available<br>3) Subject is able to understand, read and sign the study specific informed consent form after the nature of the study has been fully explained to her |

| | |
|---|---|
| **Exclusion Criteria:** | 1) Patients who, based on the physician's judgement, may be at increased risk or develop complications associated with core removal or biopsy.<br>2) Patients receiving anticoagulant therapy or may have bleeding disorders which may put the patient at increased risk of procedural complications based upon physicians judgement |
| **Hologic:** | Hologic, Inc. |
| **CRO:** | Factory CRO for Medical Devices BV |

## 2. INTRODUCTION

The Brevera Breast Biopsy System integrates tissue acquisition, real time imaging, and post biopsy handling all during the same procedure. The device will receive CE Mark and be commercially available in all of the countries as part of this protocol before any study procedures are performed. The commercial device will be utilized according to the Instructions for Use.

### 2.1 Summary of Animal Testing Data

In July 2016, Hologic conducted an animal study titled, "GLP Acute Evaluation of the Brevera Vacuum-Assisted Breast Biopsy System in the Porcine Model."

The objective of this study is to support, using attribute data, that the Gen 2 system adequately performs the following functions using tissue in an animal model:

1. Acquire core tissue samples from the biopsy site.
2. Transport tissue samples into the filter wheel.
3. Capture X-ray images of transported tissue cores in the tissue filter.

The results of this study demonstrate that the device performs to specifications and can be used in human subjects.

### 2.2 Device Description

The Brevera Breast Biopsy System with CorLumina imaging technology is a vacuum-assisted biopsy device, which is used to remove breast tissue in a minimally invasive manner using stereotactic or tomosynthesis imaging. The system is designed for biopsy and for radiographic image acquisition and display only. The biopsy device will come in contact with tissues and/or body fluids.

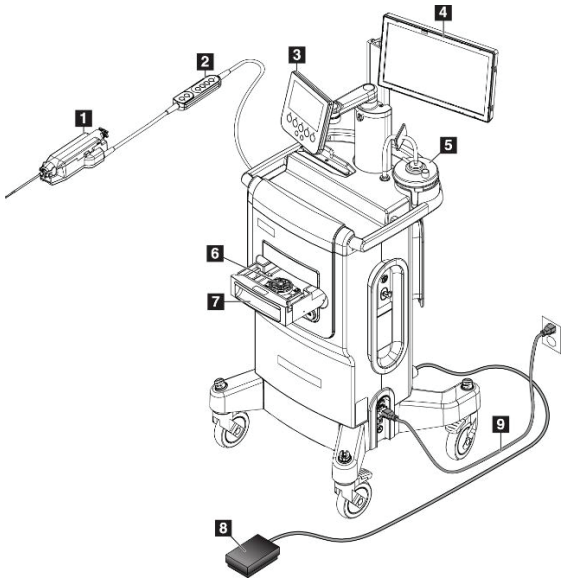



**Figure Legend**

1. Biopsy device
2. Remote control for mode control and arming or firing the biopsy device
3. Technologist display
4. Imaging display
5. Vacuum line assembly and suction canister
6. Tissue filter assembly
7. Tissue filter drawer
8. Footswitch
9. Power cord

*Figure 1: Brevera Breast Biopsy System with CorLumina Imaging Technology System Overview*

The user interface for data entry, patient selection, and image acquisition and review is on the Imaging display. The user interface for controlling the modes of the biopsy device are buttons on the Technologist display and on the remote control device. The user interface for arming and firing the biopsy device is on the remote control device. The user rotates the aperture on the biopsy device with the thumbwheel on the disposable biopsy needle. The user adjusts the size of the aperture on the biopsy device by assembling the introducer in one of two preset positions along the needle shaft.

## 2.3 Device Accountability

The Hologic operations team will keep records to document the shipment and installation of the commercial system. The Principal Investigator or an authorized designee shall keep records documenting the type, and use of the devices.

## 2.4 Intended Use/Current Indication for Use

See product specific Instructions for Use.

## 2.5 Device Procedure(s)/Training

Prior to use in clinical procedures and the implementation in the standard practice, technologists and clinicians will be trained by a Hologic representative on the use of the new device (according to Instructions for Use) and the features. This training will cover quality control procedures as well as didactic training on the equipment. The investigators selected for this study have previous experience with Breast Biopsy Core Sampling.

# 3. STUDY JUSTIFICATION

The study has been designed to collect data on the operation and to collect feedback from the medical staff and patients on the operation and performance of Brevera Breast Biopsy System with CorLumina imaging technology.

## 4. THIS STUDY FALLS IN LINE WITH HOLOGIC'S POST MARKET SURVEILLANCE PROGRAM. ACCORDING TO THE REQUIREMENTS AS SET FORTH IN THE ISO 14155, MEDDEV 2.12-1 GUIDELINES ON A MEDICAL DEVICES VIGILANCE SYSTEM, MEDDEV 2.12-2 POST-MARKET CLINICAL FOLLOW-UP STUDIES, AND MEDDEV 2.7-1 CLINICAL EVALUATION, AND AS OUTLINED IN THIS PROTOCOL, THIS POST-MARKET, REGISTRY/OBSERVATIONAL STUDY WILL PROVIDE DATA FOR MEASURING DEVICE PERFORMANCE AND OPERATION IN A REAL WORLD SETTING. THIS POST-MARKET TRIAL IS INTENDED TO EVALUATE THE CLINICAL EVIDENCE THROUGHOUT THE LIFE CYCLE OF OUR PRODUCT, TO PERFORM RISK ASSESSMENT AND TO COLLECT FEEDBACK FROM THE MEDICAL STAFF AND THE PATIENT ON THE OPERATION OF THE BREVERA BREAST BIOPSY SYSTEM WITH CORLUMINA IMAGING TECHNOLOGY. POTENTIAL RISK/BENEFIT

### 4.1 Potential Clinical Benefit

There are no clinical benefits to the patient as the patient would have the Brevera procedure whether or not they choose to participate in this study or not. Patients will undergo the same standard procedure if they choose not to participate in this study. The results learned from this study could help future patients.

### 4.2 Anticipated Adverse Device Effect(s)

Common risks associated with the use of any commercial biopsy system are limited to the region surrounding the biopsy site and include:

- Bruising and swelling of the breast
- Infection or bleeding at the biopsy site
- Altered breast appearance, depending on how much tissue is removed and how your breast heals
- Excessive pain following the procedure at the biopsy site

All of the incidents above are related to the biopsy procedure and not necessarily the devices themselves.

### 4.3 Risk Benefit Rationale

This clinical study is justified because Hologic and clinical investigators believe the potential benefits outweigh the potential risks of study participation. There are no additional risks known for the commercially available devices.

## 5. STUDY DESIGN

## 5.1 Study Objective(s)

The objective of this study is to obtain clinical, operational, and performance data and feedback on the Brevera Breast Biopsy System.

### *5.1.1 Hypotheses*

The hypothesis of this study is that the new breast biopsy system could provide:

- 50% Reduction in tissue needed for accurate diagnosis
- 25% Reduction in procedure time
- 50% Reduction in post-biopsy complications
- Weight of grams of tissue per a full 12 chamber
- # of samples needed to provide 1 gram of tissue
- 90% Reduction in discordant biopsies

Reduction in marker dislocation

The current standard of care includes obtaining breast biopsy core samples and verifying the samples using the mammography unit in a room which is next to the room with the biopsy table. With the Brevera procedure, the breast biopsy core samples are obtained, and the system shows images of the samples, providing instant verification.

The data will be compared to data already collected by Hologic, site aggregate data on the current standard of care, and relevant literature (see last page of protocol).

## 5.2 Study Design

Prospective, multi-center, controlled data collection study. This study will include collection of breast imaging from the prior exam leading up to the Brevera Breast Biopsy System Procedure.

Surveys have been created in order to obtain information related to feedback from the clinician(s), patient, and technologist(s). The surveys include questions that relate to the overall feel and aesthetic of the product as well at the overall performance of the Brevera biopsy system. The questionnaires will be given to the clinician(s), patient, and the technologist(s) at the conclusion of the procedure and will be focused for each target group. Once a patient has completed the Brevera procedure, her direct participate in the study is concluded. There are no follow-up visits for this data collection.

The surveys will be administered via paper forms to capture the questionnaire data. The results of the survey questions will be compiled and used to support publications.

## 5.3 Study Outcomes

### *5.3.1 Primary Endpoints*

Clinical data and the survey score of clinicians, patients, and technologists obtained directly after using the Brevera Breast Biopsy System.

### *5.3.1 Performance Evaluation*

- Procedural information
  - Number of core biopsy samples obtained
  - Time at six different points during the Brevera Breast Biopsy System procedure.
  - Data on whether the marker dislocated (>1cm) immediately post deployment.
  - The next steps for the patient (routine screening, diagnostic surgical biopsy, therapeutic surgery, other).
  - Safety assessment include all device and procedure related AEs that occur in the study following treatment to the device.
- Biopsy sample information
  - Whether the lesion has previously been classified as a B3 lesion (uncertain malignancy potential).
- Histology evaluation
  - Histology results of each lesion.
  - Weight of the core biopsy samples obtained for each lesion
- Clinician, Technologist and Patient questionnaire

## 5.4 Schedule of Assessment(s)

Clinicians, Patients, and Technologists will be asked about their experience as it directly relates to the procedure that they underwent or performed. Additionally, subjects shall be evaluated from the time of the procedure through their release from the outpatient treatment facility and treated per standard of care for any adverse events which are experienced. Pathology results will be recorded once they become available.

**Table 1 - Schedule of Assessments**

| Assessment | Baseline | Procedure |
|---|---|---|
| Informed Consent | X | |
| Medical History* | X | |
| Physical Assessment* | X | X |
| Adverse Event Evaluation | | X |
| Procedure* | | X |
| Questionnaires** | | X |

* Per standard of care

** To be completed by Clinicians, Patients, and Technologists

## 5.5 Subjects

This study will recruit up to 500 females 18 years of age or older with suspicious findings on mammographic screening or diagnostic exam who are sent for biopsy.

### *5.5.1 Inclusion Criteria*

1) Female aged 18 years of age or older
2) Subject has at least one breast imaging finding requiring biopsy for which images are available
3) Subject is able to understand, read and sign the study specific informed consent form after the nature of the study has been fully explained to her

### *5.5.2 Exclusion Criteria*

1) Patients who, based on the physician's judgement, may be at increased risk or develop complications associated with core removal or biopsy.
2) Patients receiving anticoagulant therapy or may have bleeding disorders which may put the patient at increased risk of procedural complications based upon physicians judgement.

### *5.5.3 Informed Consent & Enrollment Procedures*

Although the device in this study has received CE Mark for commercial use, informed consent shall be obtained in writing from the subject or their legally authorized representative and the process shall be documented before any procedure specific to the clinical study is applied to the subject, in order to collect procedural specific data.

The general process for obtaining informed consent shall:

- ensure that the Principal Investigator or his/her authorized designee conducts the informed consent process;
- include all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study;
- avoid any coercion or undue improper influence on, or inducement of, the subject to participate;
- not waive or appear to waive the subject's legal rights;
- use native non-technical language that is understandable to the subject;
- provide time for the subject to read and understand the informed consent form and to consider participation in the clinical study;
- include personally dated signatures of the subject and the principal investigator or an authorized designee responsible for conducting the informed consent process;
- provide the subject with a copy of the signed and dated informed consent form and any other written information; and,
- ensure the patient is aware that the de-identified study case report forms and images are being sent to Hologic, in the United States.

Upon signing the Informed Consent Form, the subject is considered enrolled in the study.

### *5.5.4 Subject Withdrawal/Discontinuation*

A study subject will be discontinued from participation in the study if:

- The Investigator feels that the subject can no longer fully comply with the requirements of the study or if any of the study procedures would not be in the best interest of the subject.
- The subject wishes to withdrawn their consent for participation in the study.

## 5.6 Study Duration

**Study Start:** Q1/2017
**Enrollment Completion:** Q3/2017
**Last Patient, Last Visit:** Q3/2017
**Final Report:** Q4/2017

# 6. STUDY PROCEDURES

The study will collect de-identified case report form data and patient images from biopsy procedures. This will include collection of images from the prior exam leading up to the Brevera Breast Biopsy System Procedure. The biopsy procedures will be done consistent with current clinician direction/standard of care. There are no special requirements under this protocol for how biopsies are performed.

Prior to use of the new Brevera Breast Biopsy System, normal applications training will take place in order to train the users on new features and quality control testing.

## 6.1 Efficacy Assessment

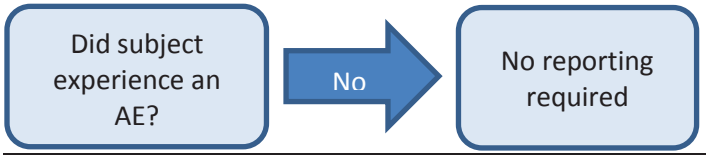
The breast biopsy systems being evaluated during the course of this study are all commercially available. All devices will have CE mark prior to being utilized clinically.

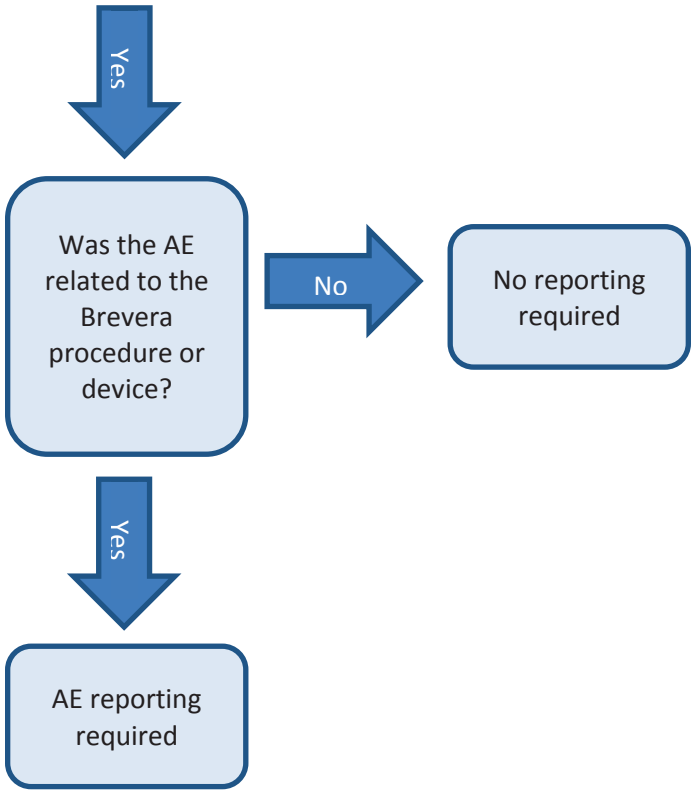
## 6.2 Safety/Device Assessment

### *6.2.1 Adverse Events*

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the study medical device. Each AE is considered either anticipated or unanticipated as described below. The site is required to report all device and procedure related AEs that occur in the study following treatment to the device manufacturer, Hologic, Inc.

**AE Reporting Flow Chart:**






The time-period for the assessment of the occurrence of an AE will begin at the time of consent until the subject has been discharged and will be based on changes in the subject's physical examination, laboratory results and/or signs and symptoms. AEs are to be monitored until they are resolved or clearly determined to be a stable or chronic condition or due to an undercurrent illness. Medical care will be provided, as defined in the informed consent, for any AE related to study participation.

There are two types of AEs: anticipated or unanticipated. Subjects who experience any untoward after-effects are instructed to contact their Investigator or study coordinator immediately. The Investigator must determine both the intensity of the AE and the event's relationship to the Clinical System.

**AE Severity Classification**: Severity will be defined according to the following criteria:

- **Mild** - Awareness of event, but easily tolerated
- **Moderate** - Discomfort enough to cause some interference with activities of daily living (ADL)
- **Severe** - Incapacitating, with an inability to perform activities of daily living (ADL)

Life threatening events, events where the subject was at risk of death, are serious AEs and must be reported in accordance with the procedures and timelines in this protocol.

**AE Relationship Classification**: Relationship to study product use will be determined as follows:

- **Not Related** - relationship to the device or procedures can be excluded when:

- The event is not a known side effect of the product category the device belongs to or of similar devices and procedures
- The event has no temporal relationship with the use of the device or the procedures
- The serious event does not follow a known response pattern to the medical device ( if the response pattern is previously known) and is biologically implausible
- The discontinuation of the medical device application or the reduction of the level of activation/exposure- when clinically feasible- and reintroduction of its use (or increase of the level of activation/exposure), does not impact the serious event
- the event involves a body-site or an organ not expected to be affected by the device or procedure
- the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect or another device, drug, treatment or other risk factors)
- the event does not depend on a false result given by the study device used for diagnosis when applicable
- harms to the subject are not clearly due to use error
- in order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/ procedures and the serious event.

- **Unlikely** - The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
- **Possible** - The relationship with the use of the device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g an underlying or concurrent illness/ clinical condition/ or and an effect of another device, drug or treatment), Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.
- **Probable** - the relationship with the use of the study device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained
- **Causal Relationship -** the serious event is associated with the device or with the procedures beyond reasonable doubt when:
  - The event is a known side effect of the product category the device belongs to or of similar devices and procedures
  - The event has a temporal relationship with the device application/use or procedures
  - the event involves a body-site or organ that:
    - the device or procedures are applied to
    - the device or procedures have an effect on
    - the serious event follows a known response pattern to the medical device (if te response pattern is previously known)
    - the discontinuation of the medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible)
    - Other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out

- Harm to the subject is due to error in use
- the event depends on a false result given by the device used for diagnosis, when applicable
- in order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event

**AE Outcome Classification**: Outcome of the event will be defined according to the following:

- **Resolved** - The event is resolved and is no longer present
- **Not resolved** - The event has not yet been resolved
- **Resolved with sequelae** - The event has resolved, but with an after affect possibly due to disease, injury, treatment or procedure
- **Fatal -** The event resulted in subject death

### *6.2.2 Serious Adverse Events (SAEs)*

**A SAE is any adverse event that:**

- Led to death
- led to a serious deterioration in health that either:
    - resulted in a life threatening illness or injury, or
    - resulted in a permanent impairment of a body structure or a body function, or
    - required in-patient hospitalization or prolongation of existing hospitalization or
    - resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or body function
- led to fetal distress, fetal death or a congenital abnormality or birth defect

### *6.2.3 Adverse Device Effect*

An AE, which in the judgment of the Investigator, results from use of the study device.

### *6.2.4 Anticipated AEs/Adverse Device Effects*

List of foreseeable AEs and anticipated adverse device effects, together with their likely incidence, mitigation, or treatment. These events are related to the biopsy procedure and not necessarily the devices being used for the study.

Anticipated, procedure-related AEs may include, but are not limited to, the following:

- Bruising and swelling of the breast
- Infection or bleeding at the biopsy site
- Altered breast appearance, depending on how much tissue is removed and how your breast heals
- Excessive post procedural pain at the biopsy site

### *6.2.5 Unanticipated Adverse Device Effect*

An Unanticipated Adverse Device Effect (UADE) is a serious adverse device effect, which by its nature, incidence, severity or outcome has not been identified, in the current version of the risk analysis report.

## 6.3 Reporting Procedures

### *6.3.1 Investigator Reporting*

The Investigator at each participating center is ultimately responsible for reporting applicable AEs to Hologic. The information to be reported on the AE CRF and should include the start date of the AE, treatment, resolution, and assessment of both the seriousness and the relationship to the device and should be captured on the AE CRF. The Investigator should report all AEs to the EC/IRB, as required.

If there is a device malfunction or other observation (deficiency), the Investigator should notify Hologic immediately via the normal complaint procedure for commercially available devices, indicate if the observation resulted in an AE, and indicate if complications are related to the device, procedure or underlying disease.

In the event of a suspected observation or device problem, a field technician will be dispatched to the site to resolve the problem. If the field engineer cannot resolve the problem, the device may be returned to Hologic/Plexus for analysis.

**Hologic Contact Information:**

[redacted]

For Germany, incidents will be reported to the Competent Authorities according to the German Safety Plan for Medical Devices (MPSV). This means that incidents (an incident is any malfunction, any failure or deterioration in the characteristics or performance of a medical device as well as any inaccuracy in the labelling or instructions for use which has led, or could have led, directly or indirectly, to the death or serious deterioration in the state of health of a patient or user or another person) that occurred in Germany, a recall of the medical device implemented in Germany, and incidents that occurred outside the European Economic Area (EEA) and led to corrective measures that are also relevant to medical devices marketed within the EEA, will be reported to the BfArM by the Sponsor and/or Investigator using the applicable forms.

Incidents should be reported without delay in accordance with the required urgency of attention but in any case within a maximum of 30 days of these becoming known. If a delay is likely to cause danger, the notification shall be made immediately. Recalls and incidents outside the EEA as described above shall be reported immediately. Other recalls and incidents that occurred outside the EEA shall be reported at the latest by the time of implementation of any measures.

# 7. STUDY MONITORING

Representatives of Hologic (or CRO) will verify patient data and ensure compliance with clinical protocol and other study requirements, according to the guidelines set forth in the applicable monitoring Standard Operating Procedures (SOP) and ISO 14155 guidelines to be utilized for the study.

### 7.1 Monitor Training

Hologic and/or designated monitors will be trained appropriately to monitor study progress as defined in the study Monitoring Plan.

### 7.2 Site/Investigator Training

Hologic and/or designated CRO will be responsible for providing training to the Investigator and appropriate clinical site personnel.

### 7.3 Site Monitoring

Hologic or designee may conduct periodic compliance assessments at the study site(s). Hologic or designee may request access to all study records including source documentation for inspection during a compliance assessment. The Investigator and research coordinator must be available to respond to reasonable requests and queries made during the compliance assessment process.

### 7.4 Regulatory Agency Inspection

In the event that an investigator is contacted by a regulatory agency regarding this study, the Investigator will notify Hologic or its designee immediately. The Investigator and research coordinator must be available to respond to reasonable requests and queries made during the inspection process. The investigator must provide Hologic or designee with copies of all correspondence that may affect review of the current study (e.g., Form FDA 483, Inspectional Observations and Warning Letters). Hologic may provide needed assistance in responding to regulatory audits.

## 8. STATISTICAL CONSIDERATIONS

The overall sample size for this study is approximately 500 subjects. This sample is expected to be sufficient to provide a basis for providing subjective evidence of clinical performance in a clinical environment. Clinical outcomes data will be collected on all subjects, and survey responses from clinicians, patients, and technologists will be collected and analyzed.

Once all of the data has been collected and cleaned, all variables will be tabulated using descriptive statistics. Continuous variables will be presented as means and standard deviations with 95% confidence intervals, as well as medians and ranges. For categorical variables, relative frequencies and 95% confidence intervals will be provided. The data will be analyzed and compared to previous data collected by Hologic Inc, and to relevant literature.

## 9. DATA HANDLING AND RECORD KEEPING

Each participating site will maintain appropriate medical and research records for this study, in compliance with, regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in this study, the site will permit authorized representatives ofHologic, Hologic's designee, and regulatory agencies to examine (and when required by applicable law, to copy) de-identified study related clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress.

Anonymization procedure code consists of assigning a specific code to the data. The code consists of a 3 digit assigned site number XXX- followed by a 3 digit protocol ID number XXX and then a 3 digit XXX sequential number (001-060). An ID may look similar to this 001-060-001.

Source data are all information, original records of clinical findings, observations, or other activities such as questionnaires and investigator assessments in a study necessary for the reconstruction and evaluation of the study.

The investigator is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Dark ink is required to ensure clarity of reproduced copies. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. Do not erase, overwrite, or use correction fluid or tape on the original.

## 9.1 Data Management Procedures

This study will obtain informed consent and survey data for 500 cases. Monitoring will be conducted to ensure patient consent was obtained. Survey Data, which will serve as source data for the details of the procedure and the inclusion/exclusion criteria will be compiled from either an electronic survey form or paper form and loaded into an electronic format. Surveys will be reviewed for missing question responses/discordant answers and will be addressed as soon as missing points are noted.

## 9.2 Electronic Clinical Data System

Hologic or designee will perform development of the primary database for the study. Hologic or designee will also be responsible for the verification, validation and quality control of the database and confirming the overall integrity of the data. The process details will be outlined in the Data Management Plan.

## 9.3 Data Retention

Study documents should be retained per as required by local regulations. No records will be destroyed without the written consent of Hologic, if applicable. It is the responsibility of Hologic to inform the investigator when these documents no longer need to be retained.

## 9.4 Investigator Records

Investigators will maintain complete, accurate and current study records. Records shall be maintained during the clinical study and for fifteen years after the later of the date on which the study is terminated or completed, or the date the records are no longer required to support FDA approval of the device. Investigator records shall include the following materials:

- ***Correspondence***: Documentation of all verbal and written correspondence with Hologic, the Clinical Monitor, the independent physician adjudicator, and other investigators regarding this clinical study or any patient enrolled therein.
- ***Subject Records***: Signed informed consent forms, copies of all completed Case Report Forms and supporting documents and records of exposure of each subject to the device. Informed consent must comply with local regulations and ISO14155.
- ***Clinical Study Plan/Protocol***: A current copy of the Clinical Study Protocol including Instructions for Use of the System and blank case report forms.
- ***Ethics Committee (EC)/Institutional Review Board (IRB) Information***: All information pertaining to IRB/EC review and approval of this clinical study including a copy of the IRB/EC letter approving the clinical study, a blank informed consent form approved by the IRB/EC, and certification from the IRB/EC Chairman that the IRB/EC complies with FDA and EC regulations/regulatory body regulations.
- ***Investigator Agreements***: Copies of signed Investigator, Co-Investigator and Sub-Investigator Agreements with accompanying curriculum vitae.
- ***Other***: Any other records that may be required by applicable state or federal laws.

## 9.5 Investigator Reports

The Investigator will prepare and submit the following reports and shall notify Hologic:

- ***MDV***: Medical Device Vigilance Reporting of all events related to the device or device malfunctions.
- ***Withdrawal of EC/IRB Approval***: Withdrawal of approval shall be reported to Hologic or designee within five working days. The Investigator will provide a written report of the reason(s) approval was withdrawn.
- ***Progress Reports***: Hologic shall provide to the Investigator progress reports on the completion of data as necessary. In addition, the Investigator may be asked to submit progress reports to Hologic or designee and the reviewing IRB/EC that include the number of study subjects, a summary of follow-up data and complications and a general description of the study progress.
- ***Final Report***: Hologic shall provide to the Investigator a final report within three months of termination or completion of the study or that Investigator's participation in the study, to provide to the EC/IRB.

- ***Other Reports***: Upon the request of Regulatory Agency/FDA, the reviewing EC/IRB, or Hologic or designee, the Investigator will provide accurate and timely information about any aspect of the clinical study.

## 10. QUALITY CONTROL AND ASSURANCE

### 10.1 Site and Investigator Selection

Hologic selects qualified investigators with appropriate experience at health care facilities with adequate resources to participate in this study. Study sites will be selected using combined current assessments of site and investigator qualifications.

### 10.2 Protocol Deviations

An investigator is not allowed to deviate from the Protocol if the deviation affects subject's rights, safety and wellbeing, or the scientific integrity of the clinical study. Such deviations shall be documented and reported to Hologic and the EC/IRB as soon as possible.

A protocol deviation is a failure to comply with the requirements specified within this clinical study protocol. An example of a protocol deviation may include enrollment of a study patient who does not meet all of the inclusion/exclusion criteria specified in the protocol. Each investigator shall conduct this clinical study in accordance with this clinical study protocol, regulatory body regulations, ISO guidelines and any conditions of approval imposed by their EC/IRB.

All deviations are reviewed and assessed for their impact on patient safety by Hologic or designee. The PI and study staff is responsible for knowing and adhering to their EC/IRB reporting requirements.

The protocol deviations for this protocol consist of, but not limited to the following:

- Failure to obtain patient's informed consent prior to any study-related activities;
- Failure to report Brevera procedure/device related AEs according to protocol requirements.

In the event of any deviation from the protocol, the Investigator will be notified of the site's non-compliance. Corrective actions will be required, if necessary. Continued protocol deviations despite re-education of the study site personnel or persistent protocol deviation may result in termination of the site's study participation. Patients enrolled at these sites will continue to be followed per the clinical protocol.

### 10.3 Protocol Deviation Process

Investigators must report protocol deviations to Hologic within 5 working days of study site knowledge of the deviation by contact to the CRO and Hologic. Any protocol deviations that affect the rights, safety or well-being of the subject or the scientific integrity of the clinical study must be reported within 24 hours to Hologic and EC/IRB, if required by the EC/IRB or national regulations.

## 10.4 Study Audit(s)

The auditing of clinical study systems shall be conducted in accordance with Hologic's written procedures or specific plan on what to audit, how to audit, the frequency of audits and the form and content of audit reports.

Hologic's audit plan and procedures for a clinical study audit shall be guided by the importance of the clinical study, the number of subjects in the clinical study, the type and complexity of the clinical study, the level of risk to the subjects and any identified problem(s). The audit results shall be documented and communicated to relevant parties, if applicable.

# 11. ETHICS/PROTECTION OF HUMAN SUBJECTS

## 11.1 Statements of Compliance

This clinical study shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, International Standard Organization (ISO 14155:2011) and any regional or national regulations.

The clinical study shall not begin until the required approval/favorable opinion from the EC/IRB or regulatory authority have been obtained, if appropriate.

Any additional requirements imposed by the EC/IRB or regulatory authority shall be followed.

## 11.2 Ethics Committee (EC)/Institutional Review Board (IRB)

Each participating institution must provide for the review and approval of this protocol and the associated informed consent documents by an appropriate EC/IRB. Any amendments to the protocol or consent materials must also be approved before they are placed into use.

## 11.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual is agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of this device will be provided to the subjects and their families. Consent forms describing in detail the study procedures, and risks are given to the subject and written documentation of informed consent is required prior to the study procedure. Consent forms will be EC/IRB-approved and the subject will be asked to read and review the document. Upon reviewing the document, the investigator (or designee) will explain the research study to the subject and answer any questions that may arise. The subject will sign the informed consent document prior to any procedures being done specifically for the study. The subject should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate, unless study timeframes do not allow for such discussions. The subjects may withdraw consent at any time throughout the course of the study. A signed informed consent document will be given to the subjects for their records. The rights and

welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

#### *11.3.1 New Information*

If new information becomes available that can significantly affect a subject's future health and medical care; that information shall be provided to the affected subject(s) in written form. If relevant, all affected subjects shall be asked to confirm their continuing informed consent in writing.

### 11.4 Subject Confidentiality

All parties involved at all times throughout the clinical study shall observe confidentiality of data. All data shall be secured against unauthorized access and all patient image data is anonymized.

The privacy of each subject and confidentiality of her information shall be preserved in reports and when publishing any data. The Principal Investigator or institution shall provide direct access to source data during and after the clinical study for monitoring, audits, EC/IRB review and regulatory authority inspections. As required, the Principal Investigator or institution shall obtain permission for direct access to source documents from the subject, hospital administration and national regulatory authorities before starting the clinical study.

## 12. PROTOCOL AMENDMENTS

The Protocol, ICF, or other clinical study documents shall be amended as needed throughout the clinical study, and a justification statement shall be included with each amended section of a document. Proposed amendments to the Protocol shall be agreed upon between Hologic and Principal Investigator, the amendments to the Protocol and the subject's informed consent form shall be notified to, or approved by, the EC/IRB and regulatory authorities, as required. For non-substantial changes [e.g. minor logistical or administrative changes, change of monitor(s), telephone numbers, renewal of insurance] not affecting the rights, safety and well-being of human subjects or not related to the clinical study objectives or endpoints, a simple notification to the EC/IRB and, where appropriate, regulatory authorities can be sufficient. The version number and date of amendments shall be documented.

## 13. TERMINATION OF STUDY OR STUDY SITE PARTICIPATION

Hologic may terminate the study at any time. If the study is terminated prior to the completion of expected enrollment for any reason, all participating centers will be notified within five working days.

Hologic reserves the right to terminate study site participation and remove appropriate study materials at any time. Specific instances that may precipitate such termination include but are not limited to the following:

- Failure to meet minimum patient enrollment requirements
- Failure to comply with protocol specified procedures and documentation

The site Investigator may also discontinue study participation with suitable written notice to Hologic.

## 14. PUBLICATION POLICY

As detailed in the study agreement.

### 14.1 Investigator Agreement

**Investigator Responsibility**

Prior to participation in the Study, the appointed Principal Investigator at the study site (hereafter referred to as "Principal Investigator") must obtain written approval from the IRB/EC. This approval must be in the Principal Investigator's name and a copy sent to Hologic, or CRO along with the IRB/EC approved Informed Consent Form.

The Principal Investigator must also:

- Conduct the study in accordance with the study protocol, the signed Clinical Study Agreement, applicable regulations (including the Declaration of Helsinki, , any conditions of approval from the IRB/EC or FDA/Regulatory Authority, this investigator agreement, and ISO 14155;
- Agree to participate in a device training program prior to study initiation, as applicable;
- Provide a copy of a Financial Disclosure form that summarizes financial interest in Hologic. In addition, Hologic will be notified if disclosed financial information changes at any time during the clinical study or up to one year following the closure of the study;
- Provide Hologic with curriculum vitae, information regarding previous clinical study experiences (including studies or research that was terminated);
- Assure that the study is not commenced until IRB/EC approval has been obtained;
- Assure that informed consent is obtained from each subject prior to enrollment, using the IRB/EC and Hologic approved forms;
- Supervise all procedures of the device involving human subjects;
- Complete all Case Report Forms and study documentation and relevant imaging assessments, and promptly forward to Hologic or its authorized representative for data management;
- Report all AEs, non-medical complaints and non-compliance to Hologic according to the protocol and regulatory requirements;
- Provide all required data and agree to source document verification of study data with patient's medical records;
- Allow staff of Hologicand its authorized representatives, as well as representatives from regulatory bodies, to review, inspect any documents pertaining to this clinical study; and,
- Oversee retention of required records and documents related to the study.

The Principal Investigator may delegate one or more of the above functions to an associate or Sub-Investigator. However, the Principal Investigator retains overall responsibility for proper conduct of the study, including obtaining and documenting patient informed consent, compliance with the study

protocol, and collection of all required data. Delegated tasks must be documented on a Delegation Log and signed by all those named on the list.

**INVESTIGATOR AGREEMENT - SIGNATURE PAGE**

The signature below constitutes the approval of this Protocol and the attachments, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable regulations.

Study Site Name: _____

Investigator Designation (please select as appropriate) :

☐ Principal Investigator ☐ Physician Sub-Investigator ☐ Non-Physician Sub-Investigator

Investigator Name (*Print*): _____

Investigator Signature: _____

Date of Signature (*DD-MMM-YYYY*): _____

## Literature list


- Bartlomiej Szynglarewicz, Piotr Kasprzak, Jan Kornafel, Jozef Forgacz, Marek Pudelko, Adam Majewski, and Rafal Matkowski. Duration time of vacuum-assisted biopsy for nonpalpable breast masses: comparison between stereotactic and ultrasound-guided procedure. Tumori, 97: 517-521, 2011.
- Heller SL, Jaglan S, Babb JS, Melsaether A, Toth HB, Moy L. Frequency of Discordant Lesions and False-negative Cancers at Stereotactic Vacuum-assisted Biopsy. Acad Radiol. 2016 Aug;23(8):994-9.
- Pinkney DM, Mychajlowycz M, Shah BA. A prospective comparative study to evaluate the displacement of four commercially available breast biopsy markers. Br J Radiol 2016; 89: 20160149.
- Preibsch H, Baur A, Wietek BM, Krämer B, Staebler A, Claussen CD, Siegmann-Luz KC. Vacuum-assisted breast biopsy with 7-gauge, 8-gauge, 9-gauge, 10-gauge, and 11-gauge needles: how many specimens are necessary? Acta Radiol. 2015 Sep;56(9):1078-84.
- Schaefer FK, Order BM, Eckmann-Scholz C, Strauss A, Hilpert F, Kroj K, Biernath-Wüpping J, Heller M, Jonat W, Schaefer PJ. Interventional bleeding, hematoma and scar-formation after vacuum-biopsy under stereotactic guidance: Mammotome(®)-system 11 g/8 g vs. ATEC(®)-system 12 g/9 g. Eur J Radiol. 2012 May;81(5):e739-45.