A PROSPECTIVE, BLOCK STRATIFIED CLINICAL TRIAL TO EVALUATE THE PERFORMANCE AND OPERATION OF THE BREVERA® BREAST BIOPSY SYSTEM

Sponsor:	Hologic, Inc. 250 Campus Drive Marlborough, MA 01752 USA Brian Sundell, Clinical Project Manager, Clinical Affairs
Clinical Trial Product:	Brevera Biopsy System with CorLumina®
Protocol Number:	16-05B
Date:	23JUN2017 – Version 2.0

HOLOGIC SIGNATURE PAGE

The present trial has been reviewed and approved.

Jennifer Bartoshevich — Director, Clinical Affairs

Hologic representative (print) — Title

Jennifer Bartoshevich — 23-Jun-2017

Signature — Date

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1. SYNOPSIS

Title:	A Prospective, Block Stratified Clinical Trial to Evaluate the Performance and Operation of the Brevera Breast Biopsy System
Device(s):	Study Device: The Hologic Brevera Breast Biopsy System with CorLumina Imaging Technology Control: Current standard-of-care breast biopsy procedure devices
Objective:	To obtain clinical/operational data and feedback on the Brevera Breast Biopsy System as compared to the current standard-of-care breast biopsy procedures
Design:	Prospective, multi-center, block stratified, controlled clinical trial
Primary Outcome:	To obtain data on the operation and feedback from the perspective of the clinician(s), patients, and technologist(s) using the systems.
Planned Enrollment:	Up to 525 subjects
Number of Sites:	Up to 10 sites in the United States
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.
Clinical Trial Duration (Estimated):	**Clinical Trial Start:** Q3/2017 **Enrollment Completion:** Q1/2018 **Last Patient, Last Visit:** Q1/2018 **Final Report:** Q2/2018
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 trial specific informed consent form after the nature of the trial 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.
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

Sponsor: Hologic, Inc.

2. INTRODUCTION

The Brevera Breast Biopsy System integrates tissue acquisition, real time imaging, and post biopsy handling all during the same procedure. This device has received FDA 510k Clearance (K163052). All commercial breast biopsy devices will be utilized according to the product's 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 that study was 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 the above referenced study demonstrated that the device performed to the intended specifications and passed validation for procedures in humans.

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.

The Brevera biopsy needle is single-use and is disposable. The user connects the biopsy needle to a reusable device driver and connects the biopsy device components to the console. The biopsy needle primarily consists of a hollow needle with a side aperture and a sharpened inner cannula that, when connected to the Brevera breast biopsy system, rotates and extends across the aperture to acquire targeted tissue. The Brevera device driver contains mechanical and electrical components that drive needle rotation and advancement. During the biopsy process, vacuum created inside the biopsy device pulls tissue into the aperture. The cannula translates and rotates to cut the tissue. The tissue sample is then aspirated through a tubing line to a tissue filter. Saline is supplied through the biopsy device to lavage the cavity and deliver tissue to the tissue filter.

When the Brevera biopsy needle is connected to the Brevera device driver, the combination is referred to as the Brevera breast biopsy device.

An introducer system, specifically designed for use with the Brevera breast biopsy system, is packaged with the biopsy needle. This introducer maintains access to the targeted area of interest and allows for deployment of a biopsy site marker. The introducer is used to control the variable aperture function of the device. The introducer also prohibits the user from administering medication through the Y-site in the tubing while the device is in the armed (pre-fire) position. The Brevera breast biopsy system with CorLumina imaging technology acquires and displays the radiographic images of core specimens contained in the tissue filter. A tissue filter, specifically designed for use with the Brevera breast biopsy system, is provided with the biopsy needle.

The Brevera breast biopsy system with CorLumina imaging technology also has the capability to display images as well as to transfer these images to external devices. The images acquired with this system are intended to confirm removal of tissue from a suspected lesion or pathology. The system is not intended for diagnostic purposes.

Radiology technologists, surgical personnel, surgeons, radiologists, and pathologists can use the specimen radiography equipment in the Brevera breast biopsy system with CorLumina imaging technology.

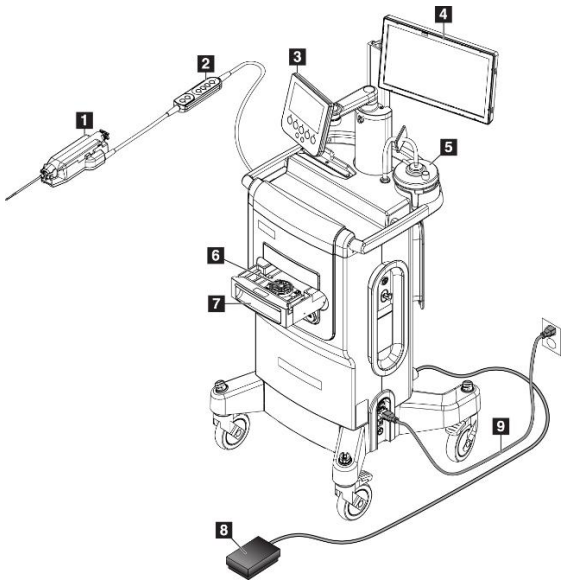


Figure Legend

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.

The control devices for this study will be the current devices already used for breast biopsy procedures.

2.3 Device Accountability

The Hologic operations team will keep records to document the shipment and installation of the commercial Brevera 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 Brevera 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 trial have previous experience with breast biopsy core sampling.

3. TRIAL JUSTIFICATION

This trial will be performed to obtain clinical/operational data and feedback on the Brevera Breast Biopsy System as compared to the current standard-of-care breast biopsy procedures

4. POTENTIAL RISK/BENEFIT

4.1 Potential Clinical Benefit

There are no clinical benefits to the patient. The results learned from this trial could help future patients.

Patients scheduled for a biopsy will still undergo a breast biopsy procedure if they choose not to participate in this trial. The biopsy may be performed with the Brevera or other commercially available system used by the site.

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 listed above are related to biopsy procedures and not necessarily the devices themselves.

4.3 Risk Benefit Rationale

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

5. TRIAL DESIGN

5.1 Trial Objective(s)

The objective of this trial is to obtain clinical/operational data and feedback on the Brevera Breast Biopsy System relative to current standard-of-care breast biopsy systems; and to evaluate potential clinical advantages conferred by the use of the Brevera Breast Biopsy System, such as reduced procedure time.

5.2 Primary Endpoint

The primary endpoint of this trial is the measured difference in procedure time between biopsies performed with the Brevera biopsy system with real time imaging and biopsies performed using the standard-of-care biopsy system at each clinical site.

5.3 Secondary Endpoint(s)

Secondary endpoints to be evaluated in this trial include differences in post-biopsy complication rates, total tissue acquisition by number of cores and sample mass, total tissue used by pathology for diagnosis, and the number of discordant biopsies.

5.4 Trial Design

Prospective, multi-center, block stratified controlled clinical trial. This trial will include collection of the breast imaging exams (both screening and diagnostic work up) leading up to the breast biopsy procedure, which may include mammograms, ultrasound or MRI images as applicable.

The trial procedure will roll out in two phases: 1) a run-in phase consisting of five (5) procedures aimed at familiarizing participating radiologists with the Brevera Breast Biopsy System ; and 2) an analysis phase consisting of a block-randomized acquisition of twenty (20) sequential acquisitions utilizing both standard-of-care biopsy system at each site and the Brevera Breast Biopsy System.

5.4.1 Phase 1 (Run-in Phase)

After obtaining subject informed consent, each radiologist participating in the study will initially use the Brevera Breast Biopsy system for enrollment of his or her first five (5) cases. The run-phase will allow

each participating radiologists to become familiar with the use of a new device. The five (5) cases per radiologist completed will be compared to the Brevera cases completed in Phase 2 for the same outcomes listed in sections 5.2 and 5.3 above so as to provide informational data related to the training and adoption of the Brevera Breast Biopsy System.

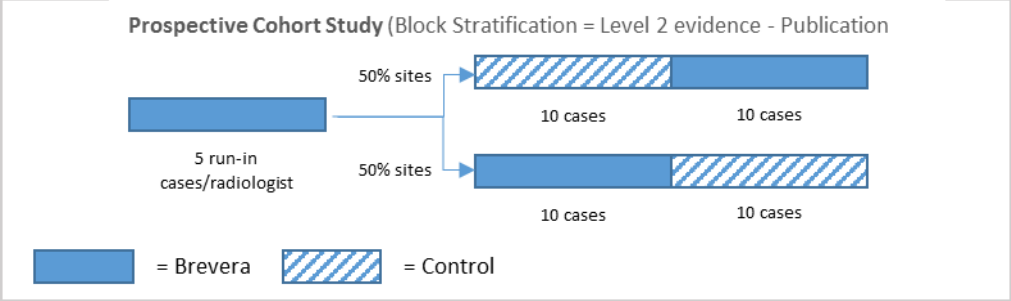
Once a clinician has completed his or her initial five (5) run-in cases, they may begin phase 2 of the study. Note that each individual radiologist participating in the study must complete their initial five (5) cases prior to beginning Phase 2; however, each individual participant may complete the initial five (5) cases at different times. Example: it may be expected that the first participating radiologist at a given site may begin in phase 2 while the second and/or third participating radiologist at the same site in the study are still completing their five run-in cases.

*5.4.2 **Phase 2 (Block Stratification Phase) –***

Each individual radiologist will enroll a maximum of twenty (20) subjects, and a maximum of three (3) radiologists may participate in this study from each representative study site. After a radiologist completes his or her five (5) cases with Brevera in Phase (1), each site will begin to sequentially enroll subjects based on a block-stratified randomization. Subjects will either be enrolled to have their biopsy procedure performed using current standard-of-care breast biopsy procedures at the site or Brevera Breast Biopsy procedures based on the block diagram given in Figure.

Randomization of enrollment will be determined prior to study start-up and provided to each site. Each radiologist will enroll 20 total subjects as part of the block stratification phase as defined in Figure 2.

Figure 2: Study Design Outline



Case Report Forms related to procedural data and 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 breast 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 breast biopsy procedure, her direct participation in the trial is concluded. There are no follow-up visits required for participation in this trial..

Surveys will be collected via paper forms to capture the questionnaire data, and subsequently abstracted into an Electronic Data Capture (EDC) system. The results of the survey questions and images obtained will be compiled and used to support marketing claims and publications, as applicable.

5.5 Trial Outcomes

Clinical data and the survey scores from clinicians, patients, and technologists obtained directly after using the Brevera Breast Biopsy System and standard-of-care breast biopsy procedures will be compared for overall preference and performance of the biopsy systems.

5.6 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 will have data and procedure metrics will evaluated from the beginning of the procedure through their release from the outpatient treatment facility. Pathology results will be recorded following the procedure once they become available.

Table 2 - 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

5.7 Subjects

This trial will recruit up to 525 females 18 years of age or older with suspicious findings on mammographic screening or diagnostic exam who are sent for biopsy. The overall recruitment numbers include the five (5) run in cases per radiologist at each site.

5.7.1 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 trial specific informed consent form after the nature of the trial has been fully explained to her

5.7.2 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.

5.7.3 Informed Consent & Enrollment Procedures

Although the device in this trial has received FDA clearance 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 trial 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 trial that are relevant to the subject's decision to participate throughout the clinical trial;
- 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 trial;
- 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 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 trial.

5.7.4 Subject Withdrawal/Discontinuation

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

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

5.8 Expected Trial Duration

Study Start: Q3/2017
Enrollment Completion: Q1/2018
Final Report: Q2/2018

6. TRIAL PROCEDURES

The trial 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 breast biopsy procedure. The biopsy procedures will be done consistent with current clinician direction/standard-of-care.

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.

Patients will be enrolled using a block randomization. Each clinician will complete ten (10) patients in block 1 and ten (10) patients in block 2. (Blocks will be defined as either the Standard-of-care biopsy system or the Brevera Biopsy system). A clinician must complete block 1 before moving on to block 2.

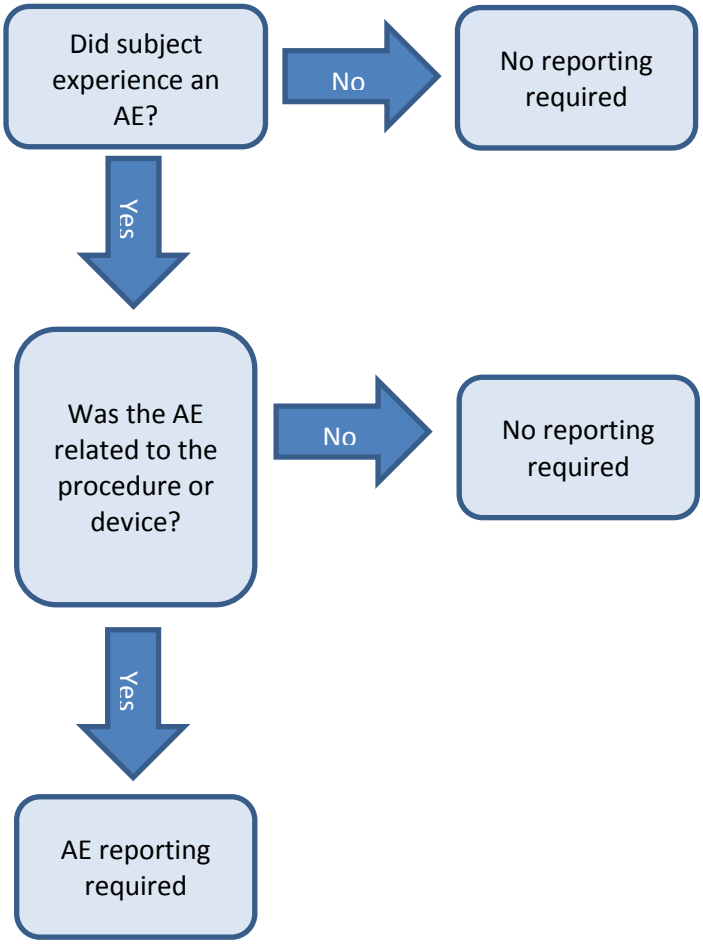
Clinical data will be collected on the procedure within each block by patient procedure. The procedures will collect data related to time of procedure, number of cores collected, post biopsy results and survey data on the system.

6.1 Safety/Device Assessment

6.1.1 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 trial 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 trial following treatment to the study sponsor, Hologic, Inc. See Figure 3 below for the AE reporting flowchart.

Figure 3: 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 trial participation.

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

6.1.2 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

6.1.3 Adverse Device Effect

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

6.1.4 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 trial.

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

6.1.5 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.

6.2 Reporting Procedures

6.2.1 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 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:
Brian Sundell
Clinical Project Manager – Hologic
Brian.Sundell@Hologic.com
781-999-7515

7. TRIAL MONITORING

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

7.1 Monitor Training

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

7.2 Site/Investigator Training

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

7.3 Site Monitoring

Hologic and/or designee may conduct periodic compliance assessments at the trial site(s). Hologic and/or designee may request access to all trial 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 trial, 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 trial (e.g., Form FDA 483, Inspectional Observations and Warning Letters). Hologic may provide needed assistance in responding to regulatory audits.

8. STATISTICAL CONSIDERATIONS

7 clinical trial sites each with 3 radiologists performing 20 biopsies (10 with local standard-of-care, and 10 with the Brevera Breast Biopsy System, as per randomization procedure) results in a total of 420 subjects enrolled in phase 2. This sample size achieves approximately 80% power to detect a difference in mean procedure time of 3 minutes between the Brevera and standard of care biopsy systems assuming a standard deviation of 12 minutes in procedure time and an intraclass correlation of 0.150 at a standard significance level of alpha=0.05. Mixed effects regression will be utilized to assess the impact of the biopsy device (e.g., Brevera or local standard-of-care) on total procedure time, post-biopsy complication rates and differences in discordant biopsies. For these analyses, biopsy device type, subject physical habitus and lesion location (i.e., “near the chest wall or axilla?” yes/no) will be considered fixed effects, and site and radiologist will be considered random effects. Total tissue acquisition by number of cores, total acquired sample mass, and total tissue utilized by pathology for diagnosis will be compared between the Brevera system and local standard-of-care using Analysis of Variance (ANOVA) testing. Lastly, sub-analyses will be performed to look at specific comparisons between the Brevera system and other biopsy systems if multiple sites utilize the same biopsy system as their standard-of-care device.

9. DATA HANDLING AND RECORD KEEPING

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

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 trial will obtain informed consent and survey data for 525 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 trial. 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

Trial 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 trial records. Records shall be maintained during the clinical trial and for at least six years after the later of the date on which the trial 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 trial 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 Trial Plan/Protocol***: A current copy of the Clinical Trial Protocol including Instructions for Use of the System and blank case report forms.
- ***Institutional Review Board (IRB) Information***: All information pertaining to IRB/EC review and approval of this clinical trial including a copy of the IRB/EC letter approving the clinical trial, 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 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 trial subjects, a summary of follow-up data and complications and a general description of the trial progress.
- ***Final Report***: Hologic shall provide to the Investigator a final report within three months of termination or completion of the trial or that Investigator's participation in the trial, to provide to the IRB.
- ***Other Reports***: Upon the request of Regulatory Agency/FDA, the reviewing IRB, or Hologic or designee, the Investigator will provide accurate and timely information about any aspect of the clinical trial.

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 trial. Trial 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 trial. Such deviations shall be documented and reported to Hologic and the IRB as soon as possible.

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

All deviations are reviewed and assessed for their impact on patient safety by Hologic or designee. The PI and trial staff is responsible for knowing and adhering to their 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 trial-related activities;
- Failure to report 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 trial site personnel or persistent protocol deviation may result in termination of the site's trial 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 site knowledge of the deviation by contact to Hologic and/or designee. Any protocol deviations that affect the rights, safety or well-being of the subject or the scientific integrity of the clinical trial must be reported within 24 hours to Hologic and IRB, if required by the IRB or national regulations.

10.4 Trial Audit(s)

The auditing of clinical trial 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 trial audit shall be guided by the importance of the clinical trial, the number of subjects in the clinical trial, the type and complexity of the clinical trial, 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 trial 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 trial shall not begin until the required approval/favorable opinion from the IRB or regulatory authority have been obtained, if appropriate.

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

11.2 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 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 trial and continues throughout the individual's trial participation. Extensive discussion of risks and possible benefits of this trial will be provided to the subjects and their families. Consent forms describing in detail the trial procedures, and risks are given to the subject and written documentation of informed consent is required prior to the trial procedure. Consent forms will be 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 trial 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 trial. The subject should have the opportunity to discuss the trial with their surrogates or think about it prior to agreeing to participate, unless trial timeframes do not allow for such discussions. The subjects may withdraw consent at any time throughout the course of the trial. 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 trial.

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 trial 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 trial for monitoring, audits, 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 trial.

12. PROTOCOL AMENDMENTS

The Protocol, informed consent form, or other clinical trial documents shall be amended as needed throughout the clinical trial, 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 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 trial objectives or endpoints, a simple notification to the IRB and, where appropriate, regulatory authorities can be sufficient. The version number and date of amendments shall be documented.

13. TERMINATION OF TRIAL OR TRIAL SITE PARTICIPATION

Hologic may terminate the trial at any time. If the trial 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 trial site participation and remove appropriate trial 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 trial participation with suitable written notice to Hologic.

14. PUBLICATION POLICY

As detailed in the trial agreement. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law.

14.1 Investigator Agreement

Investigator Responsibility

Prior to participation in the trial, the appointed Principal Investigator at the trial 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 and/or designee, along with the IRB/EC approved Informed Consent Form.

The Principal Investigator must also:

- Conduct the trial in accordance with the trial protocol, the signed Clinical Trial 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 trial 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 trial or up to one year following the closure of the trial;
- Provide Hologic with curriculum vitae, information regarding previous clinical trial experiences (including studies or research that was terminated);
- Assure that the trial 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 trial 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 trial data with patient's medical records;
- Allow staff of Hologic and its authorized representatives, as well as representatives from regulatory bodies, to review, inspect any documents pertaining to this clinical trial; and,
- Oversee retention of required records and documents related to the trial.

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 trial, including obtaining and documenting patient informed consent, compliance with the trial 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 trial 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.

Trial 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*): _____