Clinical Protocol Version K

Dated Jan 6, 2020

Protocol Title: An Open Label, Phase 2 Pharmacokinetic Study of Pre-Surgical Intramuscular and Intraductal Fulvestrant in Women with Invasive Breast Cancer or DCIS Undergoing Mastectomy or Lumpectomy

NCT: 02540330

An Open Label, Phase 2 Pharmacokinetic Study of Pre-Surgical Intramuscular and Intraductal Fulvestrant in Women with Invasive Breast Cancer or DCIS Undergoing Mastectomy or Lumpectomy

Protocol Number: **ATOS-2015-007**

Protocol Date: **Jan 06, 2020**

Protocol Version **K**

Sponsor: **Atossa Genetics, Inc.**
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Jan 06, 2020	**K**

The following signatures verify that the Clinical Research Study presented in this protocol is clearly understood and agreed upon. The requirements of the protocol including study design, subject selection, and expected outcomes are consistent with the technology being studied. The effort is feasible in terms of resources and testing requirements. Upon approval, this protocol may be implemented provided the appropriate institutional review board or ethics committee approval has been obtained and the Investigator's Agreement associated with the implementation of this study has been completed.

Signature of Sponsor Representative:
Name of Sponsor Representative: Janet R Rea, MSPH, RAC
Date:

1.0 INVESTIGATOR'S AGREEMENT

I have received a copy of the protocol number ATOS-2015-007, entitled "*An Open Label, Phase 2 Pharmacokinetic Study of Pre-Surgical Intramuscular and Intraductal Fulvestrant in Women with Invasive Breast Cancer or DCIS Undergoing Mastectomy or Lumpectomy*", Version K" dated January 06, 2020, from Atossa Genetics, Inc. I agree to the conditions as set out in this protocol and fully accept that any change requires prior written approval from Atossa. Additionally, I agree to carry out this protocol in accordance with ICH Guidelines; all applicable US Regulations (21 CFR parts 50, 54, 56 and 312) and Good Clinical Practice Guidelines, as applicable. Finally, I will ensure that the investigational agent and/or device will be used only as described in this protocol.

The information contained in this protocol is provided to me in confidence, for review only by myself, the Independent Ethics Committee/Investigational Review Board authorized to review and approve the study at this study site, the designated research staff participating in this clinical study, and applicable regulatory agencies.

I understand that the information/technology contained in this protocol is proprietary and may not be disclosed to any other party, in any form, without prior authorization from Atossa, except to the extent necessary to obtain informed consent from potential study participants.

Signature of Investigator; Date Signed

Lisa Jacobs, MD **Date**

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2.0 CLINICAL TRIAL SYNOPSIS

Study Title	An Open Label, Phase 2 Pharmacokinetic Study of Pre-Surgical Intramuscular and Intraductal Fulvestrant in Women with Invasive Breast Cancer or DCIS Undergoing Mastectomy or Lumpectomy
Study Number	ATOS-2015-007
Objectives	To study the safety and tolerability of intraductal administration of fulvestrant (Faslodex®, ICI 182,780) in women with Stage 1 or 2 invasive ductal carcinoma (or mixed ductal and lobular) or DCIS, prior to mastectomy or lumpectomy. To determine the pathological effects, specifically changes in Ki67, ER/PgR expression between the pre-fulvestrant biopsy and the post-fulvestrant surgical specimen. To compare an abbreviated (Pharmacokinetic-PK) profile of standard intramuscularly administered (500 mg) with the intraductal instillation of single-dose (500 mg maximum) fulvestrant. To determine and compare breast tissue fulvestrant distribution.
Study Drug	Fulvestrant (Faslodex®)
Study Design	This is a single-dose observational and comparative study
No. of Subjects	30 evaluable subjects with breast cancer and scheduled for mastectomy or lumpectomy.
Routes of Administration	Intramuscularly (n = 6) and intraductally (n = 24)
Dosage (Single dose)	Intramuscularly: 500 mg – to establish reference proliferation markers (Ki67) responses and PK-values. Intraductally: up to 500 mg
Delivery Device	Intramuscularly: Fulvestrant is supplied, from the manufacturer, as two, 5-mL prefilled syringes, containing 50 mg/mL (250 mg/syringe) Intraductally: Jabczenski Ductogram Cannula® Microcatheter or IntrocanSafety® IV Catheter and the FullCYTE® Breast Aspirator. Detailed instructions for intraductal fulvestrant administration are located in the administration manual provided
Inclusion Criteria	1. Female 2. 18 years of age or older 3. Scheduled to undergo mastectomy or lumpectomy for Invasive Breast Cancer (clinical stage 1 or 2, ER+ low- to medium grade) or DCIS 4. Pathological diagnosis of Invasive Ductal Carcinoma or Ductal Carcinoma *in Situ* (DCIS) requiring mastectomy or lumpectomy. Mixed ductal and lobular tumors are permitted). 5. Estrogen Receptor positive biopsy, as determined from a biopsy specimen obtained no more than 3 months prior to entry 6. ECOG performance scale of 0-1 (Appendix A) 7. Adequate organ function as defined by the following criteria: a. Absolute neutrophil count (ANC) ≥ 1500/μL b. Platelets ≥ 100,000/μL c. Hemoglobin ≥ 9.0 g/dL d. Creatinine ≤ 2 times upper limit of normal e. Bilirubin ≤ 2 times upper limit of normal f. Transaminases (AST/SGOT and ALT/SGPT) ≤ 2.5 times upper limit of normal 8. Able to sign informed consent 9. Willing to use effective contraception for at least 100-days post study drug administration if subject is pre-menopausal.

Exclusion Criteria	1. Concurrent treatment with another anti-estrogen 2. Presence of an active infection requiring systemic therapy. 3. The following conditions contra-indicating fulvestrant administration: a. Subjects with bleeding diatheses, thrombocytopenia or current anticoagulant use (excludes aspirin or anti-inflammatory agents) b. Subjects with a known hypersensitivity to fulvestrant or any of its formulation components including castor oil, alcohol, benzyl alcohol, and benzyl benzoate. c. Severe hepatic impairment. 4. Prior surgery on the ipsilateral breast which interrupts communication of the ductal systems with the nipple 5. Prior radiation to the breast 6. Pregnant or lactating 7. Impaired cardiac function or history of cardiac problems of NYHA Class 111 and IV 8. Poor nutritional state as indicated by a BMI of below 20 9. Presence of serious infection not controlled with systemic therapy 10. History of allergies to Lidocaine or Novocain 11. Concurrent participation in an experimental drug study
Study Duration	Total 12 – 36 months, active phase 6 weeks followed by inactive phase (enrollment dependent)
No. of Trial Sites	One.
Study Rationale	This study is being conducted to develop the preliminary safety and feasibility of this route of administration to provide information necessary to develop future clinical studies.

3.0 LIST OF ABBREVIATIONS & DEFINITION OF TERMS

ADH	Atypical ductal hyperplasia
AE	Adverse Event
AI	Aromatase inhibitor
AIC	Akaike Information Criterion
Alb	Albumin
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATOS	Atossa Genetics, Inc.
AUC	Area under curve
BSA	Body Surface Area
BUN	Blood urea nitrogen
CFR	The United States Code of Federal Regulations
Cr	Creatinine
CRA	Clinical research associate
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
CTMF	Clinical Trial Master File
DMP	Data Management Plan
DCIS	Ductal Carcinoma *In Situ*
DLT	Dose limiting toxicities
ER	Estrogen receptor
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
Glu	Glucose
HE	Hematoxylin and eosin
HPLC	high performance liquid chromatography
H & P	History & Physical
ICH	International Conference on Harmonization
ID	identification
IM	Intramuscular
IRB/IEC	Institutional Review Board/Institutional Ethics Committee
K	potassium
mg	milligrams
mL	milliliter
MRI	Magnetic resonance imaging
Na	Sodium
NAF	Nipple aspirate fluid
NCI	National Cancer Institute (United States)
NYHA	**New York Heart Association**
PgR	Progesterone Receptor
PK	Pharmacokinetics
PLD	Pegylated liposomal doxorubicin, trade name Doxil®
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SAE	Serious adverse event
SERM	Selective estrogen receptor modulator
Tbili	Total bilirubin

4.0 BACKGROUND INFORMATION

Breast cancer is the leading cause of cancer in women in the United States and the second leading cause of cancer related death. An estimated 215,000 American women will be diagnosed with breast cancer in 2015 and over 39,000 women will die due to their disease. Approximately 1 in 8 women in the United States will be diagnosed with breast cancer in their lifetime.[1] Because of the increased incidence in breast cancer, both *in situ* and invasive, much research has been done to identify those women at risk for the disease and ways to prevent it from occurring. Only two Selective Estrogen Receptor Modulators (SERMs), tamoxifen and raloxifene, are currently approved in the USA for the prevention of breast cancer in high-risk women. The aromatase inhibitors examestane and anastrozole have been evaluated successfully in randomized trials, but have not been approved in the US specifically for a prevention indication.

Based upon demographics and registries, data reflect that women whose first-degree relatives (e.g., mother, sister or daughter) have had breast cancer are 3 to 4 times more likely to develop breast cancer than those without family history. A woman's reproductive history, menopausal status, prior breast surgeries or breast abnormalities also increases her risk of developing breast cancer. Currently, several different statistical models, such as the Gail, IBIS and Claus models, exist which attempt to predict the 5-year, 10-year and lifetime risk of women to develop breast cancer. The models are based upon the subject's reproductive history as well as family history related to cancer, specifically breast cancer.[2, 3, 4] These models have been useful in identifying subjects at increased risk for developing breast cancer, and selection for genetic counseling or more intensive diagnostic surveillance, but do not appear to have spurred the development of new chemo-preventive strategies. The mission of this study's Sponsor, Atossa Genetics Inc. (ATOS), is to reduce the risk for breast cancer and reduce the morbidity associated with breast cancer by developing a local, minimally invasive therapy with fewer side effects than typically seen with systemic therapy.

The currently available options for prevention are oophorectomy (surgical removal of the ovaries), bilateral mastectomy, or pharmaceutical therapy, such as tamoxifen or anastrozole.[5, 6, 7] None of these options for prevention are without side effects or consequences. Oophorectomy is associated with the side effects associated with early menopause. Surgical removal of the breast tissue, although successful in reducing the likelihood of developing breast cancer by 97% is a lengthy and morbid surgery, not without complications. With long-term systemic use, tamoxifen puts women at risk for thromboembolism, cataracts, uterine cancer, and vasomotor events.[7] Much research is being conducted looking at aromatase inhibitors (AI) for prevention; however, the risk of osteoporotic fractures and complications, such as osteonecrosis of the jaw are substantial with these drugs and may preclude AIs as a viable prevention option in a majority of women.[8]

Although breast cancers are being detected at a much earlier stage and there is considerable work being done with systemically administered agents such as SERMs and AIs to prevent breast cancer, little work with regards to prevention has been done with agents administered locally, either topically on the skin, or instilled directly into the milk ducts via intraductal therapy, as proposed in this study. It is recognized that the majority of breast cancer begins in the lining of the duct.[9] Atypical lesions, such as atypical ductal hyperplasia (ADH) are thought to progress to ductal carcinoma in situ (DCIS) and to invasive

cancer, with a diagnosis of ADH conferring a 30-35% lifetime risk of developing invasive breast cancer[10]. For purposes of preventing breast cancer there is strong rationale to identify these epithelial changes and stop them from ever developing in to carcinoma.

Providing a local therapy into the ducts could reduce the morbidity associated with prevention while targeting the potential carcinoma cell.

This approach is possible because of the anatomy of the breast ductal systems. Cooper did extensive studies in 1845, and noted that there were commonly 7-10 ducts.[11] Subsequently, Sartorius performed mammographic studies, and determined there are 5-9 breast ducts, which coincides with Dietz's findings.[12, 13] A study by Love examined the anatomy of the breast using six complementary *in vivo* and *in vitro* approaches to determine the number, distribution and anatomical properties of the ductal systems of the breast which extend from the nipple orifices to the terminal duct lobular units.[14] Over 90% of the nipples studied contain 5-9 ductal orifices, generally arranged as a central group and a peripheral group. Each nipple orifice communicates with separate non-anastomosing ductal systems which extend to the terminal duct lobular units.

The idea of examining the breast ducts and ductal fluid to understand breast carcinogenesis is not a new concept. The first description by LeBourgne in 1946 was termed "ductal rinse."[15] He inserted a small catheter into the breast duct and instilled saline, removed the catheter and collected the saline as it dripped out of the ductal opening. Subsequently, in 1958, Papanicolaou, also examined breast duct fluid by placing a suction cup on the nipple to elicit small drops of fluid from the breast.[16] He studied the cells that were in the fluid in an attempt to identify abnormalities or cancer, similar to what had been accomplished by the Pap Smear and cervical cytology. Although Papanicolaou was able to identify DCIS in a cellular smear of the nipple aspirate fluid (NAF), there was little to be done with the procedure as there was no therapy available to women other than a mastectomy, which was problematic for those with atypical cells as their significance was still unknown. Because of a lack of appropriate therapy and the advent of mammography, the examination of ductal fluid and nipple ducts fell to the wayside and was not revisited again until the 1970s.

Several researchers in the 1970s began examining ductal fluid by utilizing the suction cup method and analyzing the NAF. Their research revealed that the presence of NAF alone increased the risk of developing breast cancer. Furthermore, that risk became more significant if cellular atypia was identified in the NAF. The risk further increased if the woman had a family history of breast cancer.[17, 18, 19] Additionally, Sartorius, further examined the breast ducts in a similar fashion as LaBourgne, by cannulating the nipple ducts whose NAF contained atypical cells under microscopic examination.[20] After cannulating the ducts, he instilled contrast material, performed a mammogram, then collected the contrast material out of the duct and analyzed it under the microscope. His research demonstrated that the presence of atypical cells in ductal fluid had a significant impact on the risk of developing breast cancer, similar to what had been demonstrated in NAF.

Based upon these compelling results, clinicians began exploring the collection of NAF as well as instilling fluid into the ducts and collecting it, "ductal lavage." One such researcher, Love, developed a small catheter to be used to instill fluid as well as collect fluid

from the breast nipple ducts. The catheter was commercialized through a medical device company, ProDuct Health, Inc. (Menlo Park, CA), which was later acquired by Cytyc, Inc. (Marlborough, MA, USA) in 2001, which in turn was acquired by Hologic (Waltham, MA, USA). Hologic sold the license to the catheters to Atossa Genetics, but unfortunately, it is no longer available.

Initial research shows much promise with regard to intraductal infusion in order to reduce the risk of breast cancer. Researchers have recently demonstrated the feasibility of intraductal delivery of epirubicin. Goulet and colleagues encapsulated epirubicin, a naturally fluorescent anthracycline, into biodegradable nanoparticles. The nanoparticles were then administered into mastectomy specimens in the operating room immediately after a mastectomy was performed, and the tumor specimen was removed for pathologic assessment. They reported that intact epirubicin was seen in the terminal lobules in 8 of 13 specimens.[21] This pilot study demonstrated that it is feasible to use the microcatheter to cannulate the breast ducts and infuse a substance throughout a specific duct, all the way to the terminal lobules.

Based upon numerous preclinical studies in rats and mice, Love reported the feasibility of administering intraductal pegylated liposomal doxorubicin (PLD) or Doxil® into one duct of a woman with a history of breast cancer scheduled for a prophylactic contralateral mastectomy in the unaffected side. The subject reported no discomfort during the procedure and no problems after the procedure. Six weeks subsequent to the procedure, the subject underwent mastectomy histological changes were noted in the lining of the ducts. There was not an opportunity to study the effect of the drug on cancer, as the subject was cancer free.[22] More recently, researchers at Johns Hopkins University determined the intraductal approach to breast cancer and prevention to be of great importance. Dr. Vered Stearns and her colleagues at Johns Hopkins University reported a clinical study administering Doxil into the breast ducts containing cancer of women prior to mastectomy. [23]

In collaboration with Dr. Susan Love, Dr. Wei Zhang and the Cancer Institute & Hospital at the Chinese Academy of Medical Science conducted a study in 2007 comparing intraductal pegylated doxorubicin, methotrexate and carboplatin in 31 women scheduled to undergo mastectomy. Published results of this study showed that intraductal administration was feasible, but it was suggested that duct perforation led to erratic pharmacokinetics. Study results and conclusion warrant the exploration of additional – possibly less toxic, agents for intraductal therapy. [24]

Building on to these prior studies with cytotoxic agents, this study utilizes the pure anti-estrogen fulvestrant to be injected in up to 5 ducts to determine its effect on the cancer or DCIS as well as the safety of this administration method.

5.0 CLINICAL USE OF THE ANTI-ESTROGEN FULVESTRANT (FASLODEX®)

Fulvestrant is the only endocrine therapy targeting the ER receptor that has been shown to have efficacy in tamoxifen resistant cancers in Phase 3 clinical trials. Two randomized trials have compared the efficacy of fulvestrant 250 mg IM with 1 mg oral anastrozole in postmenopausal women with advanced breast cancer whose disease had progressed after prior endocrine therapy.[31] A combined analysis of these trials showed that fulvestrant was as least as effective as anastrozole (5.5 versus 4.1 months, respectively). Based on these trial

results, fulvestrant gained approval as an intramuscular injection of 250 mg once monthly dose level as a second-line treatment for postmenopausal women with hormone- sensitive breast cancer.[31]

A subsequent randomized trial, CONFIRM, compared 250 mg with 500 mg monthly fulvestrant in 736 women and established a 500 mg dose to be superior in terms of Progression-free survival. At 18 months median follow-up PFS was 6.5 months in the 500 mg arm and 5.4 months in the 250 mg arm (p=0.006). This study established 500 mg as the standard dose as described in the product labeling in the US and Europe, with a dose of 250 mg recommended for subjects with moderate hepatic impairment. [31]

Neo-adjuvant use of fulvestrant in postmenopausal women with newly diagnosed invasive breast cancer was evaluated in the randomized "NEWEST" Phase 2 study, which randomized 211 subjects between 500 mg and 250 mg monthly intramuscular fulvestrant (with an extra dose on Day 14 of Month 1) for 16 weeks until surgery. Similar as in the study described in this protocol, change in Ki67 proliferation index 4 weeks after fulvestrant was the primary endpoint. By 4 weeks, the change from baseline in Ki67 labeling index was significantly different between the groups (-78.8 vs. -47.4%, p<0.0001). Changes from baseline in ER expression were also significantly different between the groups (p< 0.0002), but changes in PgR expression were not. No safety concerns were identified. [25]

5.1 Intraductal Doses of Cytotoxic versus Endocrine Agents

Most cytotoxic agents are given based upon BSA, whereas endocrine agents such as fulvestrant or tamoxifen are not.

Consequently, the dose used in this study will not be tailored to BSA or body weight. The maximum dose of 500 mg selected for the study is based on US labeled Intra-Muscular (IM) dose. Since milk ducts differ in size and volume, it may not be possible to administer 500 mg (10 mL) in all subjects.

It is possible, but unlikely, that peak plasma concentrations of a dose given intraductally will reach the same level as the same dose given intramuscularly (IM). This is because the agent must diffuse out of the ducts to reach the bloodstream. Eventually the entire dose will be taken up systemically but it will happen over a longer period of time (the peak plasma concentration will be lower but the area under curve [AUC] should be the same). Hence it was decided that the total amount of drug given in a single intraductal installation would not be higher than the typical IM dose of fulvestrant. There will be 5 groups, each consisting of 6 subjects. The first subject of each group will receive fulvestrant administered intramuscularly and the next 5 subjects will receive fulvestrant intraductally.

A maximum of two 5 mL vials, each containing 250 mg fulvestrant may be delivered into one duct or distributed among up to five ducts targeted for intraductal instillation. Ductal systems range in shape, size and volume just as breasts range in shape and size.[26] As noted before, there are a range of ducts (from 5-9) and each duct within a breast is a different size. [11, 12, 13] The ductal systems have the capacity to accommodate a significant amount of fluid. In a breast feeding woman, a single breast can accommodate anywhere from 47.2 mL to 62.8 mL .[27, 28] In a non-lactating woman, it is estimated that each breast duct can be distended with as little as 1 mL and may accommodate up to 20 mL without perforation and only mild discomfort.[29] Based on prior experience with intraductal therapy it was determined that no

single breast would be administered > 10 mL of fulvestrant, to be divided among up to 5 ducts targeted for instillation. This amount, in a non-lactating subject, would limit the risk of perforation and discomfort associated with intraductal instillation.

5.2 Intraductal Effects of Endocrine Agents

An important strategy in achieving Atossa's goal of developing treatments for the prevention of breast cancer and tissue-sparing alternatives to radical surgery for those with diagnosed breast cancer/DCIS, is to repurpose endocrine agents which are currently available and proven to be effective in treating cancer as a method of prevention. In order to study this, initially, subjects with invasive breast cancer or DCIS will be evaluated.

Atossa plans to evaluate the effect of fulvestrant on the ducts with breast cancer/DCIS as well as ducts without breast cancer in each subject treated in this trial.

5.3 Drug Plasma Concentration Levels

It is estimated that fulvestrant plasma levels at any given time point will be at most the same but more likely less than the levels experienced with IM delivery. It is possible but unlikely that fulvestrant will be concentrated in the plasma at the same level as when given IM but this will be further assessed in this clinical trial.

This clinical trial represents a first step to assess the feasibility and safety of intraductal endocrine therapy with fulvestrant. Hence an understanding of the pharmacokinetic effects of this route of administration is imperative.

6.0 TRIAL OBJECTIVES AND PURPOSES

6.1 Primary Objective

To study the safety and tolerability of intraductal administration of fulvestrant (Faslodex, ICI 182,780) in women with Stage 1 or 2 invasive ductal carcinoma (or mixed ductal and lobular) or DCIS, prior to mastectomy or lumpectomy.

6.2 Secondary Objectives

a. To determine the pathological effects, specifically changes in Ki67, ER/PgR expression between the pre-fulvestrant biopsy and the post-fulvestrant surgical specimen.

b. To compare an abbreviated (PK) profile of standard intramuscularly administered (500 mg) with the intraductal instillation of single-dose (500 mg maximum) fulvestrant.

c. To determine and compare breast tissue fulvestrant distribution.

7.0 TRIAL DESIGN

This is an open-label, non-randomized pharmacokinetic study of pre-surgical fulvestrant in women scheduled for mastectomy or lumpectomy. Eligible subjects will be identified upon admission to the institution for surgical management of breast cancer or DCIS, specifically mastectomy or lumpectomy. There will be 5 groups, each consisting of 6 subjects. The first subject of each group will receive fulvestrant administered intramuscularly and the next 5 subjects will receive fulvestrant intraductally. Subjects where at least 1 suitable duct is identified may undergo nipple aspiration in order to facilitate duct identification and

intraductal infusion of a fulvestrant accompanied by imaging (saline+ ultrasound). A maximum of 5 ducts will receive intraductal infusion of fulvestrant. Across all ducts, the total dose will not exceed 500 mg (10 mL). All subjects will be monitored for systemic and local adverse events during the procedure, immediately following the procedure, within 30 minutes, 1 hour, 4 hours and by phone following discharge on Days +1 and +2, +7, and pre-operative. Subsequent to mastectomy or lumpectomy, subjects will be assessed for systemic adverse events until discharge. Per schedule specified in Table 1, subjects will undergo serial blood draws to determine fulvestrant blood concentration levels.

When fulvestrant is administered at or below the dose level of 500 mg currently in routine clinical use, emergence of Dose Limiting Toxicities (DLT) is unlikely, but not impossible.

Since only a single instillation of fulvestrant is given in this protocol, dose reduction in individual subjects is not possible. However, if any of the DLT parameters reaches any of the thresholds values set in Section 10.3 the dose in subsequent subjects will be reduced to 250 mg (one 5 mL vial).

The purpose of this observational study is to understand the safety and tolerability of giving the anti-estrogen drug fulvestrant directly into the milk ducts of the breast, and collect any evidence of pathologic response. This study will be conducted under good clinical practice (GCP) guidelines as outlined in Section 15.5 Good Clinical Practice. This will be a single-dose study with two treatment groups: 500 mg administered intramuscularly (n=6) and up to 500 mg administered intraductally (n=24).

8.0 SELECTION AND WITHDRAWAL OF SUBJECTS

This trial will enroll at least 30 eligible subjects for participation to result in 30 evaluable subjects.

8.1 Selection Criteria

8.1.1 Inclusion Criteria:

1. Female
2. 18 years of age or older
3. Scheduled to undergo mastectomy or lumpectomy for Invasive Breast Cancer (clinical stage 1 or 2, ER+ low-to intermediate-grade) or DCIS
4. Pathological diagnosis of Invasive Ductal Carcinoma or Ductal Carcinoma *in Situ* (DCIS) requiring mastectomy or lumpectomy (Mixed ductal and lobular carcinoma acceptable)
5. Estrogen Receptor positive biopsy, as determined from a biopsy specimen obtained no more than 3 months prior to entry
6. ECOG performance scale of 0-1 (Appendix A)
7. Adequate organ function as defined by the following criteria:
    a. Absolute neutrophil count (ANC) ≥ 1500/µL
    b. Platelets ≥ 100,000/µL
    c. Hemoglobin ≥ 9.0 g/dL
    d. Creatinine ≤ 2 times upper limit of normal

e. Bilirubin ≤ 2 times upper limit of normal
f. Transaminases (AST/SGOT and ALT/SGPT) ≤ 2.5 times upper limit of normal

8. Able to sign informed consent
9. Willing to use effective contraception for at least 100 days post study drug administration if subject is pre-menopausal.

8.1.2 Exclusion Criteria:

1. Concurrent treatment with another anti-estrogen
2. Presence of an active infection requiring systemic therapy.
3. The following conditions contra-indicating fulvestrant administration:
   a. Subjects with bleeding diatheses, thrombocytopenia or current anticoagulant use (excluding aspirin and anti-inflammatories)
   b. Subjects with a known hypersensitivity to fulvestrant or any of its formulation components including castor oil, alcohol, benzyl alcohol, and benzyl benzoate.
   c. Severe hepatic impairment.
4. Prior surgery on the ipsilateral breast which interrupts communication of the ductal systems with the nipple
5. Prior radiation to the breast
6. Pregnant or lactating
7. Impaired cardiac function or history of cardiac problems of NYHA Class 111 and IV (Appendix C 20.4)
8. Poor nutritional state as indicated by a BMI below 20. -
9. Presence of serious infection not controlled with systemic therapy
10. History of allergies to Lidocaine or Novocain
11. Concurrent participation in an experimental drug study.

8.2 Inclusion of Special Populations

Only women will be enrolled in this trial; men lack an anatomically accessible duct system. There will not be anyone included under the age of 18 nor will pregnant women participate in this trial. All race and ethnic groups are eligible to participate.

8.3 Determination of Eligibility

Once the clinician has obtained a signed informed consent, subjects will be registered with the study coordinator and investigator. Additional testing, beyond routine pre-operative testing which may be required to determine eligibility, will be performed. This is outlined below under Section 9.2 Baseline Assessment After eligibility is established, each subject will be assigned a study number to identify them individually. Subjects will not undergo any study related drug administration until eligibility is confirmed with additional testing if necessary and the subject receives a study number.

8.4 Subject Discontinuation

All subjects have the right to terminate participation in the study at any time. The Investigator also has the right to discontinue the subject's participation at any time

regardless of whether the subject wishes to continue in the study. The Sponsor may discontinue the study at any time.

In addition, subjects may be withdrawn from the study for the following reasons:

- Occurrence of a clinically unacceptable AE
- Violation of the study protocol or lack of compliance with protocol regimens
- Subject declines further study participation
- Subject withdraws informed consent
- Investigator judges it is in the best interest of the subject

If a subject is withdrawn or discontinues study participation, reasonable efforts will be made to bring the subject in to complete the final study procedures. The subject will continue to be followed and medically managed in accordance with the arrangement that was in place prior to study enrollment. The reason(s) for a subject's discontinuation from the study are to be recorded in the source documentation and on the CRFs.

Any subject, who voluntarily or involuntarily withdraws from the study prior to mastectomy or lumpectomy, will be replaced.

9.0 TREATMENT OF SUBJECTS

9.1 Study Related Procedures

After each subject has reviewed and signed the informed consent, she will be enrolled in the study and assigned a study number as outlined below in Section 17.3 Data Collection Requirements. Further testing maybe necessary to determine eligibility and will commence upon enrollment. These tests are included in Section 9.2 Baseline Assessment. Some of the exams, tests or procedures may be a part of routine care for breast cancer and may be used as baseline assessments if conducted no more than 2 weeks prior to participation in the study. Other tests are only being done for the purpose of the study. A member of the study staff will go over, in detail, with each subject the tests that are being done specifically for the study and those that are considered routine care.

All subjects will receive fulvestrant, but the actual total dose received may vary within subjects receiving fulvestrant intraductally, as it is guided by the number of accessible ducts and volume of the ducts.

The first subject of each group will receive intramuscular (IM) fulvestrant (500 mg) and the next five subjects of that group will receive intraductal (ID) fulvestrant up to 500 mg. There are five groups, for a total of 30 subjects. After fulvestrant instillation, both signs and symptoms of local (breast and chest wall) and systemic toxicity will be evaluated using the CTCAE v. 5.0. Each Group – IM; ID, ID, ID, ID, ID.

9.2 Baseline Assessment (Day -14 to -1)

Prior to fulvestrant administration, each subject will undergo testing for baseline data collection. Any baseline tests performed within 2 weeks prior to study enrollment need not be repeated: those data will be considered adequate for baseline evaluation.

Baseline tests include all of the following:

- Registration
- Medical History
- ECOG performance Status
- Vital Sign (blood pressure, pulse, respirations, temperature)
- Digital tumor imaging if a recent digital image is not available
- Complete blood count with differential and platelet counts (includes hemoglobin, hematocrit, platelets and white blood cell count with differential)
- Chemistry panel (Includes Na^+, K^+, BUN/Urea, serum Cr, Glu, Alb, AST, ALT, Tbili)
- Pregnancy test (for women of childbearing potential/pre-menopausal)
- Concomitant Medications
- Clinical Breast Assessment
- Pathological Assessment

If any of these tests or examinations, reveal criteria rendering the subject ineligible, they will be excluded from the study. **All subjects must have at least 14-days between fulvestrant administration and surgery.**

9.3 Day of Fulvestrant Administration (Day 0)

The following procedures should be performed on Day 0 fulvestrant administration:

- Vital signs (blood pressure, pulse, respirations, temperature) - prior to fulvestrant administration
- PK - Plasma Fulvestrant Level (see Table 1)
- Pain Assessment (see Section 9.10)
- Concomitant Medications
- Adverse Events
- Pregnancy test of (for women of child-bearing potential/pre-menopausal)

9.3.1 Intramuscular Administration of Fulvestrant

The first subject of each of group will be treated with single dose 500 mg of intramuscular fulvestrant per the prescribing information, (Appendix 20.3) and can also be found at the following website: http://www.azpicentral.com/faslodex/faslodex.pdf#page=1

9.3.2 Intraductal Administration of Fulvestrant

The second through sixth (2^{nd} through 6^{th}) subject of each of 5 groups will receive intraductally administered fulvestrant Jabczenski Ductogram Cannula Microcatheter, the IntrocanSafety IV Catheter or other catheter suitable to delivery fulvestrant to the milk ducts. Fulvestrant will be infused in up to 5 breast ducts of the breast containing DCIS or invasive cancer. Ducts infused with fulvestrant will be marked with sutures. If sutures cannot be maintained until mastectomy or lumpectomy, other methods should be employed to mark the ducts, as specified in the instruction manual. At least one photograph of the breast documenting infusion location should be taken for the CRF. Do not instill more than 10 mL (500 mg) (i.e., the maximum delivered dose is never to exceed the dose currently in routine clinical use for intramuscular delivery). Detailed instructions for intraductal fulvestrant

administration and use of devices are located in the administration manual provided and will be performed on the intraductal fulvestrant subjects only.

9.3.3 Plasma Drug Concentration Levels

Subjects will have blood drawn two times on the day of intraductal administration of fulvestrant to determine plasma concentration levels. Table 1 lists the sampling schedule (below).

Table 1: PK - Plasma Fulvestrant Level Schedule

PK - Plasma Fulvestrant Level Blood Draw Schedule (Intramuscular and Intraductal)
Pre-fulvestrant – single blood sample for baseline Post fulvestrant administration: • 4.5 hours, Subjects are discharged following the 4.5 hour blood collection • Day 7 • Pre-surgery

9.3.4 Post Fulvestrant Administration and Pre-Surgery Assessment

After fulvestrant administration has been completed, subjects will be assessed for local and systemic adverse events during, immediately after and at 30 minutes, 1 hour and 4 hours. As noted above, **subjects must have at least 14 days between fulvestrant administration and surgery, but no longer than 45 days**. Pre-operative assessment, as described below, will occur before the subject undergoes mastectomy or lumpectomy 14 days following intraductal therapy, unless medical condition prohibits operative management. Subjects will complete a pain assessment at completion of fulvestrant administration, then at 30 minutes, 1 hour, and 4.5 hours until discharge from the clinic. Following discharge, the site trial staff may assess for AEs by phone. Subjects will be assessed for pain, AE, ECOG performance scale (Appendix A), blood drawn per drug schedule and vital signs (blood pressure, respiratory rate, pulse, temperature) recorded. See Table 2 to determine daily requirements for study procedures.

Subjects participating in this clinical trial will undergo either a mastectomy or lumpectomy. Notwithstanding the unlikely occurrence of an AE that affects the surgery date, participation in this trial does not alter the scheduled surgical management of mastectomy/lumpectomy or date. In order for subjects to undergo surgery, Atossa recommends but does not require the following requirements be met:

- ECOG performance scale of 0-2
- Stable vital signs (pulse, blood pressure, respiratory rate and temperature)
- Adequate organ function as determined by:
  - Absolute neutrophil count (ANC) $\geq$ 1500/µL
  - Platelets $\geq$ 100,000/µL
  - Hemoglobin $\geq$ 9.0 g/dL
  - Creatinine $\leq$ 2 times upper limit of normal
  - Bilirubin $\leq$ 2 times upper limit of normal
  - Transaminases (AST/SGOT and ALT/SGPT) $\leq$ 2.5 times upper limit of normal

The surgeon may elect to postpone the surgery if adverse events may compromise patient

safety. In the event this occurs, subjects will be treated to abate adverse events prior to surgery. They will remain in the clinical trial and be included for analysis.

9.4 Days + 1 and + 2

The following procedures will be performed on Days 1 and 2 post fulvestrant administration. Assessment by phone is allowed.

- Collection of concomitant medications
- Adverse event evaluations

9.5 Day +7 ± 2 (Day 5 to 9)

The following procedures will be performed on Day 7 post fulvestrant administration:

- Vital signs (blood pressure, pulse, respirations, temperature)
- PK - Plasma Fulvestrant Level
- Pain assessment (See Section 9.10)
- Collection of concomitant medications
- Adverse Event Evaluations

9.6 Pre-Operative (Day 14 + 7) (Day 14 to 21)

The following procedures will be done prior to surgery:

- ECOG performance status (Appendix 20.1)
- Vital signs (blood pressure, pulse, respirations, temperature)
- Digital tumor imaging
- PK - Plasma Fulvestrant Level
- Complete blood count with differential and platelet counts (includes hemoglobin, hematocrit, platelets and white blood cell count with differential)
- Chemistry panel (Includes Na^+, K^+, BUN/Urea, serum Cr, Glu, Alb, AST, ALT, Tbili)
- Pain Assessment (See Appendix 20.2)
- Concomitant Medications
- Adverse Events Evaluation
- Pregnancy test (for women of child-bearing potential)

9.7 Day of Surgery (DOS) Day 14 to 45

No study related procedures will take place during surgery. The surgeon will make every effort to maintain the bio-occlusive dressing and nipple markers in the mastectomy specimen unless surgical approach would be compromised. These markers are critical for pathological handling and processing of the mastectomy specimen to determine any effect of drug on treated and untreated ducts.

Upon complete removal of the mastectomy specimen, colored hydrogels (approximately 1 to 2ccs) will be injected into the previously treated ducts to allowed focused pathology assessment. It will then be sent to pathology for histological examination and tissue sample collection. Information regarding pathological assessment is in Section 10.1, Histological Assessment. For lumpectomy, this will not be feasible.

9.8 Post-Operative/Pre-Discharge (DOS to DOS+D/C)

Subjects will be assessed according to institutional policy after mastectomy or lumpectomy. In addition, subjects will be assessed for AEs, ECOG performance status (Appendix A), and vital signs (pulse, blood pressure, respiratory rate, temperature) recorded. In addition, as

noted above, blood will be drawn to assess organ function.

Subjects experiencing any adverse events prior to discharge which may have been caused by the study or the study drug, may stay longer in the hospital if indicated or may continue to be contacted by their doctor and study doctor. This will be recorded on the CRF.

In the absence of unresolved AEs that require follow-up after discharge, subject participation in this trial will end upon discharge from the hospital.

The following procedures will be performed post-surgery and before discharge:

- Vital signs (blood pressure, pulse, respirations, temperature)
- Concomitant Medications (collection of anesthesia, fluid support or post-surgical pain management is not required)
- Adverse Event Evaluation
- Clinical Breast Assessment
- Pathological Assessment

9.9 Subject Early Discontinuation

Subjects who discontinue after any fulvestrant administration on Day 0 will complete the following procedures.

- Concomitant Medications
- Adverse Events Evaluation
- Reason(s) for discontinuation
- Pregnancy test (for woman of child-bearing potential)

If a subject is withdrawn or discontinues study participation, reasonable efforts will be made to complete the final study procedures. The subject will continue to be followed and medically managed in accordance with the arrangement that was in place prior to study enrollment.

Table 2: Schedule of Assessments

Timeline	**Baseline**	**Fulvestrant Administration**	**Post Administration**		**Pre-Op**	**Day of Surgery**	**Day of Discharge**[12]	**Early Discontinu-ation**
	Day							
Procedures	**-14 to -1**	**0**	**1 and 2**	**7 (±2)**	**14 - 21**	**DOS (Day 14 to 45)**	**DOS +**	Post fulvestrant administratio
Informed Consent	X							
Registration	X							
~~Physical Exam~~	~~X~~				~~X~~			
Medical History	X							
ECOG PerformanceStatus	X				X			
Vital Signs[1]	X	X[2]		X	X		X	
Digital tumor imaging if needed	X				X			
PK - Plasma Fulvestrant Level		X[3]		X	X			
CBC with Diff & Platelets[4]	X				X			
Chemistry panel[5]	X				X			
Pregnancy Test[10]	X	X			X			X
Pain Assessment		X[6]		X	X			
Fulvestrant administration		X						
Concomitant Medications	X	X	X[7]	X	X		X[8]	X[7]
Adverse Event Evaluation		X[9]	X[7]	X	X		X	X[7]
Clinical Breast Assessment	X						X	
Pathological Assessment[11]	X						X	
Reason(s) for Discontinuation								X

1 Blood pressure, pulse, respiration, temperature
2 Prior to fulvestrant administration
3 On Day 0/fulvestrant administration, PK plasma samples are obtained pre-fulvestrant administration, and 4.5 hours post administration (see Table 1)
4 Includes hemoglobin, hematocrit, platelets and white blood cell count with differential
5 Includes Na^+, K^+, BUN/Urea, serum Cr, Glu, Alb, AST, ALT, Tbili
6 On Day 0/fulvestrant administration Pain Assessment completed prior to fulvestrant administration/nipple preparation (Intraductal only), Post Nipple Anesthesia (Intraductal only), at completion of fulvestrant administration, 30 minute, 1 and 4.5 hours post administration. (see Section 9.10)
7 Assessment by phone is allowed
8 Collection of anesthesia, fluid support or post-surgical pain management is not required
9 Assess adverse events during fulvestrant administration, immediately after administration, at 30 minutes, 1 hour and 4 hours
10 Only women of childbearing potential are tested at baseline or thereafter
11 Includes tissue sample collection for fulvestrant concentration
12 Participation in the trial concludes upon discharge from the hospital

9.10 Supportive Care

No other anti-estrogen medication is allowed during the study, and no estrogen therapy within 30 days prior to fulvestrant administration. Otherwise, concomitant medications and therapies deemed necessary for the supportive care and safety of the subject are allowed, provided their use is documented in the medical records and CRF. Collection of anesthesia during surgery, fluid support or post-surgical pain management is not required. Supportive care is provided as guided by institutional standards of care.

9.11 Pain Assessment

Obtain Pain Assessment (see Appendix B), minimally, according to the following schedule

Visit	Collection Time
Day of Fulvestrant Administration (Day 0)	• Prior to fulvestrant administration and prior to nipple preparation for intraductal subjects • Post Nipple Anesthetic (Intraductal Subjects Only) • At completion of fulvestrant administration/instillation • 30 minutes post administration • 1 hour post administration • 4.5 hours post administration
Day +7±2	Any time during visit
Pre-Operative (Day 14 ± 7)	Any time during visit

If, during intraductal fulvestrant infusion, the subject reports Grade 3 or 4 pain (CTCAE criteria) in the breast which does not resolve within 10 minutes after infusion of the drug, treatment of additional ducts will be discontinued. Blood draws and follow-up assessment as well as pathological assessment as described in Section 10.1 will be performed per the protocol.

9.12 Description of Medical Devices (for intraductal fulvestrant use only)

9.12.1 Name of Medical Devices

The FullCYTE® Breast Aspirator and either:

- Jabczenski Ductogram Cannula – G04303 –or most current item number (Cook Medical); or
- IntrocanSafety IV Catheter 24G x 0.55 FEP, Winged, Notched (B Braun)
- An alternative catheter may be used to facilitate drug delivery.

9.12.2 Indications for Use of the Medical Devices

The FullCYTE Breast Aspirator device may be used to identify ductal orifices for subsequent cannulation with the FullCYTE Breast MicroCatheter.

The Site may also use a Jabczenski Ductogram Cannula Microcatheter, the Intracan Safety Catheter or another analogous device that facilitates drug instillation into the milk ducts.

Detailed instructions for intraductal fulvestrant administration and use of devices is located in the administration manual.

9.12.3 Description of the Investigational Medical Device

The FullCYTE Breast Aspirator is supplied and manufactured by Atossa Genetics, Inc., using Good Manufacturing Practices (GMP) and following all regulations. Sterile microcatheters sufficient to intraductally instill fulvestrant will be obtained from acceptable suppliers. Preferred devices include the:

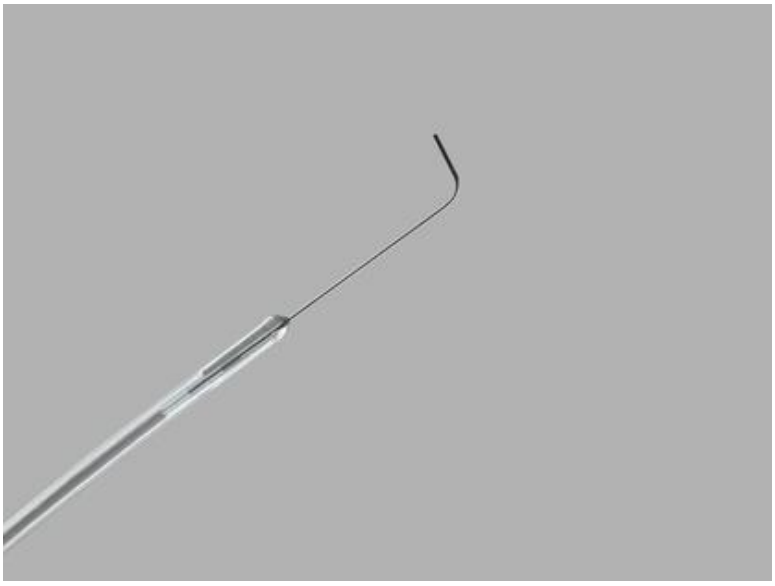
- Jabczenski Ductogram Cannula – G04303 –or most current item number (Cook Medical)
- IntrocanSafety IV Catheter 24G x 0.55 FEP, Winged, Notched (B Braun).

The FullCYTE Breast Aspirator (F-450-02) device is similar to non-powered breast pumps used to express milk from lactating women. The device is comprised of a rigid polycarbonate cup with an adhesive foam liner used to secure placement around the breast nipple. The polycarbonate cup is attached to a user supplied standard syringe, which is used to pull a gentle vacuum to express breast ductal fluid. The FullCYTE Breast Aspirator device is provided non-sterile and is intended for single patient use only. The Breast Aspirator is packaged in a sealed bag.

FullCYTE Breast Aspirator

9.13 MicroCatheters

Jabczenski Ductogram Cannula



Introcan Safety Catheter 24G x 0.55 FEP, Winged, Notched

Refer to the information provided by the manufacturer.

9.13.1 Storage and Handling and Stability

Store in a cool dry place. See the The FullCYTE Breast Aspirator and microcatheters have expiration dates provided on the device labels.

9.13.2 Device Dispensing

Fulvestrant will be infused in up to five breast ducts. A minimum of five catheters should be dispensed for each subject receiving intraductal fulvestrant administration.

9.12.3 Description of Investigational Product

Fulvestrant will be procured by the hospital pharmacy. The full prescribing information is provided in Appendix 20.3 and can be found at:
http://www.azpicentral.com/faslodex/faslodex.pdf#page=1

10.0 ASSESSMENT OF EFFICACY

While the primary objective of this study is safety and tolerability, efficacy parameters are Ki67 ER/PgR expression and tumor size by digital imagery, preferably by mammography.

10.1 Pathological Assessment

The clinic pathologist will conduct the pathologic examinations per institutional standards. Additional instructions are provided by the Sponsor.

The purpose of pathological examination is to provide objective assessment of local effect of fulvestrant on nipple skin, ductal cells (benign and malignant), and surrounding fibroadipose tissues. Specifically, the effect of fulvestrant on cell death (apoptosis and necrosis), proliferation (mitosis), and inflammatory reaction will be examined.

Mastectomy or lumpectomy specimens will be received and processed at the site's laboratory after intramuscular or intraductal therapy per institutional standards. Additional instructions are provided by the Sponsor, to include examination of the tissue for pathological evidence of response. Specific attention will be paid to identify the cannulated ducts. Aided by the colored Hydrogel of mastectomy specimens, the ducts identified in the breast parenchyma will be correlated with duct openings identified on the nipple (with suture), and compare the cannulated ducts (areas) with non- cannulated ducts (areas) for cell death, proliferation, and inflammatory response, as examined using routine hematoxylin and eosin (HE) sections. It is assumed that in most subjects, not every duct will be identified or accessed and in these cases those ducts which are not cannulated will be compared to the ones that were cannulated from a histological stand point. Samples will be stored per site's standard procedures.

A mastectomy or lumpectomy specimen will be dissected and samples taken to measure tissue fulvestrant levels.

10.2 Plasma Drug Concentration Levels

Subjects will have blood drawn several times (see Table 1) to determine plasma concentration levels pre- and post-fulvestrant administration. The blood processing procedure is provided in the lab manual.

10.2.1 Fulvestrant PK Analysis

Plasma and tissue concentrations will be determined per the described methodology in the PK report and referencing prior publications.[30]

10.3 Dose Limiting Toxicity

If Dose Limiting Toxicities (DLT) are identified meeting the definition set forth below, the dose in subsequent subjects will be lowered to no more than 250 mg total (5 mL). DLT will include any study-drug related grade 5 toxicity (death). In addition, if 20% or more (≥ 6 subjects) exhibit a single study drug-related Grade 3 or 4 adverse event (AE) per the CTCAE or SAE as defined in Section 11.2.3, the dose in subsequent subjects will be reduced to 250 mg. SAE Definition in the following categories: blood/bone marrow, cardiac, general constitutional symptoms, dermatology/skin, gastrointestinal, thrombo-embolic, hemorrhage/bleeding, infection, metabolic/laboratory, musculoskeletal/soft tissue, neurology, pain, pulmonary, upper respiratory, renal/genitourinary, or vascular this will be considered DLT and the study drug dose lowered for subsequent subjects. Additionally, if 50% or more subjects (≥ 15 subjects), experience greater than 5 study related Grade 2 AE, this will be considered DLT and the study drug dose in subsequent subjects be lowered to 250 mg. Subjects who experience an allergic reaction, including anaphylaxis, to the dyes or drugs in this study will not be considered a DLT.

11.0 ASSESSMENT OF SAFETY

This trial will use the descriptions and grading scales from the CTCAE v. 5.0 of the NCI for adverse event reporting. Information about all adverse events (AE), regardless of source (self- reported by subject, reported by questionnaire, collected through examination, laboratory or imaging) will be recorded in the medical record as well as CRF. The section below describes the procedures for collecting and reporting AE.

11.1 Procedures in Case of Emergency

The investigator is responsible for assuring that equipment, procedures and personnel with the expertise to manage medical emergencies are in place throughout the course of the study.

An emergency may constitute a serious adverse event (SAE), see Section 11.2.3 SAE Definition. In such case, the procedures outlined in Section 11.2.6 Procedures for Adverse Event Reporting for the should be followed.

11.2 Safety Monitoring and Reporting

11.2.1 Adverse Events

Both signs and symptoms of local (breast and chest wall) and systemic toxicity will be evaluated.

The most common side effects of fulvestrant when given into the muscle in the buttocks, reported from previous studies and after marketing, include:

- nausea (14%)
  - injection site pain (12%)
  - back pain (11%)
  - bone pain (9%)
  - headache (8%)
  - joint pain (8%)
  - pain in extremities (7%)
  - hot flash (7%)
  - weakness (6%)
  - vomiting (6%)

- loss of appetite (6%)
- muscle pain (6%)
- constipation (5%)
- cough (5%)
- shortness of breath (5%)

Increased liver enzymes (which may indicate liver damage) and allergic reaction may also occur, but in less than 5% of patients who receive the drug.

All of the side effects listed above may occur, but may or may not be the same in severity or frequency when fulvestrant is injected into the breast.

There are additional possible discomforts or risks from administration into the breast, as that process includes administration of anesthetic, breast duct identification using the aspirator, catheter placement and fulvestrant injection. These additional risks include:

- injury to the milk duct
- bleeding and bruising
- infection
- breast pain, discomfort or inflammation
- allergic reaction to the anesthetic, ~~dyes,~~ or the study drug, fulvestrant, used in this study.

11.2.2 Adverse Event (AE) Definition

An adverse event (AE) is defined by the NCI as any unfavorable symptom, sign, or disease (including an abnormal laboratory finding) associated with the use of a medical treatment, device or procedure that may or may not be considered related to or caused by the medical treatment or procedure. An AE also includes any newly occurring event or previous condition that has increased in severity or frequency since the initiation of the investigational procedures or administration of the investigational drug or device.

Assessment of the occurrence of an AE will be based on changes in the subject's laboratory results and/or signs and symptoms. AEs will be monitored until they are resolved or clearly determined to be due to a subject's stable or chronic condition or concurrent illness (es). Medical care will be provided, as defined in the informed consent, for any AE.

Collect all Adverse Events on the Adverse Event (AE) CRF and the MedWatch 3500 form. There are two types of adverse events, <u>expected</u> and <u>unexpected</u>. It is expected that subjects may feel slight minimal discomfort during the study procedures and post-procedure; both events are considered self-limiting. It is further expected that subjects will experience post-operative discomfort after surgery. This will be treated according to routine institution and clinician routine. Subjects who experience any untoward or unexpected after-effects following the study procedures, blood collection or surgery are instructed to contact the Principal Investigator or study coordinator immediately.

All AEs, regardless of intensity or causal relationship, are to be recorded in the CRF and source documentation. The investigator must determine both the intensity of the AE and the event's relationship to study product administration. Unexpected events such as excessive

discomfort or prolonged breast pain following the procedure, infection, persistent discharge, or any other condition reported by the subject and treated by a physician should be reported on the AE CRF.

11.2.3 AE Intensity Classification

Intensity will be defined according to the following CTCAE criteria:

Grade	Definition
1	Mild AE
2	Moderate AE
3	Severe and undesirable AE
4	Life-threatening or disabling AE
5	Death related to AE

11.2.4 AE Relationship Classification

Assess the relationship to study interventions (investigational product or device) as follows:

Relationship	Attribution	Description
Unrelated to investigational agent/intervention	Unrelated	The AE *is clearly **NOT** related* to the intervention
	Unlikely	The AE *is **doubtfully related*** to the intervention
Related to investigational agent/intervention	Possible	The AE ***may be related*** to the intervention
	Probable	The AE ***is likely related*** to the intervention
	Definite	The AE ***is clearly related*** to the intervention

11.2.5 SAE Definition

An SAE is any untoward medical occurrence that is a prolonged Grade 3 AE or any Grade 4 or 5 event as defined above or:

- Results in death
- Is life threatening (refers to an event in which the subject was at immediate risk of death at the time of the event; it does not refer to an even which hypothetically might have caused death if it were more severe)
- New or prolongs existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Requires intervention to prevent permanent impairment/damage (Devices only)

A medical event that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent a serious outcome may also be considered serious. Medical and scientific judgment must be exercised when classifying events as serious.

A distinction must be drawn between SAEs and severe AEs. A severe adverse event is a major event of its type. A severe adverse event need not necessarily be considered serious. For example, nausea, which persists for several hours, may be considered severe nausea but does not fulfill the criteria for an SAE. Alternatively, a stroke, which results in only a

limited degree of disability, may be considered to be a mild stroke but would fulfill the criteria for an SAE.

Monitor all SAEs until the event is considered resolved.

All SAEs, regardless of relationship to study procedures, must be reported to the study medical monitor and reported according to the procedures outlined in Section ~~7.2.6~~ 11.2.6 Procedures for Adverse Event Reporting.

11.2.6 Procedures for Adverse Event Reporting

An adverse event that fulfills any one or more of the criteria in Section 11.2.5 SAE Definition must be reported as an SAE according to the following guidelines:

The investigator must inform the Atossa medical monitor within 24 hours of learning of event by telephone, text or fax of any SAE which occurs during the course of each subject's study participation (e.g., from enrollment through study termination), whether or not considered causally related to the study procedure.

11.3 Sponsor SAE Contact Information

Primary	**Back-up**
Steven Quay, MD, PhD CEO & President, Atossa Genetics, Inc. e-mail: safety@atossagenetics.com e-mail: Steven.Quay@atossagenetics.com Mobile: 206-419-4873	Janet R Rea, MSPH SVP, Regulatory, Quality & Clinical Affairs Mobile: 206-799-7186 Mobile: 206-550-0226 janet.rea@atossagenetics.com

An unanticipated adverse event [as defined in 21 CFR 312] is any serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with the study intervention, it that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application, or any other unanticipated serious problem that relates to the rights, safety, or welfare of subjects.

SAEs will be reported to appropriate regulatory authorities by Atossa Genetics according to all applicable regulatory requirements for documentation and reporting of SAE (21 CFR 312). It is the responsibility of the investigator to promptly notify the IRB of all unanticipated problems involving risk to human subjects.

Adverse events classified as expected or unexpected will be tabulated and analyzed at the conclusion of the study. For adverse events that are breast specific, the unit of tabulation will be the breast. For adverse events that do not relate to the breast, the unit of tabulation will be the subject. All subjects who have received intraductal administration will be included in the safety analyses for adverse event reporting. All adverse events reported during this study will be listed with the grade, severity, relationship to study intervention, outcome, and action taken.

Should a pregnancy occur, it must be reported and recorded on the pregnancy form. Pregnancy itself, is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth

or congenital abnormality) must be followed up and documented even if the patient was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

12.0 ACCOUNTABILITY, RISKS AND BENEFITS

12.1 Accountability

Accurate records must be maintained for all investigational devices received, dispensed, and returned or destroyed. The study drug, fulvestrant, will be purchased by the hospital pharmacy. The allocation and administration of study drug to the study participants must be fully and contemporaneously recorded. The site will maintain study drug, FullCYTE Breast Aspirator and Microcatheter supplies accountability during the study on accountability logs provided by the sponsor (or the site's form is acceptable and if the following information is collected: the identification of the subject to whom the drug or microcatheters were dispensed and the date, lot number and quantity of the drug dispensed to the subject. Unused study supplies will be returned to the Sponsor. The Sponsor or designee will conduct drug accountability during the course of the study and at site closeout. Disposition of unused study drug will be handled according to institutional standards. The Sponsor or designee will conduct final study supplies accountability at site closure.

13.0 STATISTICS

The primary aim of this study is to assess safety and tolerability in subjects receiving intraductal fulvestrant. In addition, this trial aims to characterize the PK of this alternative route of administration, and compare the intraductal PK profile to that of standard intramuscular administration. A pharmacokinetic population analysis will be used to characterize biodiversity in exposure and alternative route absorption rate.

Additional analyses not described in the sections below may be specified in a Statistical Analysis Plan. A detailed Statistical Analysis Plan will be done prior to database lock.

13.1 Adverse Events Analysis

All serious adverse events will be reported. All non-serious AEs occurring in at least 10% of the subjects will similarly be reported.

13.2 Sample Size and Statistical Analyses

A total of 30 subjects who are undergoing mastectomy or lumpectomy will be included in this study: 6 will receive intramuscular, and 24 will receive intraductal fulvestrant. With respect to the sample size for the latter group with 24 subjects, it will be possible to detect an effect size of approximately 0.60 with 80% power and 0.69 with 90% power. Both of these are in the medium to large range according to Cohen's terminology and are based on the demonstration of a reduction in the Ki67 labeling index mean from baseline (diagnostic biopsy) to week 4 (surgically excised specimen) using a paired t-test. With these effect sizes and an anticipated 50% decline in the mean index, then the expectation would be a standard deviation in this reduction of about ±83.7% for 80% power and ±72.3% for 90% power.

The primary endpoint of this study is to assess safety and tolerability as measured by adverse events, subject pain assessment as well as signs of topical irritation seen on the excised specimen. In addition, the effect of the administration will be evaluated with respect to the change in Ki67 labeling index (primary efficacy endpoint) and changes in estrogen and progesterone receptor expression (secondary efficacy endpoints)

Descriptive statistics will be used to summarize the data (means/medians and standard deviations/interquartile ranges for quantitative data and proportions/percentages for categorical data such as adverse events), and numerically compare the groups with entry diagnoses of invasive ductal carcinoma and DCIS, respectively. In addition, the 6 study subjects who receive intramuscular fulvestrant will be qualitatively compared with the main study cohort of 24 subjects who receive intraductal fulvestrant.

The primary analysis of the change in Ki67 labeling index will be compared between the two time points (baseline or time of diagnostic biopsy versus 4 weeks or time of the surgically excised specimen collection) using the paired t-test (assuming normality of the differences) or the Wilcoxon signed rank test if normality cannot be demonstrated or a transformation to normality using the Box-Cox family of power transformations cannot be used. A similar analysis will be employed to evaluate the secondary endpoint of changes in mean estrogen receptor and progesterone receptor expression. In addition, 95% confidence intervals for the mean difference for these variables between the two time points will be computed using the t-statistic or a rank statistic as required by the distribution of the study data.

The results for the efficacy endpoints will be compared in a descriptive fashion with those seen by Kuter et al (Kuter I, Gee JMW, Hegg R et al): Dose-dependent change in biomarkers during neoadjuvant endocrine therapy with fulvestrant: results from NEWEST, a randomized Phase II study. Breast Cancer Res Treat 133: 237-246, 2012.

13.3 Plasma Concentration Levels

The statistical analysis used for the pharmacokinetic (PK) population study may employ one or more of several advanced analysis packages including WinNonlin, Kinetica, Matlab, or R. For each subject, plasma level time curves will be assessed individually for the absorption rate and body compartment parameters. Both a one compartment and a two-compartment model will be considered. The literature values will be used for the initial conditions of the body compartment parameters, and a weighted nonlinear routine will be used for the parameter estimation. The optimal model will be chosen based on the Akaike Information Criterion (AIC).

Equation 2. PK Model Selection Criterion

$$AIC = N^* \ln(SSQ) + 2p$$

Here, N is the number of samples, ln(SSQ) is the natural logarithm of the sum of the squared residues, and p is the number of model parameters. The model yielding the lowest AIC will be chosen.

Secondarily, standard parameters such as mass, body surface area, and body mass index will be assessed to determine if their inclusion will improve a joint parameter estimation using all subjects tested for a given agent dose. In the case that dosing for an agent was

terminated due to high AE, then such analyses will only be performed if sufficient subjects are available.

Standard PK parameters will then be calculated as appropriate to the modeling form (one or two compartmental model).

Differences between the absorption rate parameters and standard PK parameters will be assessed.

It is recognized that in some subjects, surgery may have already occurred before plasma C_{max} is reached.

13.4 Tissue Concentration

The fulvestrant concentration in the breast tissue will be determined from the specimen obtained during the pathology examination of the tissue excised during surgery.

14.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator is responsible for maintaining any original source data documentation related to the study, the subject identification list and all original signed informed consent form(s) as outlined in Section 17.6, Record Retention. Study-specific CRFs must be completed for each subject enrolled in the study as outlined in Section 17.1, Recording of Data.

14.1 Access to Source Documents

Atossa Genetics is responsible for assuring that the data collected is complete and accurate. The most effective way to assure the accuracy of the data is to review individual subject records and other supporting documents and compare those records with the reports prepared by the investigator for submission to the sponsor. Therefore, during a periodic visit, the monitor will compare a representative number of subject records and other supporting documents with the investigator's reports to determine that:

- The information recorded in the investigator's report is complete, accurate and legible.
- There are no omissions in the reports of specific data elements such as the administration to any subject of concomitant study drug or the development of an intercurrent illness.
- Missing visits or examination are noted in the reports.
- Subjects failing to complete the study and the reason for each failure are noted in the reports.
- There is no evidence of fraud or data falsification.

14.2 Monitoring

In accordance with regulatory guidelines as outlined in 21 CFR 312, the sponsor is required to monitor the progress of a clinical investigation. Proper monitoring is necessary to assure adequate protection of the rights of human subjects, the safety of all subjects involved in clinical investigations, and the quality and integrity of the data.

Following the conduct of the study initiation visit, Atossa or its representatives (e.g., CRA or representative contracted to support this clinical trial) may attend and observe some of the

study related intraductal procedures and data collection at the institution to ensure proper conduct of the study. The investigator will permit all CRA to monitor the study as frequently as the CRA deems necessary in order to ensure that the clinical facilities remain acceptable and that data recording and protocol adherence remain satisfactory. The CRFs and related source documents will be reviewed per the monitoring plan. This includes tests performed as a requirement of participation in the study (e.g., history, intraductal administration of any agent, imaging, pathology, and reports) and may include other medical records required to confirm the information contained in the CRFs.

During the review of these documents the anonymity of the study subject will be maintained with strict adherence to professional standards of conduct/and confidentiality.

Prior to each monitoring visit, the investigator should record all data generated since the last visit in each subject's CRFs. The investigator and staff will be expected to cooperate with the CRA, to be available during at least a portion of the monitoring visit to answer questions, and to make corrections and provide missing information as is deemed necessary.

The CRA will record the date of each visit in the Monitor Sign-In Log and will document all findings and a summary of the study status and progress in a monitoring report. Any proposed actions will be discussed with the investigator and will be confirmed in writing.

14.3 Written Monitoring Procedures

Written procedures for monitoring clinical investigations will be followed to assure the quality of the study and to assure that each person involved in the monitoring process carries out his or her duties.

14.4 Monitoring Visits

The schedule of monitoring visits will be detailed in the monitoring plan.

14.5 Audits and Inspections

Authorized representatives of Atossa or a regulatory agency, may visit the site to perform audits or inspections, including source data verification. The purpose of an Atossa audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. The investigator should promptly contact the Atossa representative if contacted by a regulatory agency about an inspection.

15.0 QUALITY CONTROL AND QUALITY ASSURANCE

15.1 Investigator Selection

Prior to the initiation of the clinical trial, the investigator and any co-investigators must provide Atossa with copies of their current licensure and *curriculum vitae*, including a list of publications and any other relevant documentation requested by the sponsor, the Institutional Review Board (IRB) and/or regulatory agencies.

The investigator (s) shall meet all the qualifications specified by the applicable regulatory requirement (s) of Title 21 Code of Federal Regulations (CFR) Part 312.53, shall provide evidence of such qualifications, and shall be qualified by the sponsor based upon:

- Education
- Training and experience to assume responsibility for the proper conduct of the trial
- Professional standing and experience (including licensure)
- Professional referrals
- Authors of pertinent publications
- Investigator workload
- Adequate access to study population

In addition to investigator qualifications, institutions must meet the following criteria:

- Experience in conducting clinical trials
- Adequate access to study population(s)
- Qualifications and availability of study site personnel
- Adequate equipment and facilities to conduct clinical trial procedures

15.2 Changes to the Protocol and Study Related Procedures

No change in the study protocol or any study related procedure may be implemented without the mutual, written agreement of the investigator and the medical monitor of Atossa. All changes must be documented by signed protocol amendments that are agreed to and signed by Atossa; copies provided to the IRB/IEC; and the IC revised if necessary. Trial participants may need to be re-consented depending on the nature of any protocol amendments.

It is the responsibility of Atossa to distribute any proposed amendment to the investigator at each clinical site. The investigator is responsible for the distribution of any amendments to all relevant staff concerned with the conduct of the study at the study site, as well as to the IRB.

15.3 Study Termination by the Sponsor

The Sponsor reserves the right to prematurely terminate the study if, in the opinion of the sponsor, there is sufficient reasonable cause. Sponsor will make every effort to provide 30-days written notice of study termination, except when the reason for termination concerns subject safety, in which case the clinical trial may be discontinued immediately. Written notification documenting the reason for such a termination will be provided to the investigators. Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant or unacceptable risk to the subjects
- Overall failure to enroll study subjects at an acceptable rate
- Plans to modify, suspend or discontinue the development of the study product/procedure

15.4 Site Termination by the Sponsor

Sponsor has the right to terminate an individual study site and remove all study materials from a site at any time. Reasons for termination of a study site may include, but are not limited to the following:

- It is apparent that subject enrollment is unsatisfactory with respect to quality and/or quantity of potential study subjects
- Data recording is inaccurate and/or incomplete on a consistent basis
- Insufficient adherence to protocol requirements

- Inadequate informed consent of study subjects
- Integrity of data is questionable or unable to be verified
- Preliminary data/outcomes at this study center indicate that the study product poses an unacceptable risk/health hazard to study participants.
- Consistent failure to adhere to GCPs.

15.5 Good Clinical Practices

This study will be conducted in accordance with International Conference on Harmonization, (ICH) Guidelines for GCPs and the appropriate regulatory requirement(s) of Title 21 CFR Parts 11, 50, 54, 56, 312 and 314, with the overall purpose of ensuring the safety and well-being of the participating trial subjects. The investigator will be thoroughly familiar with the appropriate use of the study product(s) and procedure(s) as described in this protocol. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files will be established at the beginning of the study, maintained for the duration of the trial and retained according to the requirements outlined in this protocol and all appropriate regulations.

15.6 Protocol Compliance

The investigator will conduct the trial in compliance with the protocol and after approval/favorable opinion by the IRB and the appropriate regulatory authority(ies). Modifications to the protocol should not be made without agreement of both the investigator(s) and the sponsor. Changes to the protocol will require written IRB approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to subjects or if the change(s) involves only logistical or administrative aspects of the trial. The IRB may provide, if applicable regulatory authority(ies) permit expedited review and approval/favorable opinion for minor change(s) in ongoing trials that have the approval of the IRB.

When immediate deviation from the protocol is required, the investigator will contact the medical monitor, if the circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented in the CRFs and source documentation.

16.0 ETHICS

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki 1989 and in compliance with 45 CFR part 46 and are consistent with ICH Good Clinical Practice, and applicable regulatory requirements.

In order to safeguard the rights, safety and wellbeing of the subjects in this study, the study protocol, subject information, subject informed consent form (ICF), and copies of any proposed advertisements to be used (if applicable), must be reviewed and receive the approval of an IRB/IEC. The opinion and notification of approval by the IRB should be given in writing and should refer to this study by title, version date and study number. In addition, a list of those present at the IRB meeting, with their positions and institutional affiliations clearly stated, should be attached whenever possible.

It is the responsibility of each investigator to forward a copy of the notification of IRB approval for both the protocol and the subject ICF to Atossa prior to the start of study

enrollment at each study center when multiple centers participate.

The investigator will also ensure that all changes in the approved research activities, and all unanticipated problems involving risks to the subjects in the study are promptly reported to the IRB; and that no changes will be made to the protocol without IRB approval, except when necessary to eliminate apparent immediate hazards to the subject. For minor changes to previously approved research, it may be possible for the investigator to secure an expedited review by the IRB as provided for under 21 CFR Part 56.110.

As part of the IRB requirement for continuing review of approved research, the investigator will be responsible for submitting periodic progress reports to the IRB at intervals appropriate to the degree of subject risk involved, but no less than annually. All correspondence to and from the IRB should be filed by the investigator in the study specific regulatory files. Copies of all such correspondence as well as notification of continued IRB approval of this trial, or withdrawal of such approval, must immediately be forwarded to Atossa by the study investigator.

All safety updates, annual progress reports and any revisions to the aforementioned documents will be provided to the IRB by the investigator. No change in study conduct will be made without the prior written approval of the IRB.

The investigator acknowledges that his/her institutional approval to conduct this clinical trial is limited to the site of investigation specified in the submission to the reviewing IRB.

16.1 Subject Information and Informed Consent

In accordance with guidelines as outlined in CFR 21 Part 50, the investigator will ensure that the subject or the subject's legal representative (as appropriate) are provided full and adequate verbal and written information about the nature, purpose, possible risks and benefits of this study. They must also be notified that they are free to discontinue their participation in this study at any time. The subject will not be entered into the trial nor will any non-routine procedures be performed prior to obtaining written informed consent from the subject.

The subject and/or the subject's legal representative should retain a copy of the signed ICF. Should modifications be made to the current ICF, the revised IRB approved version of the ICF must be signed by the subject and or the subject's legal representative prior to the institution of any proposed change in study conduct. The ICF outlines the procedures and requirements associated with participation in this clinical trial.

17.0 DATA HANDLING AND RECORD KEEPING

17.1 Recording of Data

All required data will be recorded on CRFs for each subject. It is the investigator's responsibility to ensure the accuracy, completeness, legibility and timeliness of the data reported in the subject's CRFs. Source documentation supporting the CRF data should reflect the subject's participation in the trial and should document the dates and details of study procedures, AEs and subject status.

For every study subject, the subject/medical record notes should clearly indicate at least the following:

- That the subject is/was a participant in the study (via subject and study

identification)
- All therapies and medications
- All visits to the physician's office/hospital, including those that were for study purposes only
- All AEs and SAEs, if applicable

All fields on each subject's CRF must be completed, and any missing data or discrepancies must be explained.

17.2 Financing and Insurance

The Sponsor is responsible for funding the study, and will provide insurance coverage adequate to cover each subject. Insurance will be in place prior to starting the study.

17.3 Data Collection Requirements

Upon enrollment, each subject will be provided a unique Subject ID number. A Data Management Plan (DMP) will be developed and will define all data management issues for the clinical trial from database design development and validation to data management handling of documents. All data entry personnel will be trained to the appropriate sections of the DMP prior to involvement in the clinical trial.

All data obtained during the clinical trial will be recorded on CRFs for each subject. Data entry personnel will then verify all data. All CRF data will be verified by Atossa and tracked by an audit trail documenting the following:

- Clinical Data Entry Assistant
- Date of Entry
- Value of data changes
- Date of data changes

The clinical trial database will include logic checks for applicable fields to further ensure data integrity. If necessary, the clinical sites will be contacted for data corrections or clarifications via faxed quality control reports.

17.4 Subject Data Protection

In order to maintain subject privacy, all CRFs, study reports and communications will identify the subject by the assigned subject ID number only. The investigator will grant monitor(s) and auditor(s) from the sponsor or designated contract research organization(s), the IRB and regulatory authority (ies) access to the subject's original medical records for verification of data entered on the CRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

As part of the informed consent process, the subject and/or her legal representative will be informed in writing about the possibility of audits by authorized representatives of the sponsor and/or regulatory authorities, in which case a review of those parts of the medical records relevant to the study may be required. The subject and or their legal representative will also be informed in writing that every effort to protect subject's confidentiality will be maintained.

The investigator is responsible for maintaining a list of all study subjects who have been screened and assigned a study ID number. This list should contain the subject identification

number, full name and last known address in the even that study subjects need to be contacted beyond the time of study participation.

17.5 CRF Completion

The investigator will be responsible for the accuracy and timely completion of the information entered on the CRFs as well as the timely submission of CRFs to the sponsor. The CRF and source documents, including but not limited to subject's history and physical exam (H & P), mammography, breast ultrasonography, additional breast imaging, breast MRI, cytology, histology, operative reports, progress reports, and discharge summaries must be available for review by the study monitor at each scheduled monitoring visit. The investigator will also allow clinical representatives of the sponsor, an independent auditor, the IRB, or regulatory bodies to review the information reported on the CRFs and to reconcile those data with source documents at the investigator's location.

17.6 Record Retention

FDA regulations require that each investigator retain all records and documents for this study for a minimum of two years following the date on which study is completed, terminated, or discontinued. Should the investigator be unable to continue maintaining the records for this full time period, Atossa will provide assistance with document retention. No study related documentation, included but not limited to, the clinical trial protocol and amendments, IRB approval and correspondence, sponsor correspondence, SAEs, CRFs, monitoring reports, material accountability records, and the log of screened subjects may be destroyed without the written consent of Atossa. However, Atossa requests that all records and documents for this study be maintained for at least 15 years following study completion. Should the investigator be unable to continue to maintain the records for this full time period, Atossa will provide assistance with document retention. No study related documentation, including but not limited to, the clinical trial protocol and amendments, IRB approval and correspondence, sponsor correspondence, AE, CRF, monitoring reports, material accountability records, and the log of screened subjects may be destroyed without the written consent of Atossa.

17.7 Training

All study personnel will be required to have the following training:

- Intraductal administration procedural methods
- Protocol review

This training will be documented in the Clinical Trial Master File (CTMF). Study personnel that have undergone prior training in intraductal procedures will have this training documented in the CTMF.

18.0 PUBLICATION POLICY

It is understood that there is an obligation to provide Atossa with complete data obtained during this study. The information obtained from this clinical trial will be used towards developing a body of knowledge related to intraductal therapy. All data derived from this clinical trial may be disclosed to the FDA and other regulatory agencies as required by applicable law.

Sponsor encourages the publication of study data in reputable scientific journals and at seminars and conferences. Accordingly, the Institution and Principal Investigator agree not to

publish the results of the Study without prior written review of Atossa. To that end the investigator and/or institution is required to furnish Atossa with a copy of any proposed publication, for review and comment, at least thirty (30) days prior to submission to a journal, scientific conference or disclosure to any third party. Any oral presentations or poster sessions must be submitted to Atossa fifteen (30) days prior to abstract submission for review.

All rights, title and interest to the data and results arising from the study are the exclusive property of Atossa, subject to the provisions outlined and mutually agreed upon in the Clinical Trial Agreement. The Institution and/or Investigator shall have the right to retain copies of all their onsite data and results arising from its participation in the Study for its internal archival purposes.

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20.0 APPENDICES

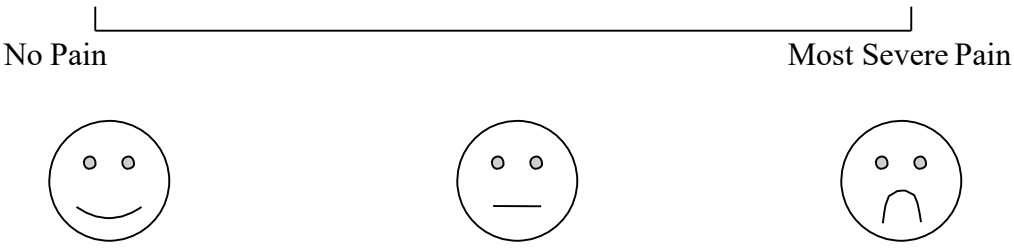
20.1 Appendix A: ECOG Performance Scale

Score	Definition
0	Asymptomatic
1	Symptomatic but fully ambulatory
2	Symptomatic; in bed less than 50% of the day
3	Symptomatic; in bed more than 50 % of the day, but not bedridden
4	Bedridden

20.2 Appendix B: Pain Analog Scale for Subject Assessment

Indicate your level of comfort with a single mark on the line below or by telling your doctor or nurse, expressing your level of pain on a scale from 0 to 10. 0 Represents no pain and 10 represent the worst possible pain.

0 **10**



No Pain Most Severe Pain

20.3 Faslodex® Full Prescribing Information

20.4 Appendix C: New York Heart Association (NYHA) Classification

Class	Objective Assessment
A	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
B	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
C	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
D	Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.