QS FDA Phase 3 Clinical Trial Protocol

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DEDICATION

This book is dedicated to pioneers Dr. Elton Kessel, Dr. Jaime Zipper, Dr. Jack Lippes, and Dr. Do Trong Hieu, for their inspiration to bring the best contraception method to women who no longer wished to have children. Each pursued this endeavor for many decades relentlessly until the end of their lives so that millions more women might live longer happier lives.

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PROTOCOL

"A Phase 3 Multi-center Clinical Investigation to Evaluate the Safety and Effectiveness of Quinacrine Hydrochloride (QH) Pellets Administered Via Quinacrine Sterilization Procedure (QS) to Female Subjects Who Voluntarily Agree to Choose QS as Their Method of Sterilization"

IND No. #74,802

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1 INTRODUCTION

Nonsurgical methods of female sterilization associated with simple delivery systems and minimum morbidity are ideal choices of contraception. This is especially true when the method is inexpensive and can be implemented without anesthesia and can be done as an outpatient procedure and requires minimal amount of recovery and down time from daily living activities.

For the past two decades in the United States, sterilization has been the most popular method of limiting family size.[1] Nearly 80% of married American couples have acquired sterilization before their partners have reached the end of their reproductive years. Of these, two-thirds of this population accepted tubal ligation, and one-third vasectomy as their choice of sterilization.

Presently, in the United States, sterilization is performed surgically and usually involves a general anesthetic and the use of high technology such as laparoscopy. Laparoscopic sterilization carries serious risks that, although rare, may be disabling and even life threatening.[2] Examples of such serious adverse

experiences {SAEs) include perforation of the great blood vessels of the pelvis with massive hemorrhage, perforation of the bowel, and perforation of the bladder. The bowel may be burned when cautery is used. Burned bowel may rupture a few days after laparoscopy and my result in severe peritonitis. It is generally agreed that the technical requirements for surgical female sterilization are important reasons for failure to satisfy the demand for voluntary sterilization.

Development of a safe and effective procedure of nonsurgical female sterilization that could be performed on an outpatient basis, economically affordable and using a procedure that is easily implemented is vital for meeting a worldwide need. A non-surgical sterilization technique that was approved "Essure" required the permanent placement of a coil made of metal and polyester fibers via a hysteroscopy. This requires an experienced OB/GYN professional.

Quinacrine sterilization is another nonsurgical method of sterilization. The procedure is simple and may be implemented without anesthesia. In addition, it can be done on an outpatient basis at an extremely low cost

compared with surgical sterilization or the Essure method.

Background

Chest surgeons have used Quinacrine as a sclerosing agent in the thoracic cavity to prevent pleural effusions known to occur with metastatic carcinoma of the lungs.[3] This technique was also used to treat noncancerous pleural effusions.[4] Quinacrine, in pellet form, was first used as a sterilizing agent by Zipper 25 years ago.[5] Zipper based his theory on the use of the long established and accepted sclerosing action of Quinacrine.[3] In response to concerns over mutagenic potential of Quinacrine, Sokal et al[6] studied the incidence of cancer in QS patients and found that the incidence of cancer in women who have had Quinacrine sterilization was not significantly different from that in women in the general population in those areas where Quinacrine sterilization procedures were carried out. This was confirmed by FHI sponsored studies by Sokal.[7] Additionally, Zipper observed no life-threatening AEs over the same 25 years.[8] It is of interest to note that the National Cancer Institute in its

1994 annual review lists Quinacrine as an antineoplastic drug.[9]

The Quinacrine pellet procedure involves transcervical insertion of Quinacrine pellets, via a Quinacrine sterilization procedure, into the uterine fundus in the proliferative phase of the menstrual cycle. Two insertions with a 30-day interval between them are administered. Quinacrine then causes an occlusive scar in the proximal tubes.[10]

Family Health International (FHI) conducted a clinical trial in San Antonio, Texas under an IND. The trial was conducted on 10 women who had Quinacrine inserted 1 day before a hysterectomy.[11] A significant finding was that Quinacrine was absorbed from the uterus into the bloodstream at the same rate as it is absorbed from the gut. This finding gave reassurance to Quinacrine sterilization researchers. By 1 hour after insertion, plasma levels had already peaked in 60% of the women at 11.8 - 99.1 ng/ml.[11] No crystals of Quinacrine were found in any of the women 24 hours after insertion.11 With oral administration, Quinacrine is likewise distributed via the bloodstream to the uterus (and all other organs). Quinacrine is stored in these organs and slowly released in constantly decreasing

amounts for about 30 days.[12] There are two important implications of this finding: 1) there is no prolonged exposure of the uterus to a high concentration of Quinacrine (a misconception that had led to concern that Quinacrine sterilization might cause cancer of the uterus). 2) Oral administration of 100 mg per day, the dose of Quinacrine administered as malaria prophylaxis and for treatment of lupus, exposes the uterus to a much higher accumulated concentration of Quinacrine. There are no reports of an increase in the uterine cancer rate (or any other cancers) after a history of 70 years of oral administration of this drug used to treat malaria and other diseases.[13]

This introduction would not be complete without a mention of the "slurry method" of Quinacrine sterilization. At the very beginning of the investigations with QS Quinacrine was used in a slurry, i.e., in a liquid form that was instilled into the uterine cavity. A few small trials were reported from Miami, Florida, Jamaica, Canada, and Thailand. In Chile, Zipper studied the Quinacrine slurry method in three hundred women. AEs were observed. It was hypothesized that the rapid absorption of Quinacrine produced cortical excitation. Although never published, three deaths were reported in letters to the

FDA from countries other than Chile. The slurry method was abandoned. To slow the absorption of Quinacrine, the pellet method was developed. Since then, no deaths have been reported.

Kessel reviewing 100,000 Quinacrine sterilization cases of the pellet method reported no mortality and only one patient required hospitalization due to a rare allergic reaction, from which the patient recovered completely. No life-threatening AEs requiring hospitalization were reported.[14] In 1993, Hieu published a paper in The Lancet reporting over 31,000 Quinacrine sterilization cases with no mortality and no life-threatening AEs requiring hospitalization.[10] In 1994, FHI undertook a retrospective trial in Vietnam, focusing on a sample of 1800 women who had Quinacrine sterilization and comparing them with women who had elected IUDs. FHl's findings confirmed the work of Hieu that Quinacrine sterilization is both safe, acceptable and well tolerated.[15, 16]

Pregnancy rates have varied. In 1980, Zipper reported a pregnancy rate of 3.1 per 100 women at 12 months using three insertions of 252 mg of Quinacrine pellets. Most investigators have obtained similar results with

two insertions of Quinacrine pellets. The insertion protocol recommended since 1993 has produced lower failure rates.[17] Peterson et al[1] have shown that surgical bilateral-tubal ligation has produced failure rates similar to those seen with Quinacrine sterilization. Peterson, in the well-regarded CDC-sponsored CREST study, reports at 5 years after surgery, bipolar coagulation, spring clip application, and interval partial salpingectomy had failures of 1.7%, 3.2%, and 1.5%, respectively.

The incidence of ectopic pregnancy among Quinacrine sterilization users was found by Hieu et al to be 0.89 per 1000 woman-years.[10] In its retrospective trial, FHI found the rate to be 1.33 per 1000 woman-years among women who had two insertions, which is well below the rate seen among women in the U.S. not using contraception (2.6 per 1000 woman-years).[18] Zipper noted only two ectopic pregnancies in 4000 cases over the last 23 years with his Quinacrine investigations in Chile.[8] No investigators who have undertaken small studies of a few or several hundred cases have ever reported more than one ectopic pregnancy in their series. There is no increase in the incidence of ectopic pregnancies reported in studies with larger number of subjects.[19] Thus, Quinacrine sterilization apparently

offers protection against ectopic pregnancy similar to that of surgical sterilization.[10, 18, 19]

No reported· cases of birth defects have been attributed to Quinacrine sterilization. This is true whether Quinacrine is introduced into a pregnant uterus or, in cases in which women became pregnant during the month following Quinacrine insertion, when diminishing quantities of Quinacrine remain in all organs, including the uterus.[20]

Women in malarial endemic regions have taken Quinacrine for years, including times when pregnant. Here too, no abnormalities of the babies have been attributed to Quinacrine.[21, 22]

One trial in Patiala, India, focused almost entirely on women who were at high risk for surgical sterilization. These 134 women presented with severe anemia, cardiovascular disease, bronchial asthma, or a history of pelvic inflammatory disease (PIO) or pelvic surgery. After a mean follow-up of 7.2 years, there have been no pregnancies or serious complications.[23]

It is estimated that more than one million American women who desire sterilization are at a high risk for

serious complications from surgical sterilization. The Centers for Disease Control (CDC) has determined that the following factors place women at high risk for surgical sterilization: obesity, diabetes mellitus, general anesthesia, previous abdominal or pelvic surgery, lung disease, or a history of pelvic inflammatory disease (PID).[24] The spread of AIDS has produced a growing population of women who are poor candidates for surgical sterilization because they are immunocompromised. Furthermore, AIDS patients find it difficult to locate a surgeon who will operate on them. Surgeons are reluctant and even fearful to do elective surgery on AIDS cases.

Three rare complications have been noted with Quinacrine sterilization: 1) hematometra, This is treated by sounding of the uterine cavity, occurring in about one in 5000 cases.[14] 2) generalized allergic reaction, which occurs in one in 30,000 cases,[14] treated with antiallergic drugs. 3) Uterine Perforation may happen once every 100 to 1500 cases. Even accidental perforation of the uterus with deposition of Quinacrine into the peritoneal cavity has not been life-threatening. With this rare accident, subjects do suffer increased but transient lower abdominal pain.[25] Side effects such as black nails and yellow skin reported

with Quinacrine therapy for prophylaxis against malaria have not been reported with the doses of Quinacrine used for female sterilization in the first documented 100,000 cases of Quinacrine sterilization. Using the definitions of the CDC for serious complications, based on studies outside the US, Quinacrine sterilization compares favorably with laparoscopic sterilization with rates of serious complications of 0.03% versus 1.7%, respectively.[10]

A body of knowledge confirming the safety of Quinacrine sterilization derives from its use in many countries, but not from the U.S. The Quinacrine sterilization (QS} method appears to be safe in third-world countries. Therefore, it is reasonable to ascertain whether the results found in developing countries can be replicated in the U.S. The only way to determine this is to conduct a Quinacrine sterilization trial in an American environment.

On October 12, 2000, the U.S. Food and Drug Administration (FDA) approved an Investigator IND (IND 60,600) to conduct a trial of Quinacrine sterilization in the U.S. This Phase 1 clinical program evaluated 10 subjects ages varied from 29 to 45 years (average age 36.8 years}. All subjects received two

insertions of Quinacrine Hydrochloride pellets (QH). Each of the two insertions of consisted of 252mg (QH) divided into seven 36mg pellets administered on two separate visits one month apart. The total amount of QH over a minimum of one month was 504mg. This trial demonstrated that the as method can be used with no serious adverse effects confirming the safety of the as procedure.

The results of this Phase 1 trial and the previous research with results of the use of as method in over 175,000 women, establish the safety of as but most importantly, the rationale for this Phase 3 clinical program.

This clinical program will evaluate the safety and efficacy of using Quinacrine Hydrochloride pellets (QS), administered via a Quinacrine sterilization procedure (QS) to female subjects who voluntarily agree to QS as their choice of sterilization.

This Phase 3 program will be a multi-center trial. Thirty-six investigators will participate in this 36-center trial. Four hundred women are anticipated to complete this trial, and each center will recruit 8 to 15 subjects. Due to the expected attrition rate a total of 500

female subjects will be screened in order to meet the required number of 400 for statistical analysis. Subjects will be recruited directly by each center or referred to the participating clinics by other physicians and clinics in their respected communities. It is planned that each investigator site will complete their evaluations in an estimated projection of time of two and half years.

2 OBJECTIVE

This is a Phase 3, multi-center trial to evaluate the safety and effectiveness of the Quinacrine sterilization procedure (QS) in female subjects who voluntarily agree to QS as their choice of sterilization.

3 GENERAL

Approximately 500 women will be recruited on a volunteer basis to participate in this trial. It is anticipated that at least 400 women will complete this trial due to possible attrition rate that might occur during the follow-up phase. Thirty-six (36) investigators will participate in this multi-center trial. It is anticipated that each investigator will recruit 8-15 subjects or more depending on subject recruitment. Subjects will be recruited directly or referred to the participating clinics by other physicians and clinics in the community. Subjects will be carefully screened to ensure that only women with profiles that indicate that they are highly likely to complete the follow-up period, who have lived for at least the past 3 years in the local areas in which the clinical trials are being conducted and can provide names and phone numbers of at least two other relations who will know their whereabouts will be selected.

After having an educational visit on all methodologies of female sterilization and alternative birth control methods, each subject will be given an Informed Consent (IC) that will detail the QS procedure including all the risks and benefits.

Once the IC is signed each subject will undergo a complete physical examination, including a medical and gynecological history as well as baseline laboratory studies.

Subjects will then be given scheduled visits where safety and efficacy will be followed for an average of 24 months.

In rare instances, if additional insertions are needed, the subject may have to participate for 1 to 2 months more (See Section 4.5.5 Additional Insertion, page 15. All Adverse Effects (AEs) will be carefully recorded and reported according to CFR 312.32. (See Adverse Experience Reporting, Section 10)

All subjects will participate in the trial for an average of 24 months. It will be impressed upon the subjects of how important it is to complete the entire time period of the trial. Investigators and their staffs must be constantly aware of any changes in addresses and telephone numbers so as not to lose follow-up contact with the subjects. Each subject will undergo a pre-screening visit (Visit 1) for educational instruction and IC completion. Before volunteering for this trial, subjects will agree to have eight additional visits. Screening visit (Visit 2) and seven additional visits: Visit 3 through Visit 9, for a total of nine visits in all.

(An optional visit may be necessary during the first week after the initial administration of QH pellets). The first insertion of the QS pellets will be inserted at Visit 3 in the next proliferative phase of the subject's menstrual cycle. Four weeks after the initial insertion of QH pellets, the second administration of QH pellets will be inserted into the subject (Visit 4).

Subsequent visits designated for safety follow-up and efficacy will occur at the following intervals: one month after the second insertion of as pellets (Visit 5), 4 months after the second insertion (Visit 6), 10 months after the second insertion (Visit 7), 16 months after the second insertion (Visit 8), and 22 months after the second insertion (Visit 9).

4 MATERIALS AND METHODS

4.1 Subject Sample

Subjects who voluntarily agree to participate and accept the QS method as their choice of sterilization will be recruited for this investigational trial. These potential subjects will include normal subjects and difficult to treat patients, including those who are smokers or obese, or those with cardiovascular or pulmonary disease, autoimmune conditions and AIDS. For many of these patients, QS may be not only their safest choice but may be their only choice to limit family size.

4.2 Age Range

Subjects eligible to participate in this trial must be between the ages of 21 years and 45 years, inclusive.

4.3 Subject Inclusion Criteria

Each subject:

1. Must have had an educational visit to understand all the methodologies of

female sterilization and alternative birth control methods.

2. Must have signed a written informed consent. Each subject must have adequate written and oral comprehension of the English language to fully understand the informed consent and be able to converse with the investigator and other trial personnel.
3. Must have given authorization for use of research information under HIPAA regulations.
4. Must fully understand that the sterilization is not reversible.
5. Must be willing to volunteer to participate for the full duration of the trial including all follow-up visits (an average of 24 months).
6. Must be willing to take Depo-Provera® or other forms of contraceptives during the period when inflammation, sclerosis and scarring of the oviducts occur. (Approx 3 months) The patient can choose to continue the method she is currently using, although Depo-Provera® is the method of choice for this trial.

4.4 Subject Exclusion Criteria

1. Desire for reversible contraception.
2. Under the age of 21 or over the age of 45.
3. Any pelvic infection or a history of PIO within the last 6 months.
4. Any evidence of pregnancy.
5. Any uterine irregularities or presence of fibroids.
6. Uterus which sounds greater than 8 cm
7. Abnormal Pap smear. (Pap smear corrected to normal will not be excluded).
8. Abnormal cervical dysplasia or purulent vaginal or cervical discharge.
9. Abnormal uterine bleeding, especially if it is greater than 10ml. or intermenstrual bleeding that is not attributable to ovulatory bleeding.
10. Endometriosis.
11. A positive culture for gonorrhea or chlamydia (If adequately treated, subject will be allowed in the trial).
12. Current evidence of alcohol or drug abuse.
13. Psoriasis.
14. Porphyria.
15. A glucose-6-phosphate dehydrogenase (G6PD) deficiency.
16. A current use of chloroquine.

17. A history of mental illness.

4.5 Trial Procedures

4.5.1 Procedures for Quinacrine Sterilization (QS)

Medical Personnel Prerequisites

All medical personnel involved in this project will be aware of the ethical principles of the Declaration of Helsinki, the International Committee on Harmonization {ICH), the obligations of Good Clinical Practice (GCP) and HIPAA requirements. (An internet course about 60 minutes long on these subjects is sponsored by the NIH at the following website: https://grants.nih.gov/policy-and-compliance/policy-topics/clinical-trials/good-clinical-training. Upon completion of the web-based tutorial, an option to print a certificate of completion is available). GCP Investigator obligation instructions will be given at the Investigators' Meeting and at the pre-investigational site visit by qualified personnel of the sponsor.

4.5.2 Prescreening (Visit 1)

Each subject who volunteers to participate in this trial and chooses sterilization as their method of limiting family size will be informed, via education: including a video and an informed consent about QS method and technique. Furthermore, all methods of contraception, including pills, injectables, implantables, barriers, and other techniques of surgical sterilization will be discussed before each subject agrees to participate in this trial. Subjects will be given a chance to ask questions and discuss all the options of birth control and sterilization. Those subjects who choose to participate in this clinical trial will be given an informed consent that will thoroughly explain every detail of the Quinacrine sterilization procedure. The informed consent will also cover the requirements of HIPAA. Subjects will have every opportunity and will be encouraged to ask questions at any time in order to clarify any issues about QS and other methods of birth control. Only those subjects who have a full understanding of Quinacrine sterilization methodology will be asked to sign an informed consent. Once this informed consent is signed, the subjects can directly go to Visit 2 or schedule a date for Visit 2.

4.5.3 Prescreening (Visit 2)

Only subjects who have signed an informed consent and meet all the inclusion and exclusion criteria will enter the screening period (Visit 2). Each subject who qualifies will undergo a complete medical and gynecological history and be administered a complete physical and gynecological examination, including an (ECG), a recent chest X-ray (within the past 6 months), a CMP (Complete Metabolic Profile), hematology, and urinalysis. Subjects will be told about any findings, negative and positive. A Papanicolaou smear (Pap} and culture for gonorrhea and chlamydia will be taken at this visit, and the results of these tests will be discussed before Visit 3 is scheduled. At this screening visit (Visit 2), a human chorionic gonadotrophin (hCG) urine pregnancy test (UPT) will be done. The UPT, which uses monoclonal antibodies against the hormone of pregnancy, i.e., human chorionic gonadotrophin, is exquisitely sensitive and able to detect as little as 25 mIU of hCG, with standard commercially available tests. Pregnant women will be excluded from the trial and referred to an obstetric/gynecology clinic. Subjects with gonorrhea or chlamydia will be excluded from the trial until adequately treated. Similarly, subjects with suspicious Pap smears will be referred to the gynecologic oncology clinic. After adequate

examinations and tests have established a normal cytology, subjects will be allowed to be re-screened for the trial providing they meet all the inclusion and exclusion criteria.

All subjects qualifying for this trial will choose a contraceptive method that will provide three months of protection to ensure that the subjects do not become pregnant between the two insertions of Quinacrine and to allow time for the scaring to occlude the oviducts. Contraceptive methods should be ascertained on Visit 2 (Screening) and must be used through Visit 6. The following lists are the suggested contraceptive methods to be used during the scar forming period.

- Depo-Provera® (medroxyprogesterone acetate) 150 mg (IM)
- IUD
- Diaphragm with jelly
- Condoms
- Abstinence
- Withdrawal

All subjects qualifying to undergo QS will be asked to call the clinic when their menses begin so that Visit 3, first insertion of Quinacrine, can be scheduled.

Patients that are on DMPA can be scheduled at a convenient time.

A Quality-of-Life Questionnaire will be done at this visit.

4.5.4 Subject Preparation and First Insertion Procedures (Visit 3)

On the day the subject is scheduled for her first QS procedure Visit 3, the medical personnel will confirm that each subject has met all inclusion and exclusion criteria and has had a complete physical and gynecological examination, a negative hCG/UPT, and that their lab work, Pap smears, cultures, recent chest X-rays, and ECGs have all been reported back as within normal limits. Patients with treatable abnormalities, such as positive Pap smears and positive cultures for STDs, will be readmitted to the trial when test results are within normal limits.

If all requirements are met and a negative hCG/UPT has been confirmed at Visit 3, the subject will be prepped for Visit 3. Each subject will be treated in a dignified manner at all times. After being dressed in a gown and covered with a clean sheet, the subject will be positioned on the examining table with legs in stirrups. A pelvic examination will be done, any

pathological findings at that time either will be treated or the subject will be referred to an appropriate clinic for evaluation and treatment and asked to return for QS procedure at a future date. If the subject meets all the inclusion and exclusion criteria and the physical and gynecological examinations are negative, a slightly warmed speculum will be placed in the vagina to expose the cervix. The vagina and cervix will be cleansed with Betadine® or some other antiseptic. The lip of the cervix will be grasped with a tenaculum. By pulling the cervix down, the uterus will be straightened. The uterine cavity will then be gently sounded for depth. If greater than 8 cm. as will not be done.

A circulating assistant will open the as package. The physician will remove the inserter from its sterile package and count the pellets in the inserter, making sure that there are seven pellets of Quinacrine Hydrochloride in the inserter. The flange on the inserter will then be adjusted to 0.5 cm short of the depth of the uterus as previously determined with the uterine sound. This depth is the measurement from the fundus of the uterus to the external os of the cervix. The inserter will be carefully placed into the uterine cavity to touch the flange to the external os. The physician will then gently and slowly insert the seven pellets by pushing on the plunger, carefully

placing all pellets at the very top of the uterine fundus.

The inserter is then removed, and the tenaculum is disconnected. The physician will assess any bleeding coming from the uterus. Blood coming from the hole in the cervix made by the tenaculum will not be counted.

4.5.5 Additional Insertion

In the rare instance, where the subject has excessive bleeding after the first insertion of the QH pellets, e.g., greater than an estimated 5 ml. of blood, the subject must be scheduled for an additional insertion of seven 36 mg of QH pellets, one month after her first insertion. This additional insertion will be administered one month prior to her normally scheduled second insertion at Visit 4. At this insertion the subject will repeat the same procedures that she received at Visit 3 (first insertion). This additional insertion is based on the clinical trial done by El-Katy, et. al[25]. They found in a small percentage of women who experienced excessive bleeding after an insertion of the QH pellets, that about ten percent of these women did not become sterilized. However, when a follow-up insertion was done, when the bleeding

ceased, there was an increase of success in 98% to 99% of the subjects.

If the subject is scheduled for this additional insertion, the information and reason why this additional insertion was done must be completed on the supplemental page in the case report form book. This page will be entitled **Visit 3A-Additional Insertion**.

Subjects will be warned about the possibility of cramps and advised to take acetaminophen if the symptoms warrant a treatment. Subjects will also be instructed to douche if they experience a yellow-green discharge that may occur that night or the next day in order to avoid itching of the vagina and vulva.

Before subjects leave the clinic after the first insertion or the additional insertion they will be asked to lie on the examining table or an adjacent couch for a minimum of 30 minutes after QS procedure. They will be evaluated for any complaints or AEs, and these complaints will be appropriately treated and recorded on the case report form. They will then be discharged from the clinic after they have scheduled a date for Visit 4, or four weeks after the initial insertion of Quinacrine pellets. Those subjects who were prescribed an additional insertion at Visit 3a

will proceed to Visit 4 and follow the same schedule as described in the following sections below.

If subjects experience any adverse experiences, they will be told to call the clinic and schedule a visit before Visit 4 (See Optional Visit, Section 4.5.6).

4.5.6 Optional Visit

Before Visit 4 (during the four weeks after Visit 3), after the first insertion of the QS procedure, some subjects may need a follow-up visit if the reported adverse effect requires treatment. All symptoms or complaints will be recorded in the case report form on the AE form. If this visit is scheduled, physical, gynecological and safety assessments will be done at this time. Any questions that the subject might have will be answered and recorded. Any additional evaluations will be entered in the CRF, under Optional Visit, along with a reason for this visit. All AEs must be reported to the Chief Investigator within 48 hours after the investigator becomes notified.

4.5.7 Second Insertion Procedures (Visit 4)

If the subject did not have to have an additional visit as stated in 4.5.5, they will immediately be scheduled after Visit 3 for their second insertion one month

later. At Visit 4 subjects will return to the clinic for a physical and safety assessment (an hCG/UPT will be done to determine that there is no pregnancy}. A Complete Metabolic Profile (CMP), hematology and urine analysis will be done. Any changes in physical findings or symptomatic reactions will be recorded or treated if necessary. Any AEs that have not been reported previously will be recorded and forwarded to the IRS, chief investigator and to the FDA. A physical examination, ECG, and laboratory tests will be performed at this visit and before the second insertion of QS is administered. All procedures to prepare the subject for the second insertion of QS, as administered in the first insertion (section 4.5.4) will be followed.

Prior to the second insertion of QS a Quality-of-Life Questionnaire will be completed.

4.5.8 Additional Insertion

Again, in the rare instance, where the subject has excessive bleeding after the second or third insertion of the QH pellets, e.g., greater than an estimated 5 ml. of blood, the subject must be scheduled for an additional insertion of seven 36 mg of QH pellets, one month after her second or third insertion. This additional insertion will be administered one month

after her first additional insertion or her second scheduled insertion. At this insertion the subject will repeat the same procedures that she received at Visit 3 (first insertion). The rationale for this insertion is the same as was stated under 4.5.5.

If the subject is scheduled for this additional insertion, the information and reason why this additional insertion was done must be completed on the supplemental page in the case report form book. This page will be entitled **Visit 4A-Additional Insertion**.

Subjects will be warned about the possibility of cramps and advised to take acetaminophen if the symptoms warrant a treatment. Subjects will also be instructed to douche if they experience a yellow-green discharge that may occur that night or the next day in order to avoid itching of the vagina and vulva.

Before subjects leave the clinic after the first insertion or the additional insertion they will be asked to lie on the examining table or an adjacent couch for a minimum of 30 minutes after QS procedure. They will be evaluated for any complaints or AEs, and these complaints will be appropriately treated and recorded on the case report form. They will then be discharged from the clinic after they have scheduled a

date for Visit 4, or four weeks after the initial insertion of Quinacrine pellets. Those subjects who were prescribed an additional insertion at Visit 3a will proceed to Visit 4 and follow the same schedule as described in the following sections below.
If subjects experience any extraordinary adverse experiences, they will be told to call the clinic and schedule a visit before Visit 4 (See Optional Visit, Section 4.5.6).

4.5.9 Visit 5

At the end of one month after the two QS procedures are completed, subjects will return to the clinic for their visit 5. They will receive a physical and pelvic examination ECG, and an hCG/UPT. In addition, they will have a CMP and hematology and urinalysis tests. Any AE assessments will also be recorded and reported accordingly.

A Quality-of-Life Questionnaire will be done at this visit.

4.5.10 Visit 6

At the end of 4 months after the second insertion of QS, subjects will return to the clinic for their visit 6. They will receive a physical and pelvic examination,

ECG and an hCG/UPT. In addition, they will have a complete CMP hematology and urinalysis tests. Any AE assessments will also be recorded and reported accordingly.

A Quality-of-Life Questionnaire will be done at this visit.

4.5.11 Visit 7

Ten months after the second QS insertion, subjects will receive a physical and pelvic examination, ECG and an hCG/UPT. In addition, they will have a CMP and hematology and urinalysis tests. Any AE assessments will also be recorded and reported accordingly.

A Quality-of-Life Questionnaire will be done at this visit.

4.5.12 Visit 8

Sixteen months after the second QS insertion, subjects will receive a physical and pelvic examination, ECG and an hCG/UPT. In addition, they will have a CMP and hematology and urinalysis tests. Any AE assessments will also be recorded and reported accordingly.

A Quality-of-Life Questionnaire will be done at this visit.

4.5.13 Visit 9

Twenty-two months after the second QS insertion, subjects will receive a physical and pelvic examination, ECG and an hCG/UPT. In addition, they will have a CMP and hematology and urinalysis tests. Any AE assessments will also be recorded and reported accordingly.

A Quality-of-Life Questionnaire will be done at this visit.

5 EVALUATIONS

5.1 Efficacy Evaluations

Efficacy will be determined on pregnancy rate only. Subjects will undergo an hCG/UPT at Visits 2, 3, 4, 5, 6, 7, 8 and 9; efficacy of QS will be based on the hCG/UPT at Visits 5 through 9.

5.2 Safety Evaluations

Safety evaluations will include the following procedures:

- Physical examination, including height, weight, and vital signs.
- Pelvic examination
- 12-lead ECG.
- A CMP (Complete Metabolic Profile)

  Automated Chemistry Panel (Serum)
  Glucose, blood urea nitrogen (BUN), creatinine, sodium, potassium, chloride, uric acid, calcium, total protein, phosphorus, albumin, globulin, albumin/globulin (A/G) ratio, total bilirubin, alkaline phosphatase, gamma-glutamyl transpeptidase

(GGTP), aspartate aminotransferase (AST [SGOT]), alanine aminotransferase (ALT [SGPT]), lactate dehydrogenase (LDH), triglycerides, and total cholesterol.

- Hematology

  Hematology (Complete Blood Count) Hemoglobin, hematocrit, MCH, MCV, MCHC, RBC, WBC, platelets, RBC morphology, haptoglobin, and reticulocytes.

- Urinalysis

  Appearance, specific gravity, pH, protein, albumin, glucose, ketones, bilirubin, urobilinogen, blood nitrite, blood (RBCs), leukocyte esterase (WBCs). (A urine dipstick may be positive for protein, hemoglobin, nitrite and leukocyte esterase, and may thus indicate a need for a microscopic exam.)

- Papanicolaou test

  Glucose-6-phosphate dehydrogenase (G6PD) deficiency test

These Safety evaluations will be conducted at Visits 2, 3, 4, 5, 6, 7, 8 and 9 as outlined in the following schedule:

Visits 2, (Screening)

The following tests will be conducted at Visit 2 before the subject is allowed to receive the first insertion.

- Physical and Pelvic examinations
- Recent Chest X-ray (within 6 mos.)
- ECG
- Complete Metabolic Profile (CMP)
- hCG/UPT
- Hematology/Urinalysis
- Papanicolaou Test, unless patient has had a negative Pap smear within the past 11 months
- Culture for Gonorrhea

Visit 3, before the first insertion of QH, the following tests will be done:

- hCG/UPT
- Pelvic examination

Visit 4, before the second insertion of QH, the following tests will be done:

- Physical and Pelvic exams
- ECG

- CMP
- hCG/UPT
- Hematology/Urinalysis

Visit 5, one month after the second insertion of QH: the following tests will be done:

- Physical and Pelvic exams
- ECG
- CMP
- hCG/UPT
- Hematology/Urinalysis

Visit 6, four months after the second insertion of QH: the following tests will be done:

- Physical and Pelvic exams
- ECG
- CMP
- hCG/UPT
- Hematology/Urinalysis

Visit 7, ten months after the second insertion of QH: the following tests will be done.

- Physical and Pelvic exams
- ECG
- CMP
- hCG/UPT
- Hematology/Urinalysis

- Papanicolaou Test, unless patient has had a negative Pap smear within the past 12 months

Visit 8, sixteen months after the second insertion of QH the following tests will be done:

- Physical and Pelvic exams
- ECG
- CMP
- hCG/UPT
- Hematology/Urinalysis

Visit 9, twenty-two months after the second insertion the following tests will be done:

- Physical and Pelvic exams
- ECG
- CMP
- hCG/UPT
- Hematology/Urinalysis
- Papanicolaou Test, unless patient has had a negative Pap smear within the past 12 months

5.3 Quality of Life Questionnaire

This will be done at Visit 2 (Screening), Visit 4, Visit 5, Visit 6, Visit 7, Visit 8 and Visit 9.

6 TRIAL MEDICATIONS AND SURGICAL MATERIALS

6.1 Trial Medication

Each subject who volunteers for the Quinacrine sterilization (OS) procedure will receive a total of 504 mg of Quinacrine Hydrochloride (OH) in two divided doses of 252 mg each. Each of the 252 mg doses will be divided into seven pellets, each pellet containing 36 mg of Quinacrine Hydrochloride. Each cylindrical pellet is 3 mm in diameter and 5.5 mm in length. Tablets can be stored in a secure area at room temperature (50° to 77°F or 10° to 30° C)

6.2 Delivery System Inserter

Delivery of the seven Quinacrine pellets at each OH insertion visit will be administered via a three-part disposable plastic inserter specifically designed and manufactured for the OS procedure. Each inserter is preloaded with seven OH pellets and individually packaged in a plastic sterile pouch. The three parts of this delivery system consists of: a hollow tube 4 mm in diameter, which will house seven OH pellets, a push rod or plunger used to expel the pellets from the tube, and an adjustable flange to assure the tip of the

inserter is properly located 0.5 cm from the very top of the uterine fundus. The hollow tube will be filled with seven 36 mg QH pellets for a total of 252mg OH. The tube has been partly rounded on one end. This partial enclosure is to prevent the pellets from escaping from the tube until the tube is correctly positioned in the uterine cavity and until the administrator delivers the pellets by pushing the plunger to expel the pellets. The packaged inserters are gamma irradiated for sterility.

6.3 Assignment of Trial Medication

Each Quinacrine sterilization subject will receive two Quinacrine sterilization procedures as described in this protocol under Sections 4.5.4 and 4.5.7. There are two packages of inserters per box. Each box will be labeled in sequence, starting with 01 to 500 (enough to allow for subject attrition). The two packaged inserters in each box will also be labeled to correspond to the box number assigned to each subject, i.e., 01A and 018. In this way, Box 01 will contain two inserters labeled 01A and 01B. Box 02 will contain 02A and 028, and so on. Each collaborating investigator will be designated specific numbers during the course of the multicenter investigation.

6.4 Labeling of Trial Materials and Storage

For those subjects assigned to the as procedure, the trial materials will be labeled according to Federal Regulations. "For investigational Use Only." Each box will be labeled in sequence starting with number 01 on the box. Each box will contain the two packaged inserters each preloaded with seven 36mg pellets of QH, one labeled 01A and the other 01B.

Quinacrine uterine inserters (sterile) are stored at controlled room temperature conditions and in 60% relative humidity.

6.5 Trial Medication Administration Procedure

Each as subject will be prepared to receive the as procedure according to the Subject preparation as described in section 4.5.4 of this protocol. As described in section 4.5.4, the flange of the inserter will then be adjusted to 0.5 cm short of the depth of the uterus as previously determined with the uterine sound. The inserter will be gently inserted into the uterine cavity. The physician will then gently and slowly insert the seven pellets by pushing on the plunger, carefully placing all pellets at the very top of the uterine fundus. The inserter is then removed and the tenaculum is disconnected.

6.6 Trial Medication Dosage

Total dosage of Quinacrine Hydrochloride is 504 mg. 252 mg will be administered at Visit 3 via 7 pellets of 36 mg each, and 252 mg will be administered at Visit 4 via 7 pellets of 36 mg each.

The schedules for insertion of the drug will be at Visit 3 or in the next proliferative phase of the menstrual cycle after the screening Visit 2 and at the next scheduled visit (Visit 4) or approximately four weeks after Visit 3.

Dosages will only be increased when the subjects need additional insertions as stated in Section 4.5.5 (Additional Insertion). In these cases, subjects will receive either a total of 756mg or 1,008mg according to how many insertions are needed.

7 DRUG ACCOUNTABILITY

When the investigator or the pharmacist receives trial supplies, he/she will check for accurate delivery, then sign and return the Drug Delivery form. The sponsor's clinical research monitor will confirm that all supplies are properly accounted for before the initiation visit. Collaborating investigators will be assigned specific numbers for an initial 4 subjects; additional supplies will be assigned as requested and according to subject recruitment. Drug medication will be sent to the participating center when written approval for the investigation is granted from the IRB for the protocol and informed consent and the Investigator has been trained on the QS method.

In accordance with Federal Regulations, all trial materials will be kept in a secure location with restricted access. All unused trial materials will be returned to the sponsor at the end of the investigation and an accountability of the drug will be recorded.

8 OVERALL DURATION OF PROCEDURAL EVALUATIONS AND TRIAL COMPLETION

The overall evaluations for each subject will be approximately 24 months starting from the screening visit to the completion of the last evaluation. Each subject will be expected to complete the full term of the trial.

The expected time for the completion of eight to fifteen subjects at each investigative site will be approximately 36 months. Investigators who do not enter at least six subjects within the first 6 months of trial initiation will be reevaluated as to their continued participation in this trial. All subjects must be entered within 10 months of the trial initiation.

9 CONCOMITANT MEDICATIONS

Other than the prescribed medications by the investigator e.g., Depo-Provera® etc., or recommended analgesics when needed, no other concomitant medication will be allowed during the course of this clinical trial. If the occasion arises where concomitant medications are necessary for the subject's well-being the investigator will follow the subject closely to assure that there are no drug interactions.

All concomitant medications must be entered in the concomitant section of the case report form. Since recall is not always reliable, patients will receive a calendar-diary to use to record any medication taken during the intervals between visits. Specific attention must be given to dates started and stopped for each concomitant medication. These calendars will be collected and discussed at each visit.

10 ADVERSE EXPERIENCES (AEs) REPORTING

Subjects will be questioned at each visit regarding the occurrence of any AEs (see Appendix 2). Any AEs reported will be completely described, including symptoms, signs, severity, time of onset, duration, evaluations, therapy, and assessment of relationship to the QS procedure. Any serious or unusual AEs reported by the subject must be reported from each investigational site to the chief investigator immediately. The following contact information of the Chief Investigator should be posted at each investigational site.

Jack Lippes, MD (Chief Investigator) State University of New York at Buffalo Women and Children's Hospital Office: 31 Hampton Hill Drive
Buffalo, New York 14221 (716) 633-6663 Office
(716) 390-4482 Cell
E-mail: jlip@acsu.buffalo.edu

or

Richard A. Guarino, MD (Project Monitor) Oxford Pharmaceutical Resources, Inc.
One U.S. Hwy. 46 West Totowa, NJ 07512

(973) 256-0600 Office
E-mail: guarino@oxfordpharm.com

Such AEs will be reported to the FDA.

11 EARLY WITHDRAWAL FROM TRIAL

Reasons for withdrawal may include, but are not limited to, the following:

Either at the investigator's request, for safety reasons (e.g., severe AEs, pregnancy), or at the subject's request.

All premature discontinuations and their causes will be documented on the clinical record. If the withdrawal is due to an Adverse Experience this must be noted on the AE form in the case report form book. Subjects who discontinue prematurely will be encouraged to return for laboratory tests before they leave the trial and will be followed up until their condition is reported as normal.

Subjects, who leave before the second insertion of as, will be warned that they may still get pregnant. Those who leave after the 2nd as insertion will be asked to return for laboratory tests and physical and pelvic examinations. Subjects are free to withdraw from participating in this trial at any time and for whatever reason, specified or unspecified, and without prejudice.

12 STATISTICAL METHODOLOGY

12.1 Data Management

All clinical data will be collected on appropriate Case Record Forms or received via secure electronic transfer from central sources, as appropriate. All clinical data will be authenticated by investigator(s) and/or qualified core laboratory staff. Processing of all clinical data will be performed using a fully validated clinical data management system and methodology, including quality control procedures for clinical review of the data, issuance of queries regarding potential data discrepancies, performing database updates based on investigator-signed responses to such discrepancies, and maintaining audit trails of all such activity. The clinical database will undergo a QA assessment prior to being locked for statistical analysis.

12.2 General Statistical Considerations

Data summaries and analyses of safety and efficacy will be conducted to evaluate relevant within-subject

changes from baseline in safety parameters and to present the primary efficacy analysis results for pregnancy rate. All such data will be presented by visit, both in summarized tabular displays and in raw data listings.

Inferential tests of statistical hypotheses of safety parameters, including adverse events and laboratory results, will be employed to assess the likelihood that any observed changes from baseline could have occurred by chance, taking into account between-subject variability in the parameter under evaluation. Because there is no prospective control group, any comparisons will be based on changes across visits. For testing purposes, alpha will be set at 0.05 and two-tailed tests will be used. The null hypothesis will be that there are no changes in parameters, scores, or incidence values from the first QS insertion visit (Visit 3) through subsequent visits. All analyses will be performed using SAS Version 8.2 or later.

12.3 Analysis Populations and Missing Data Extrapolation

Primary safety and efficacy analyses will be based on the intention-to-treat population, including all subjects who received the QS first insertion at Visit 3 and provided any follow-up data. For patients who

receive the full treatment (both insertions) but are subsequently lost to follow-up, diligent attempts will be made before the end of the study to determine whether a pregnancy has taken place, and if so, when it occurred. If no information is available after such attempts, for analysis purposes it will be assumed that the patient did not have a pregnancy. However, a sensitivity analysis will also be performed, including all patients who received at least one insertion visit, where it is assumed all such patients did become pregnant. Both sets of pregnancy incidence results will be presented. Safety data from patients who left the study after only one insertion visit will be presented separately. They will not be included in primary efficacy analyses.

For safety analyses, missing data will be extrapolated using a last-observation-carried-forward strategy. This will include laboratory data, physical examination data, pelvic examination data, ECG data, and adverse events.

12.4 Safety

Safety listings and summaries will be provided for laboratory data, physical examination data, pelvic examination data, ECG data, adverse events (including serious adverse events), and concurrent

medications. Adverse events will be coded using MedDRA and summarized and tabulated by major term and body system. Concurrent medications will be coded and summarized using WHODRUG. Data listings will display laboratory and other safety parameters by study visit. There will be no inferential testing of safety parameters; however, laboratory shift tables will be prepared to show the proportion of subjects with shifts from normal to abnormal values over time.

12.5 Efficacy

The primary efficacy objective is to evaluate the pregnancy rate in patients who received the full course of therapy (both insertion visits). The pregnancy rate will be calculated and displayed along with appropriate confidence intervals. The primary analysis will assume patients lost to follow-up did not become pregnant, unless diligent follow-up before the end of the study indicates otherwise. A second sensitivity analysis of pregnancy rate will be performed which includes all patients who received at least one insertion visit, and in that analysis, it will be assumed that all patients lost to follow-up with no known pregnancy status did become pregnant. This analysis will be characterized as the intention-to-treat analysis.

In addition, a Quality-of-Life Questionnaire will be administered.

13 REGULATORY AND ADMINISTRATIVE REQUIREMENTS

13.1 Institutional Review Board

The protocol and the informed consent document contain HIPAA requirements to be used in this trial must be submitted to the investigator's appropriate Institutional Review Board (IRS) for approval. Written documentation of approval of both the protocol and the informed consent must be provided to the sponsor before the trial is initiated.

The reviewing IRB must be in compliance with the Code of Federal Regulations (21 CFR 56). After approval by the IRB committee, the following will be sent to the sponsor before the trial supplies can be shipped to the investigators.

- A letter documenting the IRB approval of the protocol (indicating its title and number) AND the approved Informed Consent document with the HIPAA information.

- A list of the IRS members, their representative capacity, and their affiliation.

N.B. The investigator will promptly report to the IRS any changes in the research activity and will not implement those changes without IRB approval unless it is to protect the subject's safety and welfare.

13.2 Informed Consent

Each subject must sign an informed consent with the investigator before participating in the trial. The investigator will fully explain the purpose of the trial to the subject.

Subjects will be informed thoroughly, via informed consent, about Quinacrine Sterilization (QS) based upon the medical literature to date and the history and outcomes of this procedure. These will be fully explained and demonstrated at the pre-screening visit. Subjects will be given a chance to ask questions and discuss all the other options of sterilization before signing the informed consent and to clarify any issues about QS. Only those subjects who accept and have a full understanding of QS will be asked to sign an informed consent.

The investigator or sub-investigator is responsible for obtaining informed consent, signed by each subject before she enters into the trial. The person obtaining the informed consent will witness the subject's signature. A notation will be made in the subject's medical record indicating the date informed consent was obtained.

A copy of the consent form will be maintained on file in the subject's permanent medical records. The signed consent forms may be inspected at FDA's request.

13.3 HIPAA

For the purpose of this trial, HIPAA requirements will be incorporated into the informed consent. The Office of Civil Rights (OCR) as well as the FDA's General Counsel has confirmed that IRB approval of subject authorization for use or disclosure of Personal Health Information (PHI) required by HIPAA privacy rule is only required if the authorization language is going to be part of the IRB approved informed consent document for human subject review.

13.3 Regulatory Documents

The following documents will be submitted to the sponsor prior to the initiation of the trial:

1. Documents pertaining to IRS approval outlined in Section 13.1.
2. A signed completed copy of FDA Form 1572.
3. Curricula vitae of the principal investigator and sub-investigators named on FDA Form 1572.
4. A copy of the protocol agreement page signed by the investigator.
5. Clinical laboratory normal ranges, the laboratory director's curriculum vitae, and a copy of the laboratory registration certificate.

14 AMENDMENTS OR ADDENDA TO THE PROTOCOL

Neither the investigator nor the sponsor will make changes in this protocol without first obtaining the written agreement of the other. If in the investigator's opinion changes or must be made to protect the patient's safety and welfare, these must be documented and immediately reported to the IRB and the sponsor.

15 MONITORING/ON-SITE VISITS (SPONSOR AND FDA)

The investigator will be visited by a research monitor appointed by the sponsor at the investigative site prior to the trial and at regular intervals during the course of the trial.

These visits are to review the protocol and to ascertain that the facility is adequate for satisfactory conduct of the trial, as well as to discuss the obligations of both the sponsor and the investigator in complying with Good Clinical Practices (GCPs).

The monitor will visit the investigative site at regular intervals throughout the trial. The inspections are for the purpose of assessing the progress of the trial, verifying adherence to the protocol, determining the completeness and exactness of the data being entered on the CRFs, and assessing the status of trial supplies storage and accountability. During site visit, CRFs will be examined by the trial monitor(s) and verified by comparison with corresponding source documents (such as hospital and/or office records).

If requested, the investigator will permit a trained authorized employee of the FDA, to inspect all CRFs

and corresponding portion of the trial subjects' original office and/or hospital medical records.

16 ACCEPTABILITY OF CASE REPORT FORMS (CRFs)

Case report forms are to be completed for each subject. All forms must be filled out neatly in black ink or typed. Only physician Investigators (listed on the Form 1572) can make entries in the CRFs. The investigators named on the FDA Form 1572 will sign and date each CRF. Corrections of data on the CRFs may be made by crossing out (using a single line) the incorrect data and writing the correct entries next to those crossed out. All corrections must have the initials and dates of the person making the entry and the data change. Neither the sponsor nor representatives of the sponsor will be permitted to write on the original CRFs. Completed case records will be submitted to the sponsor according to instructions. Case report forms will be reviewed by the sponsor's monitor, who will make a decision as to their acceptability. Photocopies of original laboratory slips or computer printout of the relevant data must be available for inspection by the sponsor upon request.

At intervals during the trial and at the conclusion of the trial, the trial monitor will retrieve signed and dated originals and copies of CRFs from the trial site

for data entry. The investigator will keep a copy of all CRFs and source documents.

17 DRUG ACCOUNTABILITY AND RECORD KEEPING

The investigator will acknowledge receipt of and keep an inventory of all supplies received. lnvestigational supplies should be kept in a secure place and distributed only by authorized individuals. It will also be the responsibility of the investigator to accurately record the number of QS packages used for each subject. At the conclusion of the investigation, all unused supplies will be returned to the sponsor.

18 COMPLETION OF TRIAL

The investigator will complete and report (submission of CRFs) that his/her trial is in satisfactory compliance with the protocol within the agreed-upon time span. Continuation of this trial beyond this date must be mutually agreed upon in writing by both the investigator and the sponsor. It is agreed that, for reasonable cause, either the investigator or the sponsor may terminate the trial before the above date, provided that written notice is submitted at a reasonable time in advance of intended termination.

19 RECORDS RETENTION

Federal law requires that all CRFs and a copy of all records (e.g., informed consent forms, laboratory reports, source documents, dispensing record, etc.) that support CRFs of this trial be retained in the files of the responsible investigator for a minimum of 2 years after approval of an NOA or withdrawal of the application. The sponsor will notify the investigator in writing of this retention period. If the responsible investigator retires, relocates, or withdraws from this responsibility, custody may be transferred to a person who will accept this responsibility. The sponsor must be notified in writing of the name of the new custodian.

20 PUBLICATION OR PRESENTATION OF RESULTS

The investigator should not publish, present, or use any results arising out of performance of the trial for his/her own instructional research and/or publication objectives, unless prior approval is obtained from the sponsor.

21 INVESTIGATOR AGREEMENT

I have read the foregoing protocol "A Phase 3 Multi-center Clinical Investigation to Evaluate the Safety and Effectiveness of Quinacrine Hydrochloride (QH) Pellets Administered via Quinacrine Sterilization Procedure (QS) to Female Subjects Who Voluntarily Agree to Choose QS as Their Method of Sterilization"

I agree to conduct the trial according to this protocol and applicable FDA regulations, IRB and HIPAA requirements.

_____ _____

Investigator Date

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APPENDIX 1 TRAIL FLOWCHART

Procedures	Visit 1 Pre Screening	Visit 2 Screening	Visit 3 1st insertion	Visit 4 2nd insertion	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9*
Educational Instructions	X								
Informed Consent	X								
Inclusion/Exclusion Criteria		X							
Medical/Gynecological History		X							
Physical Examination including pelvic examination		X	X	X	X	X	X	X	X
Recent Chest X-Ray (within the past 6 months)		X							
ECG		X		X	X	X	X	X	X
CMP (Complete Metabolic Profile)		X		X	X	X	X	X	X
hCG/UPT		X	X	X	X	X	X	X	X
Hematology/Urinalysis		X		X	X	X	X	X	X
Papanicolaou Test		X					X		X
Culture for Gonorrhea		X							
Contraceptive Administration		X	X	X	X				
Adverse Experience Report			X	X	X	X	X	X	X
Quinacrine Pellets Inserted			X	X					
Quality of Life Questionnaire				X	X	X	X	X	X

*Providing additonal insertions are not necessary (see section 4.5.5 ADDITIONAL INSERTIONS)

APPENDIX 2 ADVERSE EXPERIENCE DEFINITION GUIDE

"**Associated with the use of the procedure**" means that there is a reasonable possibility that the experience may have been caused by the QS procedure.

"**Serious adverse experience**" (SAE} means any experience that suggests a significant hazard, contraindication, or precaution. With respect to human clinical experience, a serious adverse experience includes any experience that is fatal or life threatening, is permanently disabling, requires inpatient hospitalization, or is a congenital anomaly, cancer or overdose.

"**Unexpected adverse experience**" means any adverse experience that is not identified in nature, severity, or frequency in the current investigator brochure or in the risk information described in the general investigational plan or elsewhere in the current application. These must be reported to the Chief Investigator immediately.

The Chief Investigator will notify the sponsor who will, in a written IND Safety Report notify the FDA and all participating investigators of any adverse experience associated with use of the procedure that is both serious and

unexpected. Such notification shall be made as soon as possible and in no event later than 15 days after the Chief Investigator's initial receipt of the information. There in turn will be reported to the sponsor.

N.B. The sponsor shall also notify FDA by telephone of any unexpected fatal or life-threatening experience associated with the use of the procedure in the clinical studies conducted under the IND no later than 7 days after receipt of the information. For purposes of this section, life-threatening means that the subject was, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e. it does not include a reaction that, had it occurred in a more serious form might have caused death. For example, drug induced hepatitis that resolved without evidence of hepatic failure would not be considered life threatening even though drug-induced hepatitis can be fatal.

EPILOGUE

The process below is what is required to gain FDA approval for Quinacrine sterilization (QS), a nonsurgical female sterilization method, as a drug for a new indication. Steps 1 through 5 are complete.

1. **Conduct Preclinical Studies (to establish safety):**
    a. Toxicology[13, 28, 30, 39, 40]
    b. Pharmacology[12, 26, 27, 29]
    c. Animal studies,
        i. 2006 mouse study showed QS does not cause cancer[31]
        ii. 2010 rat study does not cause cancer except at 60 to 83 times dosages women receive[32]
        iii. ISAF addressed these issues[33, 36, 37]
    d. Mechanism of action.[38]

2. Submit Investigational New Drug (IND) Application with the FDA (allowing human testing to begin):
    a. Preclinical data[4, 5, 41]
    b. Proposed clinical trial protocols – this book
    c. Manufacturing details (available)

3. Complete Clinical Trials:

Phase I: Conduct small-scale trials to assess safety and dosage in humans.[11,42]

Phase II: Test efficacy and side effects in a larger group. Phase II testing.[2, 6, 7, 8, 10, 14, 15, 16, 17, 19, 20, 23, 25, 34, 35]

Phase III: Run large, multi-center randomized controlled trials to confirm safety and effectiveness. FDA halts approved Phase III trial in 2006 and won't release hold in 2022.

4. Submit New Drug Application (NDA): Compile clinical trial data, safety profiles, labeling, and manufacturing details into an NDA for FDA review. The FDA evaluates whether benefits outweigh risks.

5. Address Regulatory Concerns: Respond to FDA queries, particularly about genotoxicity and carcinogenicity from past studies. Re-evaluations showing flaws in the 2010 rat study could support approval.[33, 34, 35, 36, 37, 38, 39, 40]

6. Post-Market Surveillance: If approved, implement Phase IV studies to monitor long-term safety and efficacy in a broader population. Challenges include funding, addressing safety concerns from the 2010 study, and completing large-scale Phase III trials, as no randomized controlled trials exist yet.

This book contains the FDA approved protocol for an ISAF Phase 3 QS trial halted in 2006 named:

"A Phase 3 Multi-center Clinical Investigation to Evaluate the Safety and Effectiveness of Quinacrine Hydrochloride (QH) Pellets Administered via Quinacrine Sterilization Procedure (QS) to Female Subjects Who Voluntarily Agree to Choose QS as Their Method of Sterilization."

Much research has happened since the FDA halted our clinical trial in 2006.

The preferred contraceptive method worldwide (24%) is surgical female sterilization. What if American women who didn't wish to have any more children could end their fertility non-surgically with QS now? Each might save about $6,000 in contraceptives and fees, and about a week's worth of time refilling and picking up prescriptions for 20-years of their lives.

Perhaps a better question is, can we easily help the largest underserved group to be more employed, energizing our middle class to increase social benefit and economic growth? Yes, we can, and it is affordable. If women used contraception 95% of the time instead of 65% in America, it would significantly reduce unintended pregnancies, allowing more women to remain in the workforce. If women used

contraception 95% of the time instead of 65%, the female employment ratio could rise by 4-5 percentage points, potentially increasing the employment rate from 64% to about 68-69%. This estimate is based upon a landmark study by Bailey et al. (2012) which demonstrated that access to contraception in the 1960s and 1970s was responsible for about 30% of the increase in women's workforce participation during that era. More recent studies, including those by the Institute for Women's Policy Research (IWPR), estimate that restricted access to reproductive healthcare, including contraception, reduces women's workforce participation by 10%.

What would this increase in employment of women be worth? According to a BBC article quoting The McKinsey Global Institute study, "$2.1 trillion could be added if the country raised its female employment ratio from 64% to 74% . . . and 6.4 million new jobs would need to be added to the U.S." Answer, if women used contraception 95% of the time instead of 65% then 64% to 69% increase in employment would lead to $1.05 trillion added to the GDP.

Non-surgical permanent contraception for women (QS), designated as a breakthrough device, is safer than surgical tubal ligation (TL), more effective than the pill, with no long-term side effects, and should be

available to women in the United States and worldwide today. The QS procedure, without general anesthesia, can be performed by a nurse practitioner. QS has been used by over 200,000 women in 53 countries with no deaths.

Since Dr. Jaime Zipper developed his pellet method in Chile in 1976, non-surgical permanent contraception for women (QS), has used seven (7) pellets, (36) milligrams each (252 milligrams total) of quinacrine inserted into the uterus of women with an IUD inserter in two doses. The first dose is inserted within 6 to 12 days after a woman's menstrual period starts. The second dose is inserted 1 month later. Lifetime dose is 504 milligrams.

When Dr. Zipper chose quinacrine (the most studied drug) for use to close fallopian tubes, he expected generalized scaring, as is seen when quinacrine is used to treat pleural effusion of the lung. Dr. Zipper never imagined that the use of quinacrine would stimulate a response by a woman's immune system when quinacrine molecules encountered certain specialized cells that are only found in the 2-4 mg intramural segment of the fallopian tube. In 2013, Growe et al. described that when administered into the uterus, quinacrine causes an acute pro-inflammatory response in the fallopian tubes, only

occurring in humans, and occluding the fallopian tubes.

Many clinical trials and peer reviewed papers of QS date back more than 40 years describing five million plus patient years. One trial involving 31,781 women in Vietnam was completed by Dr. Do Trong Hieu in 1992 and was published in the Lancet. These patients were interviewed regarding health outcomes approximately 16 years post exposure to compare QS (10503 interviews) versus intrauterine devices (9204 interviews) or tubal ligation (1333 interviews) for contraception. A 95% response rate based on the treated population resulted in a total of 21,040 interviews and found no significant increase in the long-term risk of reproductive tract cancer, hysterectomy, or ectopic pregnancy associated with the use of the QS method.

A Phase 1 clinical trial of QS was completed in the United States in 2000. Jack Lippes, MD application to USFDA for a Phase 3 clinical trial for QS, involving 40 centers, including 18 US medical schools, was approved in 2006. On January 10, 2007, the USFDA placed the Phase 3 study on a clinical hold. ISAF CEO Dr. Mumford's paper lists the flaws invalidating the Cancel et al. rat study that WHO referenced in its Interim Statement and that influenced the USFDA to

place the clinical hold and that was the basis for our formal appeal rejection at FDA in 2016.

USFDA requires carcinogenicity studies on pharmaceuticals used for 3 months or more. Why QS? Following the USFDA's March 6, 2007, request for a large epidemiology study and before the Degge Group responded to that request at a December 18, 2014, USFDA meeting, ISAF had already invalidated USFDA's assessment of the Cancel et al. (2010) position that quinacrine was a genotoxic carcinogen based on the work of renowned experts McConnell et al. and Haseman et al. ISAF continued with the USFDA requested large epidemiology study which in 2017 and 2018 proved unequivocally that there were no significant increases in the long-term risk of reproductive tract cancer, hysterectomy, or ectopic pregnancy associated with the use of the QS method. Since 2006, FDA's hold on QS has caused the deaths of hundreds of American women who died of tubal ligation, $72 billions in contraceptives, and a lot of effort for millions of women.

Half of all pregnancies in the world are unintended (121 million annually) and 218 million women are unable to get modern contraceptives. Reference our 568-page book with the full clinical story here.

Below is **ISAF Chronology of Events with FDA Clinical Hold-Formal Dispute Resolution**

- April 4, 2006 – International Services Assistance Fund (ISAF) submits an IND application for FDA acceptance to conduct a multicenter Phase 3 clinical trial in 500 women of quinacrine hydrochloride for intrauterine application to achieve permanent contraception via fallopian tube occlusion. The application results in IND 74,802.
- June-September 2006 – Institutional Review Board approvals obtained for 36 participating clinical sites, nearly half of them in university medical hospitals, including Yale Medical School, Cornell University, University of Louisville Health Sciences Center, Meharry Medical College, etc.
- October-November 2006 – Regional investigator trainings conducted (New York – October 5; Palm Beach, FL – October 13; Chicago – October 27; Phoenix – November 3). This included orientation to study protocol, laboratory practices (LabCorp), and case report form reporting.

- November 15-16, 2006 – Trial monitors training conducted (good clinical practice and case report form monitoring procedures).
- December 18, 2006 – Family Health International (FHI) distributes, worldwide in several different languages, a Dear Colleagues letter stating that the "weight of evidence" of their research, and particularly the results of a 2-year rat carcinogenicity study (CaBio), was causing them to discontinue their research and development of quinacrine sterilization (QS). The letter reports that, "The rat study showed a dose-related increase in malignant reproductive tract tumors at the end of the two-year observation period."
- January 2007 – ISAF prepares to commence the clinical phase of the Phase 3 trial, with January 10 internally identified as the date drug would be shipped to participating sites (due to the imposition of the clinical hold, however, no drug was ever shipped to any clinic).
- January 9, 2007 – FDA's Division of Reproductive and Urologic Products (DRUP) telephones ISAF to say they need to talk about ISAF's IND. ISAF asks to coordinate a conference call the following day between DRUP, ISAF and ISAF's Contract Research

Organization, Oxford Pharmaceuticals, Inc., which is arranged.

- January 10, 2007 – Teleconference with FDA/DRUP representatives and ISAF in which ISAF is informed by Dr. Scott Monroe, DRUP director, that, effective immediately, a clinical hold is being placed on IND 74,802 due to "limited information" received from the sponsor of a carcinogenicity study and a "press release" from the sponsor, i.e. the FHI Dear Colleagues letter.
- January 10, 2007 – In a DRUP report, Dr. Alex Jordan, the DRUP/FDA pharmacologist/toxicologist responsible for the FHI CaBio (IND 60,378), recommends the clinical hold to his supervisor, Dr. Lynnda Reid. His report states "Probably need to talk to the pathologist" about the CaBio results.
- January 16, 2007 – FHI faxes to ISAF two pages of information, requested by ISAF on January 12, containing one page of "background" and key "findings" from the CaBio, and a second page containing a table titled, "Incidence and Percent Incidence of Neoplasms: Uterus, Cervix, Vagina" from the study. ISAF, based on previously published reports, immediately recognizes that the three highest doses in the study had exceeded the maximum tolerated

dose (MTD) and would result in severe and irreparable damage to the rat uterus (as documented in the literature), and thus the results from those doses were not relevant to humans.

- January 18, 2007 – Dr. Lynnda Reid, FDA supervising DRUP pharmacologist, formally recommends a clinical hold on IND 74,802 in an internal FDA memo.
- February 2, 2007 – Dr. Scott Monroe issues FULL CLINICAL HOLD letter (see Volume 2, Section 2) to ISAF c/o Oxford Pharmaceutical Resources. The letter advises ISAF that, for the hold to be lifted,

"Long-term post treatment data from women previously treated with intrauterine quinacrine hydrochloride for non-surgical sterilization, which did not demonstrate an increased risk for the development of malignant reproductive tract tumors, would be required. The data will need to be obtained from an appropriately designed study, including sufficient duration of post treatment follow up and sufficient sample size to rule out an increased risk for the development of malignant reproductive tract tumors."

- February 2007 – ISAF contacts Dr. Ernest E. McConnell, veterinary pathologist and former Director of the Toxicology, Research & Testing Program for the National Institutes of

Environmental Health Sciences/National Toxicology Program, for a pathology/toxicology review of the available data and other information regarding the CaBio. Dr. McConnell expresses his concern that the array of tumors reported in the CaBio are not expected to be seen in 2-year rat studies and that he believes this signals a problem in the study's design. He begins an investigation into the study's design.

- February 26, 2007 – In response to questions from ISAF, ISAF receives additional CaBio data from FHI.
- March 6, 2007 – First Type A meeting of ISAF with DRUP to address the clinical hold. During this meeting, ISAF attempts to discuss the problematic scientific issues evident in the CaBio, including: the maximum tolerated dose (MTD) having been exceeded in the doses producing tumors, excessive mortality, and that the mechanism of action of quinacrine in the human fallopian tube is very different from the effect of quinacrine in the rat uterus. However, though some limited discussion ensued, and though FHI had given data to ISAF, DRUP refused to discuss this data stating that the CaBio information was proprietary.

- April 10, 2007 – ISAF contracts with Dr. Judith Jones, president of the Degge Group, Ltd., to carry out an epidemiological survey to document reproductive tract cancer risk of QS to women. Dr. Jones was from 1978-1983 the Director of the FDA Office of Drug Safety. Although not required to satisfy the terms of the clinical hold letter, ISAF broadened the primary endpoint in the study to include all cancers, and added secondary endpoints (hysterectomy, ectopic pregnancy and death) in an effort to gather additional safety information.
- June 26, 2007 – FHI responds, with full cooperation and in detail, to a second list of ISAF's questions regarding the CaBio design.
- July 2007 – Dr. McConnell meets with FHI CEO Al Siemens to discuss ISAF's concerns regarding the study design used for the CaBio.
- August 1, 2008 – ISAF requests a date for a Type A meeting with DRUP "as soon as possible" to allow ISAF science advisors to present their findings on the CaBio.
- August 26, 2008 – Dr. Terry Peters, DVM, a veterinary pathologist from FDA's Division of Neurology Products, submits to DRUP an internal pharmacology/toxicology review of the FHI CaBio, and raises some of the same

questions as ISAF's scientists about the study's design. Excerpt from Peters' report:

"On the basis of the information above [presented in her review]*, the use of the rat model to assess the potential carcinogenic effect of quinacrine dihydrochloride in the human uterus is questionable. The results of this specific study with low survival rates, the use of a slurry rather than the pelleted formulation and the unconventional nature of the sponsor's conclusions are issues that should be addressed when considering use of these results in carcinogenic risk assessment."*

- September 3, 2008 – ISAF's pre-Type A meeting package is sent to DRUP, including Dr. McConnell's toxicology report and histopathologic slides. Dr. McConnell's report concludes:

"It is my opinion that while QC [quinacrine] *caused uterine tumors at the 35/35 mg/kg and above, these tumors were related to severe damage of the uterine mucosa/submucosa and possibly the muscle wall, at a dose exceeding the MTD. Note that no such tumors were found at 5/5 mg/kg in the same study. The 5/5 mg/kg is not that much different from the 3.5/3.5 mg/kg dose used in the prechronic studies where no such lesions were observed. Therefore, I suggest that the results of the 35/35 mg/kg and above should be censored from the interpretation of whether QC is carcinogenic in rats. The appropriate dose-level for*

determining the carcinogenic potential is 5/5 mg/kg in the 2-year bioassay."

- September 9, 2008 – CAC Executive Committee reaches its recommendations and conclusions regarding FHI's CaBio:

"… the inflammatory changes in the reproductive tract in quinacrine treated rats were not sufficiently different than the changes which occur in the human fallopian tubes under conditions of use and therefore the findings in rats are relevant to humans….

"The Committee concluded that quinacrine increased the number of malignant tumors in the reproductive tract of rats and are considered relevant to humans under conditions of use."

The first sentence in this excerpt appears to be the basis for the FDA position on ISAF's clinical hold.

- September 17, 2008 – DRUP sets the Type A meeting date, requested on August 1, with ISAF for November 14, 2008. ISAF immediately contacts DRUP and asks that this meeting date be moved forward, as FDA Guidance stipulates that Type A meetings be granted within 30 days, so that it can occur before the World Health Organization (WHO) meeting on QS scheduled for October. ISAF is told that DRUP prefers not to meet with ISAF and our science advisors until after the WHO meeting. Though DRUP's letter setting the

meeting date, time and place confirms that they are scheduling a Type A meeting with ISAF, DRUP's minutes of this meeting identify it as a Type C.

- October 8-10, 2008 – World Health Organization technical consultation of an international panel of toxicology experts is convened specifically to discuss the CaBio's usefulness for assessing the relationship between quinacrine, when used for intrauterine administration for non-surgical sterilization in women, and cancer risk. Attending the meeting is DRUP toxicologist, Dr. Alex Jordan, who reports to WHO participants that the FDA has dismissed Dr. McConnell's report. As noted above, though ISAF had requested a Type A meeting with DRUP on August 1 to present Dr. McConnell's conclusions and its other experts' findings from their evaluation of the CaBio, DRUP refused to schedule the meeting until after the WHO meeting had taken place.
- November 14, 2008 – ISAF meets with DRUP in the long-awaited Type A meeting to present its expert consultants' findings from their evaluation of the CaBio, showing that their evaluations all agree with Dr. McConnell's, i.e. the middle and higher doses in FHI's study

exceeded the MTD and produced chronic inflammation and other chronic toxicities in the rats' reproductive systems, and in the dose group that did not exceed the MTD, no tumors were found, and thus quinacrine is not carcinogenic in rats at doses that do not exceed the MTD and produce chronic inflammation and other chronic toxicities that are not seen in women with QS. In this meeting, Dr. Soule states that DRUP would discuss the CaBio data and the study's FDA decision-making process with ISAF if FHI sends a letter to DRUP releasing FDA records of this information to ISAF. When asked by ISAF if this information should be requested under the Freedom of Information Act (FOIA), Dr. Soule states that a letter from FHI releasing the information will suffice and that it does not need to be requested under FOIA.

Following this meeting, DRUP recommends that the Clinical Hold and Refusal to File Committee (CHC) review this case. ISAF immediately submits a request for a meeting with the CHC.

- December 17, 2008 – FHI sends DRUP a letter confirming that FHI has no objection to ISAF's request to receive from FDA copies of all

documentation related to formal communications between FHI and FDA/CAC and all CAC communications regarding the CaBio, particularly CAC's written assessment of Dr. McConnell's findings. In this letter, FHI authorizes DRUP to release this information to ISAF.

- February 25, 2009 – ISAF submits, as amendment 0007, its response to DRUP's minutes of the November 14, 2008 Type A meeting, noting significant differences in ISAF's experience/minutes of the meeting and DRUP's, including that though the meeting was scheduled by DRUP as a Type A meeting, its minutes record it as a Type C. ISAF requests a response to this amendment. Though late, at ISAF's June 19, 2009 meeting with the CHC, DRUP indicates that ISAF can expect the response when it is complete, no response has ever been received.
- March 2009 – Contrary to what we were told by Dr. Soule in the November 14, 2008 Type A meeting, DRUP informs FHI that ISAF must request the information released by FHI under FOIA.
- March 13, 2009 – ISAF requests, under FOIA, copies of the CAC and DRUP deliberations regarding the CaBio, specifically minutes of

CAC meetings regarding Dr. McConnell's report.

- Early 2009 – Based on the discussions of the WHO panel of toxicology experts, including as stated above FDA's Dr. Alex Jordan who reported to the WHO panel that FDA had already dismissed Dr. McConnell's findings, WHO releases an 'interim statement' WHO/RHR/09.21 saying that, "Until the totality of safety, effectiveness and epidemiological data has been reviewed, quinacrine should not be used for non-surgical sterilization of women in either clinical or research settings." The WHO panel interim statement also states, "that no additional *in vivo* genetic toxicity studies are recommended at this time because negative results would not negate positive *in vitro* study results that suggest a genotoxic effect of quinacrine."
- March 20, 2009 – ISAF is told by Mr. Roy Castle in the FOIA office in a telephone conversation that the information would be released in 4-6 months, i.e. by October 20, 2009.
- May 5, 2009 – ISAF submits in amendment 0008 questions regarding the CaBio design, requesting answers from DRUP. No answer is ever received to this request.

- June 19, 2009 – ISAF's meeting is held with FDA Clinical Hold and Refusal to File Committee (CHC). The CHC recommends that, in light of ISAF's concerns, the FHI CaBio should be re-evaluated by the full Carcinogenicity Assessment Committee (CAC). Though ISAF immediately submits a request for this meeting, CAC representative Adele Seifried advises that it is necessary for ISAF to complete and submit to DRUP and the CAC any new information intended for discussion at this meeting, including its own short-term rat study and other evaluations of FHI's data, two months prior to the meeting date. Because this research is ongoing, the meeting date is not immediately established.
- May 12, 2010 – In a telephone conversation with the FOIA office, Roy Castle informs ISAF that DRUP has not responded to him regarding his inquiries about ISAF's March 13 request for information, and that he would re-contact DRUP and "get back to" ISAF with his findings.
- September 23, 2010 – Response to ISAF's March 13, 2009 FOIA request is received by ISAF, including summarized minutes of CAC Executive Committee meetings and an internal toxicology/pathology review of the FHI CaBio

by Dr. Terry Peters, FDA Neurology Division. (In compliance with Dr. Monroe's March 2009 letter to FHI, ISAF made this request to the FOIA office on March 13, 2009.)

- August 2011 – ISAF submits to DRUP amendment 0012 containing the results of its Charles River Laboratories 96-hour rat study. This study further supports ISAF's and our scientific advisors' observations regarding the CaBio that the study was flawed and should not be relied upon to determine quinacrine's carcinogenicity in the rat.
- September 2, 2011 – ISAF notifies CAC project manager Adele Seifried that ISAF intends – since the development of QS cannot go forward without the clinical hold being lifted following the CAC's review of the CaBio and ISAF's new information – to submit a formal Meeting Request for a Type A meeting with the CAC, along with a meeting briefing package containing ISAF's requests for answers regarding the CaBio design and its new information related to the study.
- September 16, 2011 – ISAF receives notification from DRUP that the CAC meeting date has been set for January 10, 2012.
- December 13, 2011 – ISAF submits to DRUP and the CAC 50 copies of the CAC meeting

Complete Briefing Package as amendment 0014 to IND 74,082. In addition to background material, a description of the issues in dispute regarding the CaBio, and a list of questions for the CAC's consideration, this amendment includes the results of ISAF's research into the mechanism of action of quinacrine for fallopian tube closure, a statistical re-analysis of the necropsy data from the FHI CaBio, and Dr. Terry Peters' internal FDA pathology/toxicology review report of the CaBio.

- December 2011 – CAC representative Adele Seifried describes her understanding of how the CAC meeting will be run to Dr. Carol Danielson. The plan is for DRUP and ISAF to give half-hour presentations of their perspectives, and then hold an hour-long question and answer period. ISAF will then leave the meeting, and the Committee will take a "secret ballot" vote on the questions posed by ISAF. Seifried reiterates this plan in several communications with Dr. Danielson during December 2011 and January 2012.
- December 2011 – ISAF formally submits to DRUP Informational amendment 0015 to IND 74,802 containing the results of ISAF's research into the mechanism of action of quinacrine for

fallopian tube closure and a statistical analysis of the necropsy data from the FHI CaBio.

- January 10, 2012 – ISAF meets with the full CAC and DRUP to present for discussion our 5 years of research regarding the disputed issues in the CaBio. DRUP pharmtox reviewer Dr. Leslie McKinney presents DRUP's position first, and then ISAF's scientists present ours. The DRUP presentation asserts that the MTD was not exceeded in any dose group in the CaBio, although at the end of the meeting, the CAC voted that the top three doses had exceeded the MTD. The CAC, not fully addressing ISAF's new information, instead steers the Q&A hour's discussion toward their concerns about quinacrine's potential mutagenicity in stem cells. ISAF is blindsided by this discussion, which had not been suggested in DRUP's presentation that was supplied to ISAF prior to the meeting. After the Q&A hour, ISAF departed while the CAC voted.
- January 23, 2012 – ISAF receives the minutes of the CAC meeting (see Volume 2, Section 2) which reflect that the CAC did not vote on ISAF's formally submitted questions for the committee's consideration, but rather voted on three questions DRUP had posed at the close

of its presentation. The minutes state that the CAC relied on a 2009 "clinical hold package," DRUP's Powerpoint presentation in the meeting, the two published articles on the CaBio and ISAF's presentation and briefing package, to form their conclusions regarding the CaBio. The minutes do confirm that the CAC voted 19 to 4 that the MTD was exceeded in the CaBio.

- April 11, 2012 – ISAF submits its response to the CAC meeting minutes, as amendment 0016 to our IND (see Volume 2, Section 2), clarifying our position and requesting that the FDA answer ISAF's formally submitted questions that the CAC did not respond to.
- April 26, 2012 – ISAF requests oversight of our IND's review from Dr. John Jenkins, Director of the CDER Office of New Drugs (see Volume 2, Section 2). This request is made because ISAF has lost confidence that DRUP is fairly, and in a scientifically rigorous manner, reviewing all of our data and new information.
- May 1, 2012 – Dr. Jenkins emails Dr. Carol Danielson, ISAF regulatory agent, declining this April 26 request (see Volume 2, Section 2).
- June 19, 2012 – ISAF submits its Complete Response to the Clinical Hold package (amendment 0017) in the form of the

epidemiology study providing follow-up safety data on >10,000 QS recipients that was conducted on ISAF's behalf by the Degge Group, Ltd. This data reports no increased risk of reproductive tract cancers, hysterectomy or ectopic pregnancy in these women compared to controls. (See Volume 2, Section 2, for amendment cover letter and epidemiology study executive summary.)

- June 22, 2012 – ISAF receives an Advice Letter from DRUP responding to our response to the CAC meeting minutes. This letter is signed by the Chair of the CAC, Dr. David Jacobson-Kram from the Office of New Drugs immediate office (see Volume 2, Section 2). This letter misrepresents ISAF's position on important scientific issues related to the mechanism of action of quinacrine and the validity of the findings of the CaBio. The letter confirms that, when re-evaluating the CaBio, the CAC did not review the CaBio data, or ISAF's 96-hour rat study data, or (though it was included in our briefing package for the meeting) ISAF's new information on the mechanism of action of quinacrine for tubal occlusion.
- July 20, 2012 – ISAF receives a Continued Full Clinical Hold letter from DRUP in response to

our Complete Response to the Clinical Hold (see Volume 2, Section 2). The letter leads ISAF and The Degge Group epidemiologists and statisticians to believe that the study was not adequately evaluated prior to DRUP's response.

- August 10, 2012 – ISAF submits to DRUP an acknowledgement (amendment 0018) of the Continued Full Clinical Hold letter with a request for DRUP's transparency via the transmittal of information regarding its evaluation of the study in consultation with the FDA Office of Surveillance and Epidemiology (see Volume 2, Section 2). This request is made so that ISAF can be thoroughly informed as we formulate our rebuttal to the continued clinical hold.
- August 15, 2012 – ISAF receives an email from DRUP stating that ISAF must request the information regarding DRUP's evaluation of our epidemiology study through the Freedom of Information Act (see Volume 2, Section 2).
- August 15, 2012 – ISAF submits its response to the June 22 advice letter from Dr. Jacobson-Kram in amendment 0019 (see Volume 2, Section 2). This response corrects ISAF's position as represented in the advice letter regarding quinacrine's genotoxicity, the

validity of the CaBio's findings, and the available evidence regarding quinacrine's potential carcinogenicity in humans.

- August 31, 2012 – ISAF submits informational packet to FDA ombudsman, Laurie Lenkel, outlining our prolonged impasse.
- September 9, 2012 – ISAF medical advisory board member Dr. Henry (Hank) Foster appeals directly to Commissioner Margaret Hamburg in a personal letter describing our situation. No reply is received.
- October 19, 2012 – Per DBRUP's direction, ISAF utilizes the Freedom of Information Act to request DBRUP/FDA's evaluation of the Degge Group epidemiology study. No reply received as of June 5, 2014.
- December 21, 2012 – ISAF submits a Formal Dispute Resolution Request to CDER ombudsman, Amy Bertha. After 5½ years of unsuccessful interactions with DRUP, with their latest response indicating that we should seek a conversation with them regarding "whether there is a viable path forward for this product", ISAF decides to formally request the CDER ombudsman's intervention so that we will receive satisfactory answers to our long-standing questions about the issues surrounding our IND.

- January 24, 2013 – Formal Dispute Resolution meeting with ODEIII, Dr. Julie Beitz, director.
- February 15, 2013 – ISAF receives Dr. Beitz's dispute appeal response letter.
- March 14, 2013 – ISAF submits amendment 0024, responding to a question Dr. Beitz had posed.
- March 25, 2013 – ISAF receives Dr. Beitz advice letter in answer to 0024.
- April 26, 2013 – ISAF representatives meet in New York with the Center for Reproductive Rights to ask their advice on our case. CRR recommends legal advice and suggests three attorneys for our contact … one of them Mark Heller, the individual recommended by Penny Farthing in 2007.
- May 6, 2013 – In amendment 0025, ISAF appeals Dr. Beitz's recommendations for dispute resolution to Dr. John Jenkins.
- June 18, 2013 – Formal Dispute Resolution meeting with OND, Dr. John Jenkins, director
- July 14, 2013 – ISAF submits amendment 0026, clarification of issues raised in Jenkins FDR meeting.
- July 18, 2013 – interim response letter received from Dr. Jenkins, proposing public advisory committee to resolve issues.

- August 14, 2013 – ISAF submits amendment 0027, response to Dr. Jenkins interim letter, declining his offer.
- November 2, 2013 – ISAF medical advisory board member Dr. Henry (Hank) Foster appeals directly to Commissioner Margaret Hamburg in a second personal letter, mailed to her home, updating her on our situation. Again, no reply is received.
- November 18, 2013 – Dr. Jenkins sends general advice letter agreeing to ISAF's request for an independent review of the CaBio by qualified toxicologists prior to the proposed advisory committee meeting.
- December 6, 2013 – ISAF submits amendment 0031, responding to Dr. Jenkins' advice letter, respectfully declining his proposal for the independent toxicology review and advisory committee meeting, as envisioned in his letter, describing why (because of the obscure idiosyncrasies of the CaBio design and analysis that must be disclosed to a reviewer, and because the advisory committee is proposed to be public) and offering a counterproposal that, if the terms were met, could satisfy us.
- February 7, 2014 – Dr. Jenkins sends general advice letter responding to our

counterproposal, e.g. describing further documents that he will provide to the three CaBio reviewers and asking ISAF to suggest further documents.

- February 26, 2014 – ISAF submits amendment 0032, containing our suggestions for the documents to be provided to the three CaBio reviewers.
- May 23, 2014 – ISAF meets with Congressman David Price to inform him of our situation, acting on Penny Farthing's advice from 2007. The meeting is specifically an "FYI" meeting, stressing that no action is asked of him, but letting him know that if we do find ourselves in a position of needing congressional oversight, we wanted to brief him of the situation and talk about options for help on the Hill.
- May 28, 2014 – Responding to a voicemail query from Dr. Danielson about the status of our case, OND office liaison, Khushboo Sharma, informs ISAF in an email that OND is working on a response to 0032 and should have it to us in "a week or two."
- May 29, 2014 – Sharma informs ISAF regulatory agent in a telephone call with Dr. Carol Danielson that "there is nothing to be concerned about, [they] are just gathering the

documents" we had suggested and will have their response letter to us in a week or two.

- June 2, 2014 – ISAF receives Dr. Jenkins' response to 0032, an advice letter which effectively abandons the negotiations in process regarding information for the CaBio reviewers. The letter states that none of the documents will be provided, even those Dr. Jenkins had originally suggested himself.
- June 2, 2014 – ISAF decides to contact Mark Heller for advice and initiates this contact through Penny Farthing.
- June 3, 2014 – When Dr. Danielson speaks with our OND liaison, Khusuboo Sharma, to say that the letter was not what we were expecting, Sharma tells ISAF that Dr. Jenkins would like to schedule a teleconference with ISAF in the next few weeks so that he can explain his thinking.

November 2, 2013
Margaret Hamburg,
Commissioner FDA
Washington, DC 20016

Dear Dr. Hamburg,
I am writing with a follow-up to my September 3, 2012, letter to you regarding the plight of a family planning method that is under review at your Agency, and to fully apprise you of the difficulty encountered during this review. This family planning method - the quinacrine system of nonsurgical permanent contraception for women, or QS - is being sponsored at FDA by the nonprofit, International Services Assistance Fund (ISAF), on whose medical advisory board I am proud to serve.

As I wrote previously, QS has been used in over 150,000 women, with no serious adverse events requiring surgery reported. Numerous epidemiology studies report that the method does not increase a woman's risk of reproductive tract cancer or other serious health outcomes.

My letter, of over a year ago now, described how ISAF's IND for QS was placed on full clinical hold in January of 2007 by the Division of Reproductive and Urologic Products (DRUP, now DBRUP), due to

reported results from a 2-year rat carcinogenicity study (CaBio), and how ISAF has since, with the assistance of prestigious toxicologists, pathologists and biostatisticians, deconstructed the study. These experts' review of the CaBio resulted in the identification of serious flaws in its design, conduct, analysis and interpretation-flaws that undermine certain aspects of the study's scientific integrity, and the reported results.

Since my last communication, your ombudsman, Laurie Lenkel, has told ISAF that reviewers at FDA now realize that there are "problems with the study." However, for nearly seven years ISAF has encountered persistent difficulties in receiving responses from DBRUP about those problems, so that the issues may be resolved.

In an effort to gain the Agency's response to ISAF's formally submitted requests for clarification about the study's design and interpretation, in December of 2012 ISAF entered formal dispute resolution proceedings with DBRUP, proceedings that are now at the OND level.

For ISAF's re-assessment of the CaBio, they identified, in addition to Dr. Ernest McConnell, whom I mentioned in my previous letter, other esteemed

scientific advisors - leading experts in their respective subspecialties - to review and evaluate the CaBio and its relevance to the use of QS in women.

Their review of the study substantiated ISAF's original position that its inappropriate design caused the results from the top three doses to be confounded. Those three doses, all exceeding the maximum tolerated dose (MTD), were the only doses in which tumors were found and that caused DBRUP to place ISAF's IND on hold. Below, please find a list of ISAF's reviewers:

- Dr. Ernest E. McConnell, veterinary pathologist/toxicologist (former Director of the Toxicology, Research & Testing Program for the National Institutes of Environmental Health Sciences/National Toxicology Program);
- Dr. Errol Zeiger, genetic toxicologist (former Head of the Genetic Toxicology Testing Program at the National Institute of Environmental Health Sciences, National Toxicology Program;
- Dr. Joseph Haseman, biostatistician (former Director of Statistical Consulting at National Institutes of Environmental Health Sciences/National Toxicology Program);

• Dr. Michael I. Luster, immunotoxicologist (former Chief of the Toxicology and Molecular Biology Branch, Health Effects Laboratory Division of the National Institute for Occupational Safety and Health (NIOSH));
• Dr. Patricia Fail, reproductive toxicologist (former Manager, Laboratory of Reproductive and Endocrine Toxicology, Center for Life Sciences and Toxicology, Research Triangle Institute International (RTI); and study director for Family Health International's rat dose feasibility studies of quinacrine and erythromycin conducted at RTI);
• Dr. Jack Llppes, Obstetrician/Gynecologist, Professor Emeritus of Obstetrics and Gynecology, State University of New York, Buffalo, and Sponsor-Investigator for the phase 1 study in QS.

This panel of world-class scientists has conclusively shown that the study is scientifically unsound in several important areas, and that the doses that developed cancers should be censored from the study's evaluation. When they are, the remaining data show that the study is negative for carcinogenicity.

These experts have repeatedly accompanied ISAF to meetings with FDA, attempting to engage in a detailed dialog regarding their findings with their FDA peers, and specifically their points of scientific dispute regarding the CaBio. Unfortunately, in nearly seven years of trying - first with DBRUP, then the Clinical Hold and Refusal to File Committee, then the full Carcinogenicity Assessment Committee, and now in Formal Dispute Resolution (FDR) meetings with ODEIlI and ONO - ISAF has been unable to achieve an in-depth discussion of and resolution to its well-defined scientific disputes about this CaBio.

ISAF has instead encountered a rigid resistance on the part of the FDA to thoroughly and objectively address the disputed issues, with FDA continuing in the meantime to claim that the CaBio is relevant to the use of QS in women. Furthermore, in ISAF's meetings with the Agency, FDA has introduced new issues that were not identified in FDA's clinical hold letters as requiring resolution prior to resumption of the clinical trial, and that distract from ISAF's well-defined disputes.

ISAF's consulting experts have concluded that it was predictable, based on previously published reports, that the top three doses in the CaBio would have

destroyed the uterus and produced a lifetime of chronic inflammation in the rats, and as a result the study would have been predicted to cause cancer. Critically, in the dose that did not exceed the MTD and did not result in the destruction of the uterus, the study produced no cancers. This finding supported an earlier neonatal mouse study of quinacrine that was negative for carcinogenicity.

Additionally, as I mentioned in my earlier letter, the three excessive doses administered in the study killed 30% of the rats in the two highest dose groups, thus violating FDA's own guidelines for such studies. As Dr. McConnell has noted, FDA/ICH guidelines for the conduct of carcinogenicity studies, which he essentially oversaw the development of at the National Toxicology Program, indicate that no animals should die due to dosing in such studies, and that even a 1% mortality rate - much less 30% as allowed in this CaBio- would never be acceptable. Yet FDA has refused to discuss in detail this or any of the other serious anomalies identified in the CaBio with ISAF/ their experts.

Furthermore, Dr. Joseph Haseman, the former head of statistical analysis of rodent studies at NTP, has conclusively shown, via his statistical re-analysis of the study's data, that the chronic inflammation

induced in the CaBio's three high dose groups produced the cancers, not the test article quinacrine - a critical point that he has presented to FDA on multiple occasions without any meaningful response.

As a result of their painstaking review, ISAF's experts have indeed documented that, when the study is properly evaluated according to accepted toxicology practice, i.e., censoring the doses that exceeded the MTD from evaluation, the study is negative for carcinogenicity.

This adds to the weight of evidence that quinacrine is not mutagenic in vivo, as Dr. Errol Zeiger, former head of NTP's genetic toxicology testing program, has concluded and presented to the FDA. Yet the FDA has not readily concurred with this vital conclusion or shown interest in exploring the findings - even after being given Ors. Haseman's and Zeiger's compelling analyses.

Since their IND was initiated in 2006, ISAF has complied with each of FDA's requests, including carrying out a large epidemiology study with The Degge Group, Ltd., to determine if QS increases a woman's risk of reproductive tract cancer, which was the requirement of the clinical hold letter issued by

DBRUP. The results of this study were submitted to ISAF's IND in June of 2012.
The study concludes that there is no increased risk of reproductive tract cancers with 10,503 QS users, compared to a matched cohort of women using intrauterine device or tubal ligation for contraception. Dr. Judith Jones, as I informed last year, was the principal investigator of this study and has reported her findings to DBRUP as a complete response to the clinical hold, and also to ODEIII and ONO in ISAF's FDR meetings. Dr. Jones is president of The Degge Group, and the former director of the FDA Office of Drug Safety (now the Office of Epidemiology and Surveillance). Though the study achieved less power (76%) than 95% as originally designed, it is not far short of the 80% power widely adopted as a reasonable level for such studies and adds to the previously published epidemiology studies also showing no increased cancer risk with QS.

However, ISAF's IND was placed on hold, and FDA requested the large epidemiology study, due to the CaBio's results. But regardless of the compelling science ISAF has generated for discussion with the Agency, FDA continues to avoid answering ISAF's formally submitted questions for clarification about the CaBio, so that its correct interpretation will reveal

whether it should have been used to stop ISAF's clinical program.
Initially, DBRUP stonewalled ISAF's requests regarding the CaBio entirely. But most recently, in a non-decisional response to ISAF's FDR appeal to the Office of New Drugs, ONO opted- instead of initiating a scientific discussion specific to ISAF's formally disputed, well-defined issues - to declare that a public advisory committee would be convened next year (at least an additional 8-month delay) to consider the issues. This advisory committee would discuss, in addition to the CaBio and epidemiology study results, issues of ethics, clinical study design and risk-benefit, before making a decision on ISAF's appeals regarding the CaBio.

However, as you can well appreciate, and as ISAF wrote in response to Dr. Jenkins at ONO, until there is agreement whether the CaBio is positive or negative for cancer, and the implications are put into proper context, an advisory committee tasked with an evaluation of the risks and benefits of QS and its ethical use in healthy populations cannot provide an informed opinion. Therefore, ISAF notified ONO that they cannot accept the advisory committee as proposed, since it would place QS in a no-win situation. ISAF has been awaiting Dr. Jenkins'

response to this letter since it was sent to him on August 16.

Since 2007, ISAF has spent over $5 million attempting to work with FDA. Rather than an environment of transparency and responsiveness that the Agency espouses as its model, however, ISAF has encountered primarily a consistent disregard for their scientific entreaties and as such, a pattern of unreasonable delay regarding the progress of its IND.

The myriad issues surrounding ISAF's impasse are complex, and ISAF and I would be happy to meet with you to discuss them in detail. I will not, however, attempt to further describe all the nuances of the case in this letter.

I am primarily writing to let you know that, because ISAF has, most unfortunately, lost confidence that their scientific disputes will be addressed at FDA, or that science will determine the outcome when they are, they feel they must soon resort to a wider public audience if fair consideration of the science is to prevail.

Laurie Lenke}, whom ISAF contacted in August of 2012 for help in moving this process along, has assured ISAF that decisions at FDA are science-based.

But ISAF's science does not appear to be receiving serious evaluation. And so I am appealing to you. I am hopeful that you will take a close look at this interminable issue and thus, assist in the resolution of this scientific dispute. It would be not only most welcome but potentially most beneficial to millions of women - including thousands here in the United States, where some women are medically contraindicated for surgery (tubal ligation), fear a surgical procedure, and/or cannot use or afford the single other nonsurgical option available.

In closing, Dr. Hamburg, I am cognizant of the enormous responsibility the FDA has to bear in assuring that the highest standards are met in its review process; this, of course, is as it must be. What is being is sought with this correspondence is an assurance that a thorough and objective hearing is being provided for ISAF's IND for QS. Thanks for any input you can provide; it will be greatly appreciated.

Sincerely,
Henry W. Foster, Jr., MD, FACOG Professor Emeritus and former Dean & Vice President for Health Affairs Meharry Medical College &
Professor of Obstetrics and Gynecology Vanderbilt University

ABOUT THE AUTHORS

Dr. Stephen D. Mumford is the founder and President of the Center for Research on Population and Security. He has his doctorate in Public Health. His principal research interest has been the relationship between world population growth and national and global security. He has been called to provide expert testimony before the U.S. Congress on the implications of world population growth.

Dr. Mumford has decades of international experience in fertility research where he is widely published. In 1981, he received the Margaret Mead Leadership Prize in Population and Ecology. He has been recognized for his work in advancing the cause of reproductive rights by the Feminist Caucus of the American Humanist Association, and has addressed conferences worldwide on new contraceptive technologies and the stresses to the security of families, societies and nations that are created by continued uncontrolled population growth. He has

written extensively on the pivotal role of the Catholic hierarchy in thwarting efforts to tackle the world's burgeoning population.

In 1974, President Richard Nixon requested the authoritative interagency study that came to be known as NSSM 200 (National Security Study Memorandum 200). The NSSM 200 report states: "There is a major risk of severe damage [from continued rapid population growth] to world economic, political, and ecological systems and, as these systems begin to fail, to our humanitarian values." However, the implementation of NSSM 200 recommendations that were already approved by President Ford was blocked by the swift action of the Vatican. As CIA Director, George H.W. Bush was in the position most concerned with such a grave threat to the United States and global security. Just days after leaving his post at the agency, he told Dr. Mumford, author of *Population Growth Control* (1977), "I agree with everything you are saying here," referring to the book, "and I can assure you the folks at the CIA agree with you too."

As president of the Center for Research on Population and Security, Dr. Mumford continues his work of more than four decades as lead scientist in the development and evaluation of contraception methods and advancing the cause of reproductive rights. Collaborating with health providers and scientists in more than 20 countries, his office is in North Carolina where he makes his home. His wife of 40 years, a Chinese immigrant and leading cancer researcher, focuses much of her investigation on

environmental cancers affecting large populations of poor women.

In addition to his books on biomedical and social aspects of family planning, as well as scientific articles in more than a score of journals, Dr. Mumford's major works include American Democracy and the Vatican: Population Growth and National Security (Amherst, New York: Humanist Press, 1984), The Pope and the New Apocalypse: The Holy War Against Family Planning (Research Triangle Park, North Carolina: Center for Research on Population and Security, 1986), and The Life and Death of NSSM 200: How the Destruction of Political Will Doomed a U.S. Population Policy (Research Triangle Park, North Carolina: Center for Research on Population and Security, 1996).

The following is a sampling of some of the articles, excerpts and presentations by Dr. Mumford that we feature on this site. There is a much wider selection available here.

How far is the Vatican willing to go to insure its survival?

Why the Catholic Church has survived for 2000 years while all other tyrannies have failed The Catholic Church and Sex

How the undemocratic activities of the Catholic Church silences critics Catholicism – both a religion and an

ambitious, arrogant political institution

The Roman Catholic hierarchy: a cabal of power that moves under the guise of benevolence Postponing Self-Destruction of the Catholic Church

Overcoming Overpopulation: The Rise and Fall of American Political Will

What happened to American political will to deal with the overpopulation problem? The Vatican's Role in the World Population Crisis: The Untold Story

Vatican Control of World Health Organization Policy: An Interview with Milton P. Siegel NSSM 200, the Vatican, and the World Population Explosion

Eight kinds of power the Vatican exercises to control Catholics

Why The Pope Can't Change The Church's Position On Birth Control: Implications For Americans

ABOUT THE AUTHORS (cont.)

Don Collins, Jr. is a senior technical sales manager, a business development manager, consultant, and senior engineering manager in the computer industry and holds 65 patents. His R&D teams had more than a million products installed worldwide. He has founded and served on the boards of nonprofits for more than a decade, is President of ISAF a 501(c)(3), holds his B.S. from Temple University, and his M.S. in Electrical Engineering from NTU. He is an author and speaker.

ABOUT THE BOOK

This book is the FDA approved protocol for ISAF's Phase 3 Clinical trial in 2006 for Quinacrine Sterilization (QS) in the United States entitled: "A Phase 3 Multi-center Clinical Investigation to Evaluate the Safety and Effectiveness of Quinacrine Hydrochloride (QH) Pellets Administered via Quinacrine Sterilization Procedure (QS) to Female Subjects Who Voluntarily Agree to Choose QS as Their Method of Sterilization." Non-surgical permanent contraception for women (QS), should be designated as a breakthrough medical device, is safer than surgical tubal ligation (TL), more effective than the pill, with no long-term side effects, and should be available to women in the United States and worldwide today. The QS procedure, without general anesthesia, can be performed by a nurse practitioner. QS has been used by over 200,000 women in 53 countries with no deaths making it safer than surgical tubal ligation as described in our 568-page book of clinical trials available here. In 1979, CDC defined the mortality rate for surgical tubal ligation to be 3.6 deaths per 100,000 or approximately 21 per year. FDA refuses to allow ISAF clinical trial to move forward despite the QS method's higher safety and efficacy rate than surgical tubal ligation. Why?