1 TITLE PAGE

Clinical Study Report

An Open Label, Single Center, Study to Evaluate the Safety and Effectiveness of Ekobi™ Embolization Microspheres in Uterine Artery Embolization for the Treatment of Premenopausal Women with Symptomatic Uterine Fibroids

Test Product:	Occlusin® 500 Artificial Embolization Device; rebranded and marketed as Ekobi™ Embolization Microspheres
Indication:	Uterine Fibroid Embolization
Sponsor/Sponsor Signatory:	Michael W. Stewart, President and Chief Executive Officer IMBiotechnologies Ltd. Suite 215, Advanced Technology Centre 9650 20th Avenue NW Edmonton, Alberta T6N 1G1 Canada Tel: 780-945-6609
Protocol No.:	OCL500-P3-UFE-02
Study Initiation Date:	27 November 2017
Study Completion Date:	3 September 2019
Principal Investigator:	Dr. Richard Owen Department of Radiology University of Alberta Hospital Edmonton, AB, Canada

This study was performed in accordance with Good Clinical Practice, including the archiving of essential documents.

Date of the Report: 23 September 2019

APPROVAL SIGNATURE(S)

An Open Label, Single Center, Study to Evaluate the Safety and Effectiveness of Ekobi™ Embolization Microspheres in Uterine Artery Embolization for the Treatment of Premenopausal Women with Symptomatic Uterine Fibroids

Protocol No. OCL500-P3-UFE-02

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Sponsor:

M.W. Stewart ..... 23 Sep 2019

Michael W. Stewart, MSc — Date
President and Chief Executive Officer
IMBiotechnologies Ltd.

Quality Assurance:

....

Irwin Griffith, PhD — Date
Management Representative, Quality Assurance
IMBiotechnologies Ltd

Investigator Signature:

....

Richard Owen, MD — Date
Principal Investigator
University of Alberta Hospital

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Michael W. Stewart, MSc — Date
President and Chief Executive Officer
IMBiotechnologies Ltd.

Quality Assurance:

..... 24 Sep 2019

Irwin Griffith, PhD — Date
Management Representative, Quality Assurance
IMBiotechnologies Ltd

Investigator Signature:

....

Richard Owen, MD — Date
Principal Investigator
University of Alberta Hospital

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President and Chief Executive Officer
IMBiotechnologies Ltd.

Quality Assurance:

....

Irwin Griffith, PhD — Date
Management Representative, Quality Assurance
IMBiotechnologies Ltd

Investigator Signature:

Richard Owen ..... Sept 24 2019

Richard Owen, MD — Date
Principal Investigator
University of Alberta Hospital

2 SYNOPSIS

Name of Company: *IM*Biotechnologies Ltd.	
Name of Finished Product: OCL 504, OCL 505	
Name of Active Ingredient: Not applicable	
Title of Study: An Open Label, Single Center, Study to Evaluate the Safety and Effectiveness of OCL 500 Embolization Microspheres (OCL 500) in Uterine Artery Embolization for the Treatment of Premenopausal Women with Symptomatic Uterine Fibroids	
Principal Investigator: Dr. Richard Owen	
Study Center: University of Alberta Hospital, Edmonton, Alberta, Canada.	
Publication (reference): None.	
Study Period: 27 November 2017 to 3 September 2019	
Objectives: <u>Primary Objectives:</u> • Outcome of embolization with OCL 500 as determined by change in fibroid volume. • Outcome of embolization with OCL 500 as determined by change in fibroid perfusion. • Safety of embolization with OCL 500. <u>Secondary Objectives:</u> • Outcome of embolization with OCL 500 as determined by change in volume of uterus. • Quality of life (QOL) following embolization with OCL 500. Exploratory Objective: • Change in appearance of embolized vasculature, in comparison to baseline, as measured by ultrasound 1 day, 1 month, and 6 months post-embolization.	
Methodology: This is a single center, open label, single-arm study. After screening and baseline testing, eligible patients underwent transarterial embolization of the uterine arteries with OCL 504 or OCL 505.	
Number of Patients (Planned and Analyzed): It was planned that 13 patients be treated. Enrolment with treatment was terminated at twelve (12) patients. Twelve (12) patients with symptomatic uterine fibroids have undergone uterine fibroid embolization and have been followed to end of study follow up.	
Diagnosis and Main Criteria for Inclusion: Presence of symptomatic leiomyomata (uterine fibroids) in premenopausal women.	

Name of Company: *IM*Biotechnologies Ltd.	
Name of Finished Product: OCL 504, OCL 505	
Name of Active Ingredient: Not applicable	

Test Product, Dose and Mode of Administration, Lot Number(s), Expiry Date(s):

Occlusin® 500, rebranded and marketed as Ekobi™ Embolization Microspheres, is a vascular embolization device comprising a family of embolization microsphere sizes designated as Class II under special guidance controls by the United States Food and Drug Administration and class IV by Health Canada. Ekobi™ Embolization Microspheres were provided in a sealed glass vial as 400 mg of sterile dry microspheres. Sufficient vials of OCL 504 (212-300 µm) or OCL 505 (300-425 µm) vials were administered to achieve near stasis in the target vasculature.

Infusion of embolic material was transarterial via catheter, following the Instructions For Use (IFU) and hospital's clinical practice. 400 mg OCL 504 or OCL 505 microspheres were resuspended by the physician in a mixture of saline and contrast agent to achieve an iso-buoyant suspension. The suspension was drawn into a 3 mL sterile plastic syringe and delivered by angiocatheter to the uterine artery(ies) and monitored by fluoroscopy. OCL 504 or OCL 505 was delivered to near stasis in the target vasculature. Near stasis embolization was defined as stasis of contrast agent in the uterine artery for 3 to 5 cardiac beats.

The following lot numbers were used in the study: E7536 (OCL 504), E7537 (OCL 505)

Duration of Study Drug Treatment:

OCL 504 or OCL 505 was delivered into the uterine vasculature until near stasis of blood flow in the target vasculature was achieved. Each patient received one embolization treatment only.

Reference Product, Dose and Mode of Administration, Lot Number(s), Expiry Date(s):

Not applicable.

Criteria for Evaluation:

Safety:

- Laboratory studies (Haematology, coagulation, blood chemistry, liver function, luteinizing hormone (LH), follicle stimulating hormone (FSH)
- Occurrence of unanticipated adverse device effects (UADEs) and serious adverse events (SAEs).

Effectiveness:

- Fibroid volume (primary)
- Fibroid perfusion
- Uterine volume (secondary)

Other:

- Uterine Fibroid Syndrome Quality of Life Assessment (UFS-QoL)
- Uterine vasculature ultrasound assessment

Statistical Methods:

Statistical analysis was conducted for the primary end-point efficacy assessment of change in fibroid volume in comparison to baseline. Changes in fibroid perfusion, uterine volume, and UFS-QoL were also be evaluated relative to baseline measurements. Statistical analysis was conducted using SAS version 9.4 by an independent biostatistician.

Summary of Results:

Seventeen (17) subjects were screened. Four (4) subjects failed screening. One (1) subject exited the study before treatment due to time commitments. Six (6) subjects were treated with OCL 504 and 6 subjects were treated with OCL 505.

Effectiveness:

All 12 treated subjects have been followed to 6 months post-embolization. The mean ± sd decrease in fibroid volume relative to baseline was 45.9 ± 26.9% (N=12; p=0.0015) at 6-month followup (end of study, EOS). The mean ± sd decrease in uterine volume relative to baseline was 28.8% ± 19.6% (N=12; p = 0.0005) at 6-month EOS followup. The mean ± sd decrease in fibroid perfusion for the 12 treated subjects was -50.8% ± 55.5% at 6-months EOS post-

Name of Company: *IM*Biotechnologies Ltd.	
Name of Finished Product: OCL 504, OCL 505	
Name of Active Ingredient: Not applicable	

embolization (p = 0.01). Mean symptom scores as determined by UFS-QoL improved in the 12 subjects at 6-months post-embolization relative to baseline by 36.3 ± 20.7% (p = 0.0005). Quality of life scores as determined by UFS-QoL improved in the 12 subjects at 6 months post-embolization relative to baseline by 43.7 ± 26.4% (p = 0.0001).

Safety and Tolerability Results:

No adverse events (AEs) attributed to the administration of the study device occurred. Of the 12 subjects treated, all subjects reported low to moderate pain scores 1-week post-embolization (range on a 10-point scale = 0.5 to 4.5). On average, pain scores (0-10-points) decreased from a mean of 2.0 ± 1.6 at 7-days post-embolization to 1.6 ± 2.2 at 6-month EOS post-embolization. There were no clinically significant findings in vital signs, physical examination, or clinical laboratory assessments in any of the patients. One subject showed an increase in FSH and LH hormone levels 1-month post-embolization with return of her menstrual cycle at 5 weeks post-treatment followed by menopause. No AEs leading to subject withdrawal from the study were reported.

Ultrasound assessment of the delivered microspheres confirmed localization of the microspheres in the target tissue, with no indication of the product traveling to non-target locations.

Date of Report: 23 September 2019

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3.1 List of In-text Tables

3.2 List of In-text Figures

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADE	Adverse device effect
AE	Adverse event
CA	Competent authority
CBC	Complete blood count
CI	Confidence interval
CSR	Clinical Study Report
eCRF	Electronic case report form
EOS	End of Study
FSH	Follicle stimulating hormone
GCP	Good clinical practice
GLP	Good laboratory practice
HRQL	Health-related quality of life
ICF	Informed consent form
ICH	International conference on harmonization
IFU	Instructions for use
INR	International normalized ratio
IRB	Institutional review board
LH	Luteinizing hormone
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
OCL 504	A size range within the Occlusin® 500 family (212-300 µm)
OCL 505	A size range within the Occlusin® 500 family (300-425 µm)
PI	Principal Investigator
PLGA	Poly-DL-lactide-co-glycolic acid
PT	Prothrombin time
QoL	Quality of life
SADE	Serious adverse device effect
SAE	Serious adverse event
SD	Standard deviation
SIR	Society of Interventional Radiology
SOC	Standard of care
UADE	Unanticipated adverse device effect
UAE	Uterine artery embolization
UFE	Uterine fibroid embolization
UFS	Uterine fibroid syndrome
VAS	Visual analog scale
WSRT	Wilcoxon Sign Rank Test (Non-parametric)

4 ETHICS

4.1 Independent Ethics Committee or Institutional Review Board

Written approval of the protocol, the final informed consent document, relevant supporting material, and patient recruitment information were obtained from the University of Alberta institutional review board (IRB) prior to study initiation.

4.2 Ethical Conduct of the Study

This study is being conducted in accordance with current applicable regulations, International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and local legal requirements. The study complies with the ethical principles described in the Declaration of Helsinki World Medical Association, 2002.

4.3 Patient Information and Consent

The Patient Informed Consent Form (ICF) and consent process were in compliance with the requirements of Health Canada guidelines. The Principle PI (PI) or his delegate explained the nature of the study, purpose, procedures, duration, potential benefit and risk of participation in the study before any procedure associated with the study was performed. Patients were advised who to contact for advice regarding the study, and what to do in the event of an adverse reaction during the study. The ICF stated that scientific representatives from IMBiotechnologies Ltd., its designee or government regulatory agencies may review the study data in their files. Patients were free to withdraw their consent at any time. Once a patient agreed to participate in the study, the patient signed the approved ICF. The original signed ICF was placed in the patient's permanent file. The PI kept a copy of the signed ICF on file and gave another copy to the patient.

The ICF and written information provided to patients were revised whenever important new information that may be relevant to the patient’s consent became available. The PI informed the patient of any changes in a timely manner and obtained the patient’s consent to continue participation in the study by requesting the patient to sign the revised form. Any revision to the patient information or ICF must have received Sponsor and IRB approval in advance of use.

No study procedures took place until the patient had given written consent.

5 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Role in Study	**Name and Contact Details**
Sponsor	Michael Stewart President and Chief Executive Officer, IMBiotechnologies Ltd. Suite 215, 9650 - 20th Avenue NW Edmonton, Alberta T6N 1G1 Canada
Medical Monitor	Dr. Ruth Collins-Nakai
Principal Investigator	Dr. Richard Owen Site Leader, Radiology and Imaging University of Alberta Hospital Edmonton, Alberta T6G 2B7 Canada
Radiology	Dr. Chris Fung
Central Laboratory	University of Alberta Hospital
Biostatistics	Dr. Maryna Yaskina Women & Children's Health Research Institute (WCHRI) 5-083 Edmonton Clinic Health Academy 11405 87 Avenue NW Edmonton, AB T6G 1C9 Canada
Provision of study device	Keystone Labs 7225 Roper Road NW Edmonton, AB T6B 3J4 Canada

6 INTRODUCTION

6.1 Background

Uterine leiomyomata or uterine fibroids are common benign tumors of the uterine muscle in pre-menopausal women. From 20 to 40 percent of women age 35 and older have symptomatic uterine fibroids. These tumors may cause excessive bleeding (menorrhagia), pelvic pain, and pressure symptoms (urinary frequency, urgency, and retention). Many women suffering from these symptoms undergo major surgery for the removal of the fibroids. 40% of in the United States, per annum, are for the treatment of uterine fibroids. Common treatments for uterine fibroids include medical therapy, uterine artery embolization (UAE), hysterectomy, and myomectomy.

Uterine leiomyomata are benign tumors resulting from the neoplastic transformation of a single smooth muscle cell. Fibroids range in size from several millimeters to more than 20 centimeters. Although the mechanisms controlling fibroid growth are not fully understood, their growth appears to be regulated by steroid hormones (estrogen and progesterone), peptide growth factors (epidermal growth factor), and the availability of adequate vascular perfusion (Parker et al, 2007).

Uterine fibroids are generally asymptomatic with some studies estimating that 60% to 90% of such tumors fail to cause any symptoms (American College of Obstetricians and Gynecologists [ACOG] Technical Bulletin, 1994). Uterine fibroids that produce symptoms typically do so from the late reproductive years up to the perimenopausal period. Their size and location may play a role in determining which myomata will become symptomatic, but these factors alone do not explain the wide variation in patient symptomatology.

Abnormal menstrual bleeding is the most common symptom in women with uterine fibroids at presentation. The exact mechanism by which fibroids cause increased menstrual blood loss is not known, although several theories have been advanced. Myomata located within the walls of the uterus (intramural myomata) may compress uterine veins as they grow, leading to venular ectasia and perhaps impairment of normal hemostatic mechanisms. Submucosal myomata have been postulated to cause increased bleeding as a result of ulcerations developing over the tumor. Fibroids may also significantly increase the surface area of the endometrium, thereby increasing the area from which menstrual blood loss may occur.

Leiomyoma can also cause pelvic pain, either through a mass effect or by the spontaneous necrosis of the tumor. Acute onset pelvic pain occurs when a myoma outgrows its blood supply, producing a necrotic central core, or when a pedunculated fibroid undergoes torsion on its stalk and becomes ischemic. Pelvic discomfort, pressure, or pain also results from compression of adjacent organs by an enlarging fibroid uterus. Urinary frequency and constipation may result from compression of bladder and bowel.

Primary medical therapy for patients suffering from excessive bleeding consists of hormonal agents such as progestins, combined oral contraceptives or short-term treatment with gonadotropin releasing hormone (GnRH) agonists. Non-hormonal treatments include NSAIDs and anti-fibrinolytic agents. Progestin releasing intra-uterine devices may be used to treat menorrhagia.

Since medical therapy fails to control symptoms in up to two-thirds of patients with bleeding and an even higher proportion of those with mass related symptoms, many women undergo

hysterectomy or myomectomy for symptom relief. In the U.S. approximately 600,000 hysterectomies are performed annually (Lepine et al 1997; National Center for Health Statistics, 1996) with close to 1/3rd of the procedures conducted to treat uterine fibroids. While it is a relatively safe procedure with a major complication rate of 1% to 2% and a death rate of 0.1%, and guarantees permanent relief from symptoms of myomata (Bernstein et al, 1997), it is nevertheless major surgery with a substantial recovery period. Hysterectomy also removes an organ that plays a role in sexual function, guarantees infertility, produces immediate menopause (when total hysterectomy is performed), and has psychological implications for many women.

Myomectomy may provide relief from fibroid symptoms without some of these drawbacks. As noted by the Mayo Clinic in a brochure to fibroid patients contemplating myomectomy, myomectomy however, remains a surgical procedure and has been associated a number of problems. There may be excessive blood loss in some patients, which in patients who are already anaemic can have major ramifications. The procedure requires incisions in the uterus, which may lead to tissue adhesions with sequelae such as fallopian tube obstruction or bowel obstruction. Since the uterus is conserved in myomectomy, future childbearing may be possible and the sexual and psychological implications of hysterectomy may also be avoided. However, the Mayo Clinic cautions that myomectomy can increase certain risks during delivery, if deep incisions in the uterus were required to remove the fibroid(s) as part of the myomectomy procedure (Mayo Clinic Patient Brochure; URL www.mayoclinic.org/tests-procedures/myomectomy/details/risks/cmc-20205375). According to the US Department of Health and Human Resources (HCUP database), approximately 40,000 myomectomy procedures were performed in the USA in 2016 (URL www.hcupnet.ahrg.gov).

Uterine artery embolization is a minimally invasive technique for reducing symptoms from uterine fibroids. It has been demonstrated to be a less invasive alternative to surgical treatment of these common, benign uterine tumors. Since U.S. gynecologists perform more than 150,000 hysterectomies and 40,000 myomectomies each year to relieve symptoms of uterine fibroids, UAE has the potential to benefit a great many patients. Reduction in uterine and leiomyoma volumes is evident several weeks after embolization (Stokes et al, 2010). SIR recently published updated quality improvement guidelines for UAE (Dariushnia et al, 2014). The guidelines provide recommendations for performing UAE, including special circumstances where patients present with adenomyosis, pedunculated subserosal leiomyomas, and patients with fibroids who wish to become pregnant.

Evaluation of new embolic particles in the treatment of uterine fibroids is recommended prior to routine clinical use (Spies, 2009; Worthington-Kirsch et al, 2011).

Uterine fibroids are generally diagnosed during a physical examination by the finding of an enlarged or irregularly shaped uterus in the absence of other pathology. Confirmed diagnosis of uterine fibroids and their location in the uterus is routinely determined using ultrasound due to ease of access to ultrasonography and the minimally invasive nature of the procedure (Marnach et al, 2019). Treatment of uterine fibroids by embolization therapy is accomplished by inserting a catheter into either the femoral or radial artery(ies) using ultrasound to confirm access to the vascular lumen (Mortensen et al, 2019), and directing the catheter to the target vasculature using fluoroscopy.

This investigation has been designed to collect longer term data on safety, as well as on the effectiveness of Ekobi™ Embolization Microspheres to act as an embolization agent and to promote vascular occlusion in this patient population.

6.2 Rationale

This study was designed to collect data on safety, as well as on the ability of Ekobi™ Embolization Microspheres to act as an embolization agent and to reduce the symptoms of uterine fibroids. Primary endpoint measurement of fibroid volume was chosen based on study design employed by key opinion leaders conducting uterine artery embolization studies. Evaluation of of the fibroids pre- and post-embolization using ultrasound was conducted to determine the location of the hyperechoic Ekobi™ Embolization Microspheres.

7 STUDY OBJECTIVES

7.1 Primary Objectives

The primary objectives of this study were to:

- Outcome of embolization with OCL 500 as determined by change in fibroid volume.
- Outcome of embolization with OCL 500 as determined by fibroid perfusion.
- Safety of embolization with OCL 500.

7.2 Secondary Objectives

The secondary objectives of this study were to:

- Outcome of embolization with OCL 500 as determined by change in volume of uterus.
- QoL following embolization with OCL 500.

7.3 Exploratory Objectives

The exploratory objectives of this study were to determine:

- Change in appearance of embolized vasculature in comparison to baseline as measured by ultrasound 1 day, 1 month, and 6 months post-embolization.

8 INVESTIGATIONAL PLAN

8.1 Overall Study Design and Plan Description

This is a prospective, open-label, uncontrolled, non-randomized safety and effectiveness study of Occlusin® Embolization Microspheres, rebranded and marketed as Ekobi™ Embolization Microspheres, in women with symptomatic uterine fibroids. Subjects were treated with OCL 504 (212-300 μm) or OCL 505 (300-425 μm) on Day 1. Only properly trained and qualified study personnel administered OCL 504 or OCL 505 to the patient in the hospital. Ekobi™ Embolization Microspheres comprises a family of vascular embolization microspheres designated as a Class IV device by Health Canada and marketed under Medical Device License 101802 for the treatment of hypervascularized tumors and enlarged prostates due to benign prostatic hypertrophy/hyperplasia (BPH).

Prior to entering the study, all patients underwent pre-study assessments, including compliance with inclusion and exclusion criteria, laboratory assessments, health and reproductive history, menstruation history, pelvic examination, pelvic MRI/MRA, and pelvic ultrasound.

Following conventional catheter angiography each patient received transarterial embolization with OCL 504 or OCL 505. The microspheres were administered intra-arterially via a 4F or larger angiocatheter until there was stasis of blood flow (persistent visualization under fluoroscopy of contrast within the target uterine vasculature for 3 to 5 cardiac beats). Following the embolization, SOC supportive therapy was given to ameliorate the effects of the post-embolization syndrome, if required.

Patient assessments, including laboratory testing, MRI/MRA, pelvic ultrasound, UFS-QoL, and patient interviews were conducted at 1 month, and 6 months post-embolization.

8.2 Discussion of Study Design Including Choice of Control Group(s)

The assessments and procedures used in this study are typically used to monitor safety and effectiveness of the treatment of symptomatic uterine fibroids by UAE/UFE. Study subjects were treated by a single episode of embolization.

Patient's baseline data were used as control in comparison to data collected for each patient at time points specified in the study.

Ekobi™ Embolization Microspheres comprise a series of microsphere diameters, manufactured in specific size ranges. The various size ranges are OCL 501 (40 to 75 μm), OCL 502 (75 to 150 μm), OCL 503 (150 to 212 μm), OCL 503P (150 to 180 μm), OCL 503L (180 to 212 μm), OCL 504 (212 μm to 300 μm), OCL 505 (300 to 425 μm) and OCL 507 (500 to 800 μm). Ekobi™ Embolization Microspheres were demonstrated to be non-toxic and biocompatible in *in vitro*, preclinical *in vivo* studies, and clinical studies. Ekobi™ Embolization Microspheres have been shown to be safe in preclinical studies including laboratory studies, biocompatibility assessment, and histological analysis. Preclinical studies have shown OCL 503 and OCL 505 to be a safe and effective artificial embolization device in sheep (uterine arteries) and pigs (renal and hepatic arteries), respectively.

A clinical study in uterine fibroid patients has shown OCL 503 to be a safe and effective artificial embolization device.

A clinical study in benign prostatic hypertrophy/hyperplasia patients has shown OCL 503 to be a safe and effective artificial embolization device.

8.3 Selection of Study Population

8.3.1 Inclusion Criteria

Women diagnosed with symptomatic uterine fibroids, who are not considered to be part of a vulnerable population, were eligible for this study if they met the following criteria:

1. Premenopausal women diagnosed with symptomatic uterine leiomyomata who have menstrual cycles lasting between 22 and 35 days.
2. Are willing and able to give informed consent and to comply with all study related procedures.
3. Uterine leiomyomata visible on either ultrasound or on non-contrast MRI which are not obscured by overlying bone or bowel.
4. Uterine leiomyomata with a minimum diameter of 4 cm for a single fibroid or 3 cm where there are two or more fibroids and where minimum total fibroid burden is 33 cm^3.
5. Symptomatic uterine leiomyomata, based on:
    a. The presence of one or more of the following symptoms: abnormal menstrual bleeding, prolonged menstrual period, pelvic pain, or bulk related symptoms that are attributed to uterine leiomyomata, and
    b. The intensity of the uterine leiomyomata-related symptoms are considered sufficiently severe to warrant UAE, and
    c. The patient's medical history, physical examination, and the results of imaging by ultrasound or MRI.
6. Have no known condition that would contraindicate the procedure.
7. Have documentation of ovulation using urine luteinising hormone (LH) testing, serum progesterone >4 ng/dL or endometrial biopsy showing secretory endometrium in a cycle between 24 and 35 days.
8. Have an FSH value obtained within 3 months prior to the procedure of <40 IU/L.
9. Have had a pelvic examination by a gynaecologist within the previous six months.
10. Have had a normal Pap smear within the last 12 months.

8.3.2 Exclusion Criteria

Patients were excluded from this study if they met any of the following criteria:

1. Positive serum or urine pregnancy test
2. Uterine size greater than 20 weeks gestation
3. Leiomyomata that are more than 50% sub mucosal
4. Individual fibroids greater than 12 cm in diameter, or total fibroid burden greater than 905 cm^3.
5. Have pedunculated subserosal leiomyomata with an attachment to the uterus less than 50% of the greatest diameter of the fibroid.

6. Leiomyomata situated in the cervix
7. Have abnormally large ovarian arteries, as assessed by MRI
8. Uterine pathology, including uterine adenomyosis other than a leiomyoma
9. Have a history of gynaecological malignancy
10. Active pelvic infection or a history of pelvic inflammatory disease
11. Have an undiagnosed pelvic mass outside of the uterus
12. History of chemotherapy or radiation to the abdomen or pelvis
13. Intrauterine Contraceptive Device in position
14. History of, or ongoing, haemolytic anaemia
15. Severe cerebrovascular disease defined by a cerebrovascular accident or transient ischaemic episode within six months
16. Anticoagulant therapy or known bleeding disorder
17. Have been treated with gonadotropin releasing hormone (GnRH) agonists within the previous six weeks
18. Have received another investigational agent within the past twelve weeks
19. Have compromised hematopoietic function (haemoglobin < 100 g/L; lymphocyte count < 500 $x10^6$/L; neutrophil count < 1.5 x 10^9/L; platelet count < 150 x 10^9/L)
20. Have hepatic dysfunction defined as serum bilirubin > 1.5, or either AST or ALT >2.5 times the upper limit of normal
21. Have renal dysfunction as defined by a serum creatinine > 1.5 mg/dL
22. Patients with a BMI >38
23. Patients have claustrophobia
24. Contraindication to angiography
25. Contraindication to MRI or MRI contrast agent such as gadolinium
26. An allergic reaction to contrast
27. An allergic reaction to bovine collagen
28. Patient wants to become pregnant, or does not agree to contraception during study

8.3.3 Removal of Patients from Treatment or Assessment

Patients could be withdrawn from the study for the following reasons:

1. The patient withdraws consent.
2. The PI determines that it was not in the best interests of the patient to continue in the study.
3. The patient experiences an adverse reaction that, in the opinion of the PI, necessitated the removal of the patient from the study, including any unresolved serious adverse event (SAE).
4. Intercurrent illness or other reasons that would, in the opinion of the PI, affect assessment of clinical status or conduct of the study to a significant degree.

The reasons for withdrawing the patient were documented by the PI. Patients who withdraw from the study were followed up, where possible.

Patients were considered to have exited the study for any of the following reasons:

1. The patient died.
2. The patient withdrew consent for the study.
3. The patient did not withdraw consent but was unable to complete the study.
4. The patient completed the study protocol.

8.3.4 Study Stopping Criteria

The PI in consultation with the Sponsor was to stop the study if there were more than 3 device-related severe AEs or if there was more than 1 device-related life-threatening or disabling AE following treatment with the embolic agent.

8.4 Investigational Device

8.4.1 Administration of OCL 504 and OCL 505

OCL 504 or OCL 505 were administered during a uterine fibroid embolization procedure. Following a pelvic angiogram to delineate the uterine vasculature, embolization procedures of the left and right uterine arteries were performed on each patient. OCL 504 (212-300 μm) or OCL 505 (300-425 μm) microspheres were delivered by 5F angiocatheter, with a starting dose of 400 mg (1 vial). The OCL 504 or OCL 505 microspheres were administered intra-arterially using pulsatile delivery. Additional vials of OCL 504 or OCL 505, consisting of 400 mg/vial, were administered until there was persistent visualization under fluoroscopy of contrast within the target uterine artery for 3 to 5 cardiac beats. Once the endpoint of near blood flow stasis in the target vasculature was reached, contrast agent was again injected after a 5-minute waiting period to determine whether additional embolic material was needed.

8.4.2 Identification of Investigational Device

For this study, Ekobi™ Embolization Microspheres were provided as 212-300 μm diameter (OCL 504) or 300-425 μm diameter (OCL 505). OCL 504 and OCL 505 are compatible for use with angiocatheters 4F or larger. Ekobi™ Embolization Microspheres are hyperechoic and have a density of approximately 1.3 g/mL.

OCL 504 and OCL 505 were provided in a sealed glass vial as 400 mg of sterile dry microspheres to be reconstituted and administered via angiocatheter to the uterine artery/arteries. Instructions for Use (IFU) were provided with each shipment of vials.

As is true for other vascular embolization devices, at the time/point of use, the OCL 504 or OCL 505 microspheres were suspended in an aqueous delivery vehicle consisting of sterile sodium chloride injection (0.9% United States Pharmacopeia; not included with the product) and radiopaque contrast agent, such as Omnipaque™ 240 (not included with the product). The bolus of contrast agent elutes from the vascular bed to leave a radiolucent, embolized vessel.

DSM Biomedical (Exton, PA) manufactured OCL 504 and OCL 505 for IMBiotechnologies in compliance with Good Manufacturing Practice. The following lot numbers were used in the study: E7536 (expiry: 28 May 2019) and E7537 (expiry: 28 May 2019).

OCL 504 and OCL 505 were packaged in unit dose vials, each vial being intended for the administration to a single patient. An example of the vial label is provided in the protocol.

OCL 504 and OCL 505 were shipped to the study facility in an insulated container with cold packs. Upon arrival, OCL 504 and OCL 505 were stored in a cool dry location, at room temperature, and protected from light in a locked storage cabinet. Temperature within the storage cabinet containing the study device was monitored constantly.

The Research Coordinator was responsible for storage of OCL 504 and OCL 505 in the Department of Radiology, University of Alberta Hospital.

8.4.3 Selection of Doses in the Study

The starting dose of OCL 504 or OCL 505 microspheres was 400 mg (1 vial) administered intra-arterially. Additional vials of OCL 504 or OCL 505 consisting of 400 mg/vial were administered until there was persistent visualization under fluoroscopy of contrast within the target uterine vasculature for 3 to 5 cardiac beats.

8.4.4 Selection and Timing of Dose for Each Patient

See 8.4.1.

8.4.5 Blinding

This was an open label study.

8.4.6 Prior and Concomitant Therapy

The following medications were not to be given to patients during the study period unless required in the management of the patient:

- Other investigational drugs or medical devices.

Patients who experienced post-embolization syndrome (pain, nausea, fever) were permitted to receive center standard of care (SOC) treatment for symptoms, including:

- Hydration for 24 hours following the procedure.
- Narcotics, analgesics.
- Antipyretics.
- Antiemetics.

Any treatments administered were documented on the eCRF.

8.4.7 Treatment Compliance

Administration of the investigational device (OCL 504 or OCL 505) was performed under the direct supervision of the PI; therefore, measures to ensure patient compliance were not required. The details of administration of study treatment were documented in the patient's eCRF.

The study coordinator contacted patients several days in advance of scheduled visits to facilitate compliance with protocol scheduled study visits.

8.5 Effectiveness and Safety Variables

8.5.1 Effectiveness and Safety Measurements Assessed and Flow Chart

The schedule of assessments is presented in Table 8-1.

Table 8-1 Schedule of Assessments

	Pre-Study						End of Study	Unscheduled Visits
TIME (weeks)	Within 6 months of study start	Within 1 month of study start		1		4	24	
TIME (calendar days)	-180	-28	1	2	7±2	30±7	180±7	
VISIT NO.		1	2	3	4	5	6	
Confirmation of menstruation		X						
Confirmation of symptomatic fibroids	X							
Pap Smear	X							
Pelvic Examination	X							
Biopsy/bacterial cultures[1]	X							
Informed Consent		X						
History (Medical, Surgical)		X						
Reproductive History		X						
Physical Examination, vital signs		X	X			X	X	X
MRI/MRA Imaging of Pelvis		X		X		X	X	X
Ultrasound		X	X[2]	X		X	X	X
Pregnancy Test (serum)		X	X[3]			X	X	X
Patient Interview					X	X	X	X
Administration of Ekobi™ Embolization Microspheres			X					
Complete Blood Cell Count		X	X			X	X	X
Serum Chemistry		X	X			X	X	X
FSH, LH		X	X			X	X	X
Coagulation Profile		X	X			X	X	X
Uterine Fibroid Symptom – QOL Instrument		X				X	X	X
Adverse Events			X	X	X	X	X	X
Chart Review & Concomitant Medications			X	X	X	X	X	X

1. Cultures as appropriate to patient history
2. Ultrasound to be conducted pre-embolization to evaluate vasculature to be embolized
3. Testing must occur within 72 hours prior to UAE procedure

8.5.1.1 Effectiveness Assessments

8.5.1.1.1 Fibroid Volume

Fibroid volume was measured pre-embolization (baseline) and 1-day, 1-month, and 6-months post-embolization. Dominant size of the fibroid was determined by a blinded radiologist by measuring length, width, and depth of the fibroid. From these measurements fibroid volume was determined using the formula:

Fibroid Volume (cm^3) = 4/3π x length (cm)/2 x width (cm)/2 x depth (cm)/2

$$\text{Change in Fibroid Volume (\%)} = \frac{\text{(Follow-up fibroid volume – Baseline fibroid volume)}}{\text{Baseline fibroid volume}} \times 100$$

8.5.1.1.2 Fibroid Perfusion

Change in fibroid perfusion, relative to baseline, was conducted 1-day, 1-month, and 6-months post-embolization using a standard gadolinium contrast agent. At each timepoint, the studies were conducted with and without contrast.

8.5.1.1.3 Uterine Volume

Uterine volume was measured pre-embolization (baseline), 1-day, 1-month, and 6-months post-embolization. Size of the uterus was determined by a blinded radiologist by measuring length, width, and depth of the uterus. From these measurements uterine volume was determined using the formula:

Uterine Volume (cm^3) = 4/3π x length (cm)/2 x width (cm)/2 x depth (cm)/2

$$\text{Change in Uterine Volume (\%)} = \frac{\text{(Follow-up uterine volume – Baseline uterine volume)}}{\text{Baseline uterine volume}} \times 100$$

8.5.1.1.4 UFS-QoL and Patient Interview

Quality of life (QoL) and symptom severity assessments were conducted pre-embolization (baseline), 1-month and 6-months post-embolization. Changes in these scores relative to baseline were determined at 1-month and 6-months post-embolization. Patient interviews were conducted at 1-week, 1-month, and 6-months post-embolization to assess pain by visual analog score (VAS).

8.5.1.2 Safety Assessments

8.5.1.2.1 Adverse Events

Safety was assessed and documented at every study visit from Day 1 (Study Visit 2; day of the embolization procedure). Definitions and details of reporting, grading, and recording of AEs, SAEs, adverse device effects (ADEs), serious ADEs (SADEs), and unanticipated ADEs (UADEs) are provided in Section 13 of the protocol.

8.5.1.2.2 Laboratory Safety Assessments

Standard laboratory tests, conducted at the local laboratory were performed at the times specified in Table 8-2. Laboratory tests for hematology, coagulation, blood chemistry, and hormone levels were performed to assess effects of the study treatment. The PI assessed the results of all

laboratory tests as to their clinical significance. Any post-baseline laboratory value that was found to be clinically significant was evaluated by the PI for causal relationship to the administration of the study device and any medically appropriate action was taken.

Any laboratory outcomes considered an AE were reported as specified in the protocol.

The laboratory safety assessments performed during the study are presented in Table 8-2.

Table 8-2 Laboratory Safety Assessment

Hematology: Complete blood count	**Coagulation:** Prothrombin time (PT/INR)
Serum chemistry:	
Albumin	Calcium
Alkaline phosphatase	Phosphate
Aspartate aminotransferase	Glucose
Alanine aminotransferase	Uric acid
Bilirubin (total)	Bicarbonate
Lactate dehydrogenase	Chloride
Total Protein	Potassium
Alpha-fetoprotein	Sodium
Creatinine	
Urea	
FSH, LH hormones	
Pregnancy	

8.5.1.2.3 Physical Examination

Outcomes of physical examinations (cardiovascular, respiratory, neurological, musculoskeletal systems) were documented on the appropriate eCRF page.

8.5.1.2.4 Vital Signs

Measurements of vital signs (pulse, blood pressure, respiratory rate, temperature [oral]) were documented on the appropriate eCRF page.

8.5.1.3 Quality of Life Assessments, Patient Interview and Chart Reviews

Quality of life information was recorded directly in the eCRF and formed part of the patients' original record.

Patient interviews were conducted per the PI's usual procedure with therapeutic embolization patients. Patient interview questions assessed pain associated with the procedure and pain which may have occurred since the procedure. Interviews were conducted at 7 days, 1 month, and 6 months post-embolization. The interview at 7 days assessed patient well-being from the day of treatment to the 7-day time point. Study subject interviews at the 1-month and 6-month time points assessed patient well-being at the specific time point.

Chart reviews took place per center SOC at each study visit.

8.5.2 Appropriateness of Measurements

The assessments used in this study have been widely used and are generally recognized as being reliable, accurate, and relevant.

8.6 Data Quality Assurance

Training of the investigational team (Investigators and staff) was the responsibility of the Sponsor or Sponsor's authorized representative. Training of all study personnel to ensure appropriate use of the device included:

- Proper reconstitution of the device.
- Proper administration of the device.

The Sponsor or Sponsor's authorized representative (Monitor) documented completion of site preparation and training. Training necessary to ensure compliance with the protocol is detailed in Section 15 of the protocol.

The Sponsor or authorized delegate visited the investigation site periodically during the clinical investigation to ensure adherence to the Protocol, accurate data recording on the eCRFs and to monitor adherence to follow-up schedules. The PI permitted and assisted the Monitor to carry out verification of completed eCRFs against data in the source documents.

The Monitor informed the Sponsor about any problems relating to facilities, technical equipment or medical staff at the investigational site. During the Monitoring Visits, the Monitor checked that appropriate written informed consents had been obtained. The Monitor was also responsible for notifying such deficiencies in writing to the PI and for convening with the investigational site personnel to conduct timely corrective actions.

The Monitor submitted written reports to the Sponsor, after each visit or contact with the PI or investigational site personnel.

8.7 Statistical Analysis

8.7.1 Statistical and Analytical Plans

Statistical analysis was conducted regarding change in dominant fibroid volume, change in fibroid perfusion, change in uterine volume, change in quality of life score, and change in symptom score using SAS (version 9.4) software by an independent biostatistician. Refer to Appendix 15.1 for statistical analysis. Statistical calculations were generated using the Student's t-test (parametric data) or the Wilcoxon Signed Rank Test (WSRT; non-parametric data).

8.7.1.1 Study Populations

Not applicable.

8.7.1.2 Statistical Methods

An analysis of the clinical data collected for this study was performed. The analysis of the biological data derived from this study involved analysis of dominant fibroid volume, fibroid perfusion, and uterine volume. Statistical analysis of symptom improvement and quality of life scores was conducted at 6-month EOS.

Statistical calculations were provided relative to data presentation (parametric versus non-parametric).

Safety analyses was based on the clinical and laboratory adverse effects observed in patients entered into the study. The analysis was primarily descriptive.

The number of patients withdrawn from the study and the reasons for withdrawal was examined. Protocol deviations (especially those related to non-compliance such as missed visits, visits out of the scheduled time window, etc.) were identified together with the reasons for the deviations.

Individual patient data are presented in line listings that summarize information captured in the eCRF. Descriptive statistics were used to present the data and to summarize the results. Continuous variables were summarized by presenting the number of observations, mean, standard deviation, median, minimum, and maximum values. Primary analysis of AE reporting was based on patient counts. A patient with more than 1 event was counted only once toward an event rate based on the total number of patients with AEs.

8.7.1.2.1 Demographic and Baseline Characteristics

Demographic and baseline data were collected at Screening and entered in the individual eCRFs.

8.7.1.2.2 Concomitant Medication

Concomitant medications, including any medication used to treat AEs, was listed in the individual patient eCRFs.

8.7.1.2.3 Extent of Exposure and Compliance

The amount of OCL 504 or OCL 505 administered and the duration of the embolization procedure was collected and listed in the individual patient eCRFs.

8.7.1.2.4 Effectiveness Analysis

Effectiveness analyses was based on change in dominant fibroid volume at 1-day, 1-month, and 6-months post-embolization relative to baseline. Uterine volume was assessed at 1-day, 1-month, and 6-months post-embolization. Patient quality of life was assessed by questionnaire and interview at 1-week, 1-month, and 6-months post-embolization.

8.7.1.2.5 Safety Analysis

Safety analyses was based on the clinical and laboratory adverse effects observed in all patients entered into the study. The analyses was primarily descriptive.

8.7.2 Sample Size

Enrollment in this study was planned to continue until 13 women with symptomatic uterine fibroids were treated with OCL 504 or OCL 505. The total enrollment was up to 18 patients to allow 13 evaluable patients. Enrollment in the study was closed after twelve (12) patients were treated with the study device due to a slow down in recruitment.

8.7.3 Control of Systematic Error/Bias

Patients were alternately treated with OCL 504 or OCL 505 based on chronological order of treatment (see Table 11-1). The PI assessed the relationship of any events to the test device, as is

standard in clinical studies. There was no opportunity for Sponsor bias to be introduced in the assessment of AEs. An independent reviewer assessed radiological (MR and ultrasound) images.

9 STUDY PATIENTS

Patient disposition and protocol deviation data were collected in the individual patient eCRFs.

9.1 Disposition of Patients

Seventeen (17) patients signed informed consent forms and were enrolled in the study. Four (4) patients were not treated as they failed to meet all the inclusion/exclusion criteria, 1 patient exited the study before treatment due to time commitments, and 12 patients were treated with the study product. Study recruitment was stopped after treating the 12th patient. Table 9-1 provides a summary of screen failures for consented patients.

Table 9-1 Screen Failures

Study Subject	Criterion and Number	Reason for Screen Failure
001	Inclusion 4	Fibroid burden did not meet minimum volume criterion
004	Inclusion 6	FSH level > 40 IU/L
012	Exclusion 3	Fibroids > 50% submucosal
017	Exclusion 8 Exclusion 9	Uterine pathology other than leimomyoma Gynaecological malignancy

9.2 Protocol Deviations

Subject 005 had follow up testing out of window for her 6 month end of study visit. The Sponsor was informed and approved the deviation. Subect 006 had follow up testing out of window for her 6 month, end of study, visit. The Sponsor was informed and approved the deviation. Subject 007 failed exclusion criterion 13 (intrauterine contraceptive device [IUD] in position) during screening. The subject had the IUD removed and was subsequently treated as a participant in the study. The treating physican informed the Sponsor that the subject had her IUD removed. The Sponsor approved treatment of the subject. Subject 009 had follow up testing out of window for her 6 month, end of study, visit. The Sponsor was informed and approved the deviation. Subject 016 had testing for her Visit 2 timepoint that was out of the specified time window. The Sponsor was informed and approved the deviation.

The protocol deviations did not affect the integrity or relevance of the data collected.

10 EFFECTIVENESS EVALUATION

Data presented was monitored by contracted clinical research associate.

10.1 Data Sets Analyzed

Not applicable.

10.2 Demographic and Other Baseline Characteristics

Demographic data and medical and surgical history was captured in the individual patient eCRFs.

10.2.1 Demographic Characteristics and Screening Results

Demographic characteristics and screening results for all treated patients enrolled, to date, are presented in Table 10-1. Height, weight and BMI were not determined for patients that failed screening.

Table 10-1 Demographic Baseline Characteristics of Treated Subjects

Parameter	002	003	005	006	007	009	010	011	013	014	015	016
Age (years)	51	34	48	53	32	43	47	46	44	45	51	37
Race	White	White	White	White	White	White	White	White	White	White	Asian	White
Height (cm)	166	165	168	158	160	158	163	156	155	161	165	173
Weight (kg)	59.2	85	83	59	56	67	76.6	66.6	59.6	76.3	99.0	75.0
BMI (kg/m^2)	21.5	31.2	29.4	23.6	21.9	26.8	28.8	27.4	24.8	29.4	36.4	25.1

Abbreviations: BMI=body mass index
Only subjects treated with the investigational product are presented in Table 10-1

The average age of the subjects treated in the study (n=12) is 44.3 ± 6.8 (sd) years, with an age range of 32 to 53 years (median = 45.5).
The average BMI of the subjects treated in the study (n=12) is 27.2 ± 4.2 (sd), with a range of 21.5 to 36.4 (median = 27.1).

10.2.2 Medical and Surgical History

Medical and surgical history for all enrolled patients is presented in Table 10-2. All enrolled subjects were diagnosed with symptomatic uterine fibroids.

Table 10-2 Health History of Treated Subjects

Patient	Disease / Procedure	Start Date	Stop Date	Ongoing / Prior Medication
002	Migraines	2000	Ongoing	Eletripan
	Breast Implants	2002	2002	
	Knee Surgery (1)	1988	1988	
	Knee Surgery (1)	1991	1991	
	Other	Unknown	Ongoing	DHEA, Progesterone (hormone replacement); Ortho 1/35 (birth control)
003	Depression	2017	Ongoing	Effexor
	Appendectomy	1999	1999	
	Anxiety	2016	Ongoing	
005	Fracture of Radius/Ulna	1977	1977	
	Anxiety	2015	Ongoing	Wellbutrin, Ativan
	Other	2017	2018	Fibristal (uterine fibroids)
006	Tubal Ligation	2006	2006	
	Arthritis	2010	Ongoing	Gabapentin
	Left Inguinal Hernia	1975	1975	
	Other	2018	2018	Tylenol (uterine fibroids)
007	Dilation and Curettage	2016	2016	
	Other	2018	2018	Cephalexin (infection); Levonorgestrel (birth control)
009	Tonsillectomy	1992	1992	
	Breast Augmentation	2014	2014	
010	Urethra Surgery	1973	1973	
	Gastro-Esophageal Reflux Disorder (GERD)	2014	Ongoing	
	Headaches	1986	Ongoing	
011	Anemia	2016	Ongoing	Ferrous Polyride
				Mefanamic Acid
				Tranexamic Acid
013	Abdominoplasty	2002	2002	Tranexamic Acid
014	Cesarean Section	2000	2000	
015	ACL Repair	2013	2013	
	Tubal Ligation	1988	1988	
	Ankle Injury	1982	1982	

016	Anxiety	2005	Ongoing	Quetiapine
	Depression	2005	Ongoing	Pristiq
	Acid Reflux	2013	Ongoing	Pantaloc
	Hemorrhoids	2019	Ongoing	

Reproductive history for each treated subject is shown in Table 10-3. The number of times the subject has become pregnant (gravida) and the number of live births (para) are presented.

Table 10-3 Reproductive History of Treated Subjects

Patient	Gravida Number	Para Number
002	3	3
003	0	0
005	3	2
006	3	3
007	3	2
009	4	2
010	3	3
011	2	2
013	7	5
014	5	4
015	2	2
016	0	0

10.3 Measurements of Treatment Compliance

Not applicable.

10.4 Effectiveness Results and Tabulations of Individual Patient Data

Efficacy data were collected in the individual patient eCRFs.

10.4.1 Effectiveness Analysis

10.4.1.1 Fibroid Volume and Perfusion

The results for dominant fibroid volume for each treated subject are presented in Table 10-4.

Table 10-4 Fibroid Volume (ml)

Subject Number	Pre-Embolization Baseline	Post-Embolization Follow-up		
		1 Day	1 Month	6 Months (End of Study)
002	27.7	27.1	15.3	12.8
003	777.2	826.2	710.1	555.1
005	228.7	177.1	80.6	70.8
006	251.1	270.4	167.2	77.2
007	100.7	126.0	99.8	112.9
009	197.1	151.4	97.1	80.7
010	135.4	199.5	120.3	73.0
011	206.9	166.5	74.9	62.7
013	284.6	250.3	169.3	250.8
014	91.4	96.9	69.4	61.8
015	59.0	50.6	32.5	15.8
016	47.7	38.2	28.6	19.8

Baseline dominant fibroid volume of the 12 treated subjects was 200.6 ± 200.6 ml (range 27.7 to 777.2; median = 166.2). The mean fibroid volume at the 1-month followup time point was 138.8 ± 186.5 ml (range 15.3 ml to 710.1 ml; median 88.8 ml). Mean decrease in dominant fibroid volume for the 12 subjects at 1-month post-embolization was 35.6 ± 20.8% (p=0.0005, WSRT; range 0.9 to -64.7%; median = 40.2%). The mean fibroid volume for the 12 subjects followed to 6-months post-embolization continued to decrease relative to the 1-month time point (mean =116.6 ml ± 151.6 ml; median = 71.9 ml; range = 12.8 ml to 555.1 ml). The mean percent decrease in the dominant fibroid volume for the 12 subjects followed to 6 months was 45.9% ± 26.9% (p=0.0015 WSRT; median = 55.6%; range = 12.1% to -73.1%).

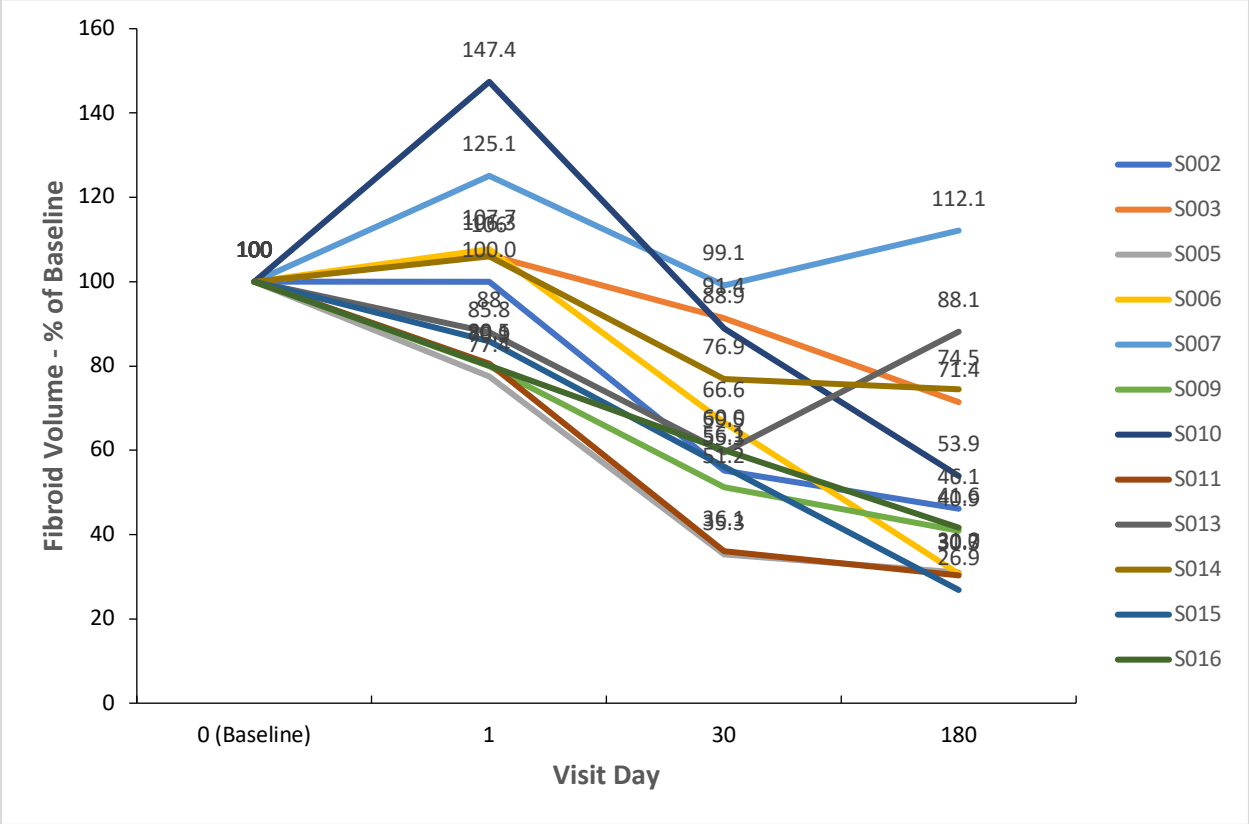
Table 10-5 presents fibroid volume mean, SD, range and median at baseline, 1-month, and 6-month follow-up, for the subjects treated with either OCL 504 or OCL 505.

Table 10-5 Fibroid Volume Changes with Treating Agent

Agent	Baseline			1-Month			6-Months		
	Mean	**SD**	**Median**	**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**
OCL 504	139.3	99.5	118.0	86.3	56.9	90.2	89.3	87.7	71.9
% Change from Baseline	-	-	-	34.5%	23.8%	42.6%	40.3%	33.7%	50.0%
OCL 505	261.9	263.8	202.0	191.2	258.3	86.0	143.9	202.6	72.7
% Change from Baseline	-	-	-	36.8%	19.5%	36.7%	51.7%	19.7%	58.7%

Figure 10-1 plots the percentage change in dominant fibroid volume relative to baseline for the 12 subjects followed to 6-months post-embolization.

Figure 10- 1 Change in Dominant Fibroid Volume



The results for dominant fibroid perfusion for each treated subject are presented in Table 10-6.

Table 10-6 Fibroid Perfusion (%)

Subject Number	Pre-Embolization Baseline	Post-Embolization Follow-up		
		1 Day	1 Month	6 Months (End of Study)
002	100	0	0	0
003	100	20	20	20
005	100	5	5	5
006	100	10	10	5
007	100	40	100	100
009	100	5	5	5
010	100	0	0	0
011	20	40	75	90
013	100	20	90	90
014	60	60	60	60
015	100	20	60	70
016	80	0	0	0

Mean decrease in fibroid perfusion 1-month post-embolization was 64.6% ± 38.6% (p = 0.01; range 0% to 100%; median = 85.0%). Mean decrease in fibroid perfusion at 6-months post-embolization was 62.9% ± 58.8% (p = 0.01; range 0% to 100%; median = 87.5%). The mean decrease in fibroid perfusion at 1-month for subjects treated with OCL 504 and OCL 505 was 42.5 ± 45.9% and 48.3 ± 61.5%, respectively. The mean decrease in fibroid perfusion at 6-months for subjects treated with OCL 504 and OCL 505 was 55.0 ± 46.8% and 46.7 ± 67.4%, respectively.

10.4.1.2 Uterine Volume

The results for change in uterine volume for each treated subject are presented in Table 10-7.

Table 10-7 Uterine Volume (ml)

Subject Number	Pre-Embolization Baseline	Post-Embolization Follow-up		
		1 Day	1 Month	6 Months (End of Study)
002	637.4	609.8	502.7	380.5
003	854.2	1127.4	1194.0	976.7
005	679.8	691.4	478.8	423.4
006	819.6	829.1	495.7	240.2
007	428.4	527.0	519.2	400.6
009	730.2	695.3	670.7	583.7
010	644.9	741.1	599.9	527.4
011	640.1	642.3	312.4	288.5
013	887.3	835.3	674.4	799.4
014	480.4	456.9	434.1	378.2
015	378.5	410.6	265.7	241.5
016	302.8	308.3	311.7	233.9

Mean baseline uterine volume for the 12 treated subjects was determined to be 640.6 ± 221.8 ml (range 302.8 to 1070.7 ml; median = 642.5 ml). Mean uterine volume for the 12 subjects at 1-month post-embolization was 538.3 ± 245.7 ml (range 265.7 to 1194.0 ml; median = 499.2 ml). The mean relative change in uterine volume for the 12 subjects at 1-month was a change of -15.4% ± 22.2% (median = -15.4%; range = 21.2% to -51.2%). The mean uterine volume at 6-months post-embolization was 456.2 ± 232.8 (range = 233.9 to 976.7; median = 390.5). The mean relative decrease in uterine volume at 6-months post-embolization was 28.8% ± 19.6% (p = 0.0005, WSRT; range = 6.5% to 70.7%; median = 22.0%).

The mean decrease in uterine volume at 1-month for subjects treated with OCL 504 and OCL 505 was 15.0 ± 19.6% and 15.7 ± 24.5%, respectively. The mean decrease in fibroid perfusion at 6-months for subjects treated with OCL 504 and OCL 505 was 36.0 ± 2.1% and 33.1 ± 24.1%, respectively.

10.4.1.3 UFS-QoL

Subjects' symptom severity and quality of life were assessed using the UFS-QoL questionnaire. The results of the UFS-QoL are presented in Table 10-8.

Table 10-8 UFS-QoL

Subject Number	Pre-Embolization Baseline		Post-Embolization			
			1 Month		6 Months	
	Symptoms[1]	HRQL[2]	Symptoms	HRQL	Symptoms	HRQL
002	42.5	55.2	32.5	75.0	0.0	99.1
003	50.0	50.0	40.0	54.3	45	45.6
005	67.5	22.4	65.0	31.0	20.0	90.5
006	80.0	0.9	5.0	98.3	0.0	100
007	50.0	45.7	60.0	41.4	10.0	88.8
009	57.0	75.9	15.0	75.0	7.5	89.7
010	32.5	62.1	37.5	79.3	20.0	90.5
011	67.5	28.4	27.5	62.9	30.0	62.9
013	50.0	27.6	40.0	34.5	12.5	60.3
014	20.0	125.0	32.5	48.3	7.5	100.0
015	22.5	37.9	27.5	53.4	15.0	92.2
016	60.0	30.2	50.0	32.8	25.0	80.2

[1]Transformed symptom scores (higher number = worse symptoms); [2]Transformed HRQL score (higher number = better quality of life)

The mean baseline symptom score for the 12 treated subjects was 52.3 ± 15.9 (range = 22.5 to 80.0; median = 50.0). The mean symptom score for the 12 subjects at the 1-month followup was 36.4 ± 17.1 (range = 5.0 to 65.0; median = 35.0). The mean symptom score for the 12 subjects followed to 6 months was 16.0 ± 13.0 (range = 0 to 45.0; median = 13.8). The mean relative change in symptom score for the 12 subjects followed to 6 months was -36.3 ± 20.7 (p = 0.0005 WSRT; range = -80.0% to -5.0%; median = -37.5%). The mean decrease in symptom score at 1-month for subjects treated with OCL 504 and OCL 505 was 4.2 ± 11.9 and 32.5 ± 23.7, respectively. The mean decrease in symptom score at 6-months for subjects treated with OCL 504 and OCL 505 was 31.7 ± 17.2 and 41.3 ± 24.5, respectively.

The mean baseline quality of life score for the 12 treated subjects was 39.7 ± 19.9 (range = 0.9 to 75.9). The mean quality of life score for the 12 subjects at the 1-month followup was 64.9 ± 21.3 (range = 31.0 to 98.3; median = 53.9). The mean quality of life score for the 12 subjects followed to 6 months was 83.4 ± 17.5 (range = 46.6 to 100.0; median = 90.1). The mean relative change in quality of life score for the 12 subjects followed to 6 months was 43.7 ± 26.4% (p = 0.0001, t-test; range = -3.4% to 99.1%; median = 43.5%). The mean increase in quality of life

score at 1-month for subjects treated with OCL 504 and OCL 505 was 10.6% ± 8.9% and 24.4% ± 38.0%, respectively. The mean increase in quality of life score at 6-months for subjects treated with OCL 504 and OCL 505 was 45.1% ± 14.5% and 42.4% ± 36.3%, respectively.

10.4.2 Statistical/Analytical Issues

10.4.2.1 Adjustments for Covariates

Not applicable.

10.4.2.2 Handling of Dropouts or Missing Data

Subjects that dropout before treatment were not included when conducting statistical analysis. No subjects dropped out of the study following treatment.

10.4.2.3 Interim Analyses and Data Monitoring

No formal interim analysis, comprising a database lock, was performed for this study.

10.4.2.4 Multicenter Studies

This is a single-center study.

10.4.2.5 Multiple Comparisons/Multiplicity

Not applicable.

10.4.2.6 Use of an Effectiveness Subset of Patients

Not applicable.

10.4.2.7 Active Control Studies Intended to Show Equivalence

Not applicable.

10.4.2.8 Examination of Subgroups

Subjects treated with OCL 504 or OCL 505 were analyzed separately and as a single group.

10.4.3 Tabulation of Individual Response Data

Not applicable.

10.4.4 Drug Dose, Drug Concentration and Relationships to Response

Not applicable.

10.4.5 Drug-Drug and Drug-Disease Interactions

Not applicable.

10.4.6 Effectiveness Summary – Primary Endpoint

The primary endpoint for this study is change in dominant fibroid volume at 6-months post-embolization. All 12 subjects were followed to 6-months post-embolization and 11 subjects

demonstrated a decrease in dominant fibroid volume. A statistically significant decrease in fibroid volume relative to baseline was noted at 6-months post-embolization (p=0.0015; WSRT).

10.4.7 Effectiveness Summary – Secondary Endpoints

A statistically significant decrease in fibroid volume was noted at 1-month post-embolization (p = 0.0005, WSRT; N = 12). A mean decrease in dominant fibroid perfusion of 52.5 ± 51.9% (p = 0.01, WSRT) and 50.8 ± 55.5% (p = 0.01, WSRT) was seen at 1-month and 6-months post-embolization, respectively.

Uterine volume decreased in 9 of 12 subjects at 1-month post embolization. The mean relative decrease in uterine volume was 15.4% ± 21.2% (p = 0.11, WSRT) at 1-month post-embolization. The mean relative decrease in uterine volume 6-months post-embolization was 28.8% ± 19.6% (p=0.0005, WSRT).

Subjects were assessed using the UFS-QoL assessment. This questionnaire scores the subject's symptoms and quality of life. A high symptom score is indicative of worse symptoms. A high quality of life score is indicative of better quality of life. Symptom scores improved over the study period. Scores decreased from a mean baseline score of 52.5 ± 15.9 to 34.2 ± 14.8 at 1-month followup, and 16.0 ± 13.0 (p = 0.0005, WSRT; N=12) at 6-months follow-up. Quality of life improvement was reflected in higher quality of life scores over the study period. Scores improved from a mean baseline score of 39.7 ± 19.9 to 57.2 ± 21.3 at 1-month and 83.4 ± 17.5 (p = 0.0001, t-test; N=12) at 6-months, post-embolization.

11 SAFETY EVALUATION

The dose of OCL 504 or OCL 505 administered, duration of procedure, and safety data were collected in the individual patient eCRFs.

11.1 Exposure to Investigational Product

The dose of OCL 504 or OCL 505 administered, duration of embolization procedure, and outcome (whether near stasis was achieved for the target vasculature) for treated subjects are presented in Table 11-1. Near stasis embolization was defined as retention of contrast agent in the target vasculature for 3 to 5 cardiac beats.

Table 11-1 Administration of Investigational Product

Subject Number	OCL 504 Administered (mg)	OCL 505 Administered (mg)	Near Stasis Embolization	Embolization Time (min)	Radiation Exposure (min)	Radiation Exposure (grays)
002	2000	-	Yes	49	18.2	1538
003	-	2800	Yes	31	13.5	2788
005	2000	-	Yes	33	13.5	2125
006	-	2347	Yes	30	14.5	2812
007	3120	-	Yes	31	16.8	2121
009	-	3200	Yes	30	12.4	1416
010	3200	-	Yes	35	12.9	2450
011	-	3100	Yes	33	16.1	2067
013	4775	-	Yes	35	11.8	1967
014	-	2000	Yes	29	12.5	1715
015	1867	-	Yes	20	10.8	Unavailable[1]
016	-	3200	Yes	35	20.9	Unavailable[1]

[1]Data lost during equipment service.

Near-stasis bi-lateral embolization was achieved in all subjects treated (successful embolization). The time required for embolization ranged from 20 to 49 minutes.

Investigational product was stored in a secured safe within a secured office. Access to investigational product was limited to the PI and the Study Coordinator. Temperature within the secured safe was monitored constantly, with readings recorded weekly. No temperature excursions were observed.

11.2 Pain Score and Patient Interview

The pain score associated with the procedure and at follow-up for each treated patient as determined using the visual analogue pain score (VAS; 10-point scale), is presented in Table 11-2.

Table 11-2 VAS Pain Score

Subject Number	Pain Score (Scale = 0 to 10; high score = more pain)		
	Within 7 Days	At 1-month	At 6-months
002	4.5	0	0
003	4	1	6
005	0.5	1.5	1
006	1.0	1.8	0
007	2.0	0.5	0
009	0	3	0.5
010	2	3	0
011	4	0	1
013	1	5	2
014	3	2	0
015	2	0	4
016	0	6	5

The mean peak pain score within 7-days of the procedure for the 12 treated subjects was 2.0 ± 1.6 (median = 2.0). The mean pain score for the 12 subjects at the 1-month followup was 1.9 ± 1.9; (median = 1.7). The mean pain score for the 12 subjects followed to 6-months post-embolization was 1.6 ± 2.2 (median = 0.8).

Response to interview questions at follow-up visits are summarized in Table 11-3.

Table 11-3 Responses to Interview Questions

Subject Number	Question	Post-embolization Follow-up		
		7 Days	1-month	6-months
002	Have you experienced pain in your abdominal pelvic regions since the procedure?	Y	N	N
	Have you experienced fever since the procedure?	N	N	N
	Have you experienced cramping since the procedure?	Y	Y	N
	Have you experienced vaginal discharge since the procedure?	Y	Y	N
	Have you experienced nausea since the procedure?	Y	Y	N
	Do you feel BETTER, SAME, or WORSE?	Better	Better	Better

003	Have you experienced pain in your abdominal or pelvic regions since the procedure?	Y	Y	Y
	Have you experienced fever since the procedure?	N	N	N
	Have you experienced cramping since the procedure?	Y	Y	Y
	Have you experienced vaginal discharge since the procedure?	Y	Y	N
	Have you experienced nausea since the procedure?	Y	Y	N
	Do you feel BETTER, SAME, or WORSE?	Better	Better	Worse
005	Have you experienced pain in your abdominal or pelvic regions since the procedure?	Y	Y	Y
	Have you experienced fever since the procedure?	N	Y	N
	Have you experienced cramping since the procedure?	Y	N	Y
	Have you experienced vaginal discharge since the procedure?	Y	Y	Y
	Have you experienced nausea since the procedure?	Y	N	N
	Do you feel BETTER, SAME, or WORSE?	Better	Better	Better
006	Have you experienced pain in your abdominal or pelvic regions since the procedure?	Y	Y	N
	Have you experienced fever since the procedure?	N	N	N
	Have you experienced cramping since the procedure?	N	Y	Y
	Have you experienced vaginal discharge since the procedure?	Y	Y	Y
	Have you experienced nausea since the procedure?	Y	Y	N
	Do you feel BETTER, SAME, or WORSE?	Better	Better	Better
007	Have you experienced pain in your abdominal or pelvic regions since the procedure?	Y	Y	Y
	Have you experienced fever since the procedure?	N	Y	Y
	Have you experienced cramping since the procedure?	Y	Y	Y
	Have you experienced vaginal discharge since the procedure?	Y	Y	Y
	Have you experienced nausea since the procedure?	Y	N	N
	Do you feel BETTER, SAME, or WORSE?	Same	Worse	Better
009	Have you experienced pain in your abdominal or pelvic regions since the procedure?	Y	N	N
	Have you experienced fever since the procedure?	N	N	N
	Have you experienced cramping since the procedure?	Y	Y	N
	Have you experienced vaginal discharge since the procedure?	Y	Y	N
	Have you experienced nausea since the procedure?	N	N	N
	Do you feel BETTER, SAME, or WORSE?	Better	Better	Better
010	Have you experienced pain in your abdominal or pelvic regions since the procedure?	Y	N	N

	Have you experienced fever since the procedure?	N	N	N
	Have you experienced cramping since the procedure?	Y	Y	Y
	Have you experienced vaginal discharge since the procedure?	Y	Y	N
	Have you experienced nausea since the procedure?	Y	N	N
	Do you feel BETTER, SAME, or WORSE?	Same	Better	Better
011	Have you experienced pain in your abdominal or pelvic regions since the procedure?	Y	N	N
	Have you experienced fever since the procedure?	N	N	N
	Have you experienced cramping since the procedure?	N	Y	Y
	Have you experienced vaginal discharge since the procedure?	Y	Y	N
	Have you experienced nausea since the procedure?	N	N	N
	Do you feel BETTER, SAME, or WORSE?	Better	Better	Better
013	Have you experienced pain in your abdominal or pelvic regions since the procedure?	Y	Y	N
	Have you experienced fever since the procedure?	N	N	N
	Have you experienced cramping since the procedure?	N	Y	N
	Have you experienced vaginal discharge since the procedure?	Y	Y	N
	Have you experienced nausea since the procedure?	N	N	N
	Do you feel BETTER, SAME, or WORSE?	Better	Same	Same
014	Have you experienced pain in your abdominal or pelvic regions since the procedure?	Y	Y	N
	Have you experienced fever since the procedure?	N	N	N
	Have you experienced cramping since the procedure?	Y	Y	N
	Have you experienced vaginal discharge since the procedure?	Y	Y	N
	Have you experienced nausea since the procedure?	Y	Y	N
	Do you feel BETTER, SAME, or WORSE?	Better	Same	Better
015	Have you experienced pain in your abdominal or pelvic regions since the procedure?	N	N	Y
	Have you experienced fever since the procedure?	N	N	N
	Have you experienced cramping since the procedure?	Y	Y	Y
	Have you experienced vaginal discharge since the procedure?	Y	Y	Y
	Have you experienced nausea since the procedure?	Y	Y	N
	Do you feel BETTER, SAME, or WORSE?	Same	Same	Better
016	Have you experienced pain in your abdominal or pelvic regions since the procedure?	N	Y	Y
	Have you experienced fever since the procedure?	N	N	N
	Have you experienced cramping since the procedure?	Y	Y	Y

	Have you experienced vaginal discharge since the procedure?	Y	Y	Y
	Have you experienced nausea since the procedure?	N	N	N
	Do you feel BETTER, SAME, or WORSE?	Better	Better	Same

11.3 Adverse Events

One subject (S007) experienced flu-like symptoms at 3 weeks after treatment and was given antibiotics. The subject subsequently exhibited an upper respiratory tract infection and the symptoms were deemed unrelated to the study device or the study procedure.

11.4 Deaths, Other Serious Adverse Events and Other Significant Adverse Events

There were no deaths, SAEs, SADEs, UADEs or significant AEs to date in the study.

11.5 Clinical Laboratory Evaluation

Subject 006 experienced an increase in FSH level before embolization on the day of treatment and an increase in FSH and LH levels at 1-month post embolization. Normal menses returned for Subject 006 at 5 weeks post-embolization. Subject 006 is now in menopause, assessed to be unrelated to treatment by the study agent. No other laboratory values were remarkable. All remaining subjects demonstrated normal menses post-embolization.

11.6 Vital Signs, Physical Findings, and Other Observations Related to Safety

11.6.1 Vital Signs

No clinically significant vital sign results were observed in the study, to date.

11.7 Physical Examination

No abnormal, clinically significant, physical examination results were observed in the study, to date.

11.8 Safety Conclusions

In the studied population of women with symptomatic uterine fibroids:

- OCL 504 and OCL 505 was well tolerated with low to moderate pain associated with the procedure in all patients.
- Post-embolization syndrome, characterized by nausea, pain, or fever was noted in all treated subjects and expected as a normal consequence of fibroid embolization.
- Administration of OCL 504 or OCL 505 had no effect on ovarian function as determined by clinically significant changes in FSH and LH levels.
- There were no AEs leading to withdrawal from the study and no SAEs, SADEs or UADES. There were no clinically significant findings in vital signs, physical examination, or clinical laboratory assessments.

12 TECHNICAL EVALUATION

OCL 504 or OCL 505 was suspended in Omnipaque™ 240 and administered through a Merit Impress 5F catheter. Table 12-1 provides a summary of the amount of product and contrast agent used for each embolization.

Table 12-1 Embolic Agent Dose and Contrast Agent Volume

Subject	Product	Vials Used	Dose (mg)	Contrast Agent Delivered with Ekobi™ Microspheres	
				Contrast/vial	Total Contrast
002	OCL 504	5	2000	20 ml	100 ml
003	OCL 505	7	2800	15 ml	105 ml
005	OCL 504	5	2000	15 ml	75 ml
006	OCL 505	6	2347	15 ml	88 ml
007	OCL 504	8	3120	15 ml	117 ml
009	OCL 505	8	3200	15 ml	120 ml
010	OCL 504	8	3200	12 ml	96 ml
011	OCL 505	2	3100	15 ml	101 ml
		6		12 ml	
013	OCL 504	2	4775	12 ml	103 ml
		10		8 ml	
014	OCL 505	5	2000	12 ml	60 ml
015	OCL 504	5	1867	15 ml	73 ml
016	OCL 505	8	3200	15 ml	120 ml

The volume of contrast agent used to resuspend a vial of Ekobi™ Microspheres ranged from 8 ml to 20 ml. Based on perfusion results, the optimal volume of contrast agent used to resuspend a vial of microspheres was 15 ml to 20 ml. Adding less contrast agent did not affect microsphere

travel through the catheter, but contributed to the decision to prematurely stop particle infusion leading to fibroid perfusion. The recommended volume of suspending medium is > 15 ml for 400 mg of study agent.

13 EXPLORATORY OBJECTIVE

The exploratory objective of this study was to assess the effect of administration of OCL 504 and OCL 505 on the vasculature of the uterus including fibroids, as assessed by B-mode ultrasound. The echogenicity of the fibroid tissue was evaluated at baseline and at 1-day, 1-month, and 6-months post-embolization. Table 13-1 summarizes the observed echogenicity at each time point.

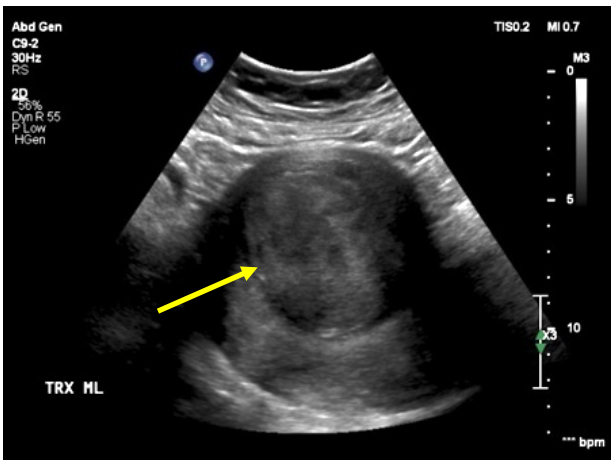
Table 13-1 Echogenicity of Fibroid Tissue

Subject Number	Embolic Agent	Baseline	Echo-genic Response Post-Embolization		
			1-Day	1-Month	6-Months
002	OCL 504	Hypo-echoic	Hyper-echoic +++ punctate	Hyper-echoic +	Hypo-echoic
003	OCL 505	Hypo-echoic	Hyper-echoic +++ linear	Hyper-echoic +	Hypo-echoic
005	OCL 504	Hypo-echoic	Hyper-echoic +++ linear	Hyper-echoic +	Hypo-echoic
006	OCL 505	Hypo-echoic	Hyper-echoic +++ linear	Hyper-echoic +	Hypo-echoic
007	OCL 504	Hypo-echoic	Hyper-echoic ++++ punctate	Hyper-echoic +	Hypo-echoic
009	OCL 505	Hypo-echoic	Hyper-echoic ++++ linear	Hyper-echoic +	Hypo-echoic
010	OCL 504	Hypo-echoic	Hyper-echoic ++++ linear	Hyper-echoic +	Hypo-echoic
011	OCL 505	Hypo-echoic	Hyper-echoic ++++ linear	Hyper-echoic +	Hypo-echoic
013	OCL 504	Hypo-echoic	Hyper-echoic ++++ linear	Hyper-echoic +	Hypo-echoic
014	OCL 505	Hypo-echoic	Hyper-echoic ++++ linear	Hyper-echoic +	Hypo-echoic
015	OCL 504	Hypo-echoic	Hyper-echoic ++++ linear	Hyper-echoic +	Hypo-echoic
016	OCL 505	Hypo-echoic	Hyper-echoic ++++ linear	Hyper-echoic +	Hypo-echoic

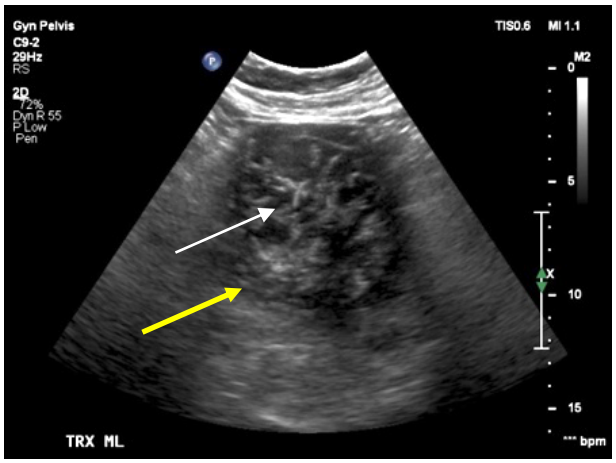
Figure 13 shows representative ultrasound images at baseline, 1-day post-embolization, 1-month, and 6-months post-embolization of a subject treated with OCL 504 (212-300 µm).

Figure 13- 1 Ultrasound Assessment (S005; OCL 504)

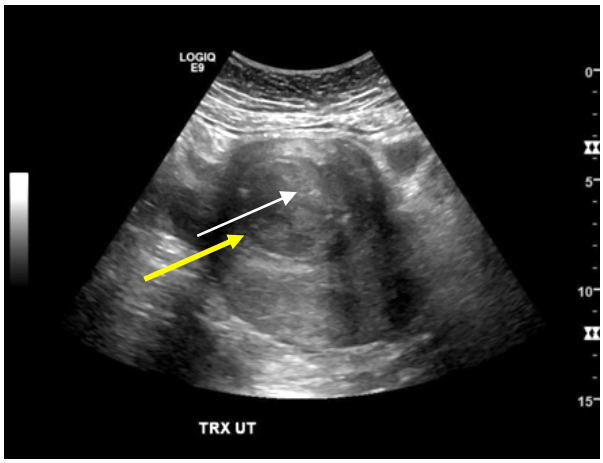
Pre-Embolization



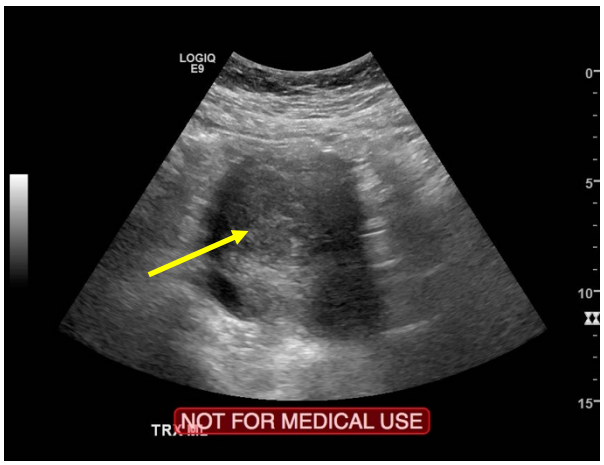
1-Day Post-Embolization



1-Month Post-Embolization



6-months Post-Embolization

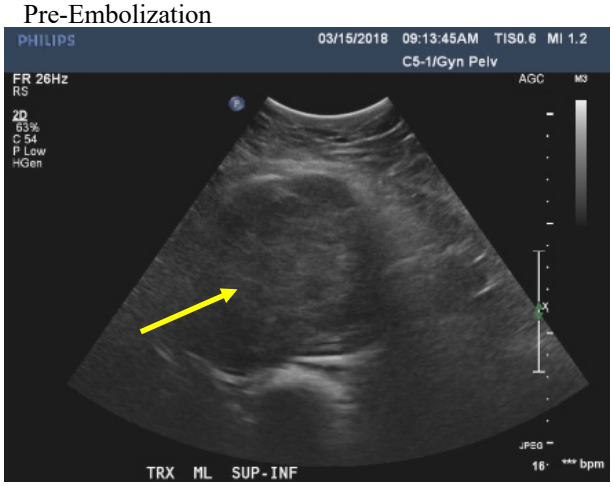


Yellow arrows = fibroid; White arrows = hyper-echoic area

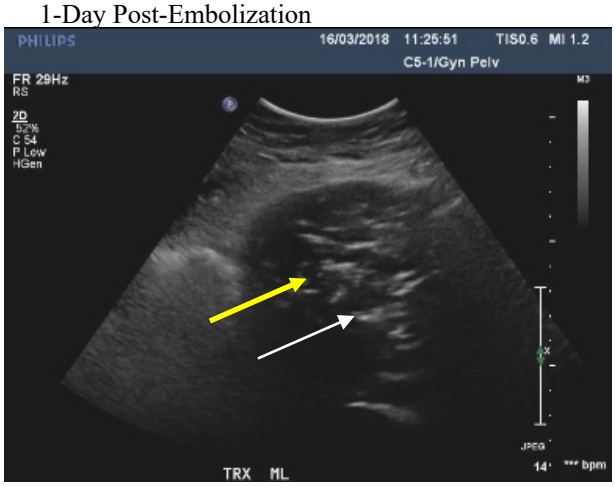
Figure 13-2 shows representative ultrasound images at baseline, 1-day post-embolization and 1-month post-embolization of a subject treated with OCL 505 (300-425 µm).

Figure 13- 2 Ultrasound Assessment – (S003; OCL 505)

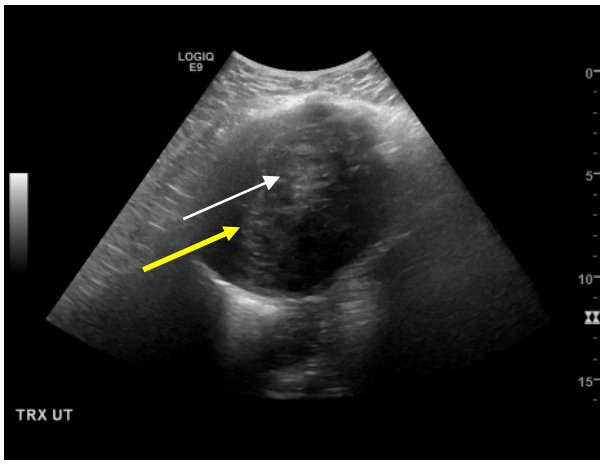
Pre-Embolization



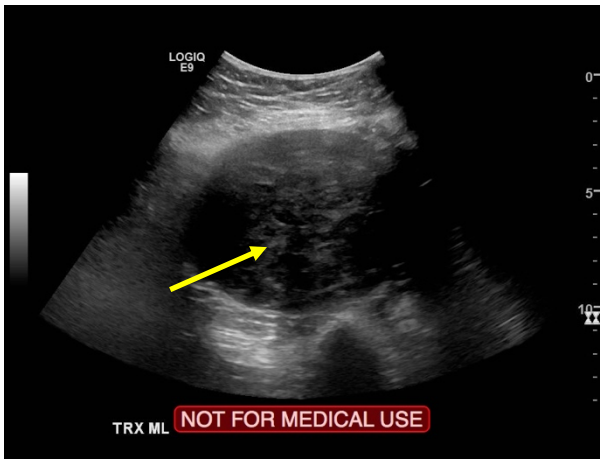
1-Day Post-Embolization



1-MonthPost-Embolization



6-months Post-Embolization



Yellow arrows = fibroid; White arrows = hyper-echoic area

13.1 Exploratory Objective Conclusions

In the women with symptomatic uterine fibroids treated with OCL 504 or OCL 505:

- Administration of OCL 504 or OCL 505 resulted in hyper-echoic areas associated with delivery of the embolic agent to the target tissue fibroids 1-day post-embolization.
- Previous hyper-echogenicity associated with the target tissue fibroids decreased at 1-month post-embolization follow-up consistent with the degradation profile of the embolic agent (Owen et al, 2012).
- Previous hyper-echogenicity associated with the target tissue fibroids was not seen at 6-months post-embolization, consistent with the degradation profile of the embolic agent (Owen et al, 2012).

14 DISCUSSION AND OVERALL CONCLUSIONS

14.1 Discussion

This prospective, open label, uncontrolled pivotal study was designed to assess the safety and effectiveness of OCL 504 and OCL 505 in the treatment of women with symptomatic uterine fibroids. Twelve subjects were treated; 6 subjects received OCL 504 and 6 subjects received OCL 505. All subjects were embolized, bilaterally, to near-stasis blood flow in the uterine vasculature.

The primary objectives of the study were assessment of safety as determined by AEs, and effectiveness as determined by change in dominant fibroid volume.

Table 14-1 provides a summary of outcomes and statistical assessment relative to baseline.

Table 14-1 Outcomes and Statistical Analysis Relative to Baseline

Parameter	6-Months Post-Embolization	
	T-Test (parametric)	WSRT (non-parametric)
Fibroid Volume (ml)	0.0001	0.0015
Uterine Volume (ml)	0.0003	0.0005
Perfusion (%)	0.009	0.01
Symptom Score	0.0001	0.0005
HRQL	0.0001	NA

A statistically significant decrease in dominant fibroid volume, relative to baseline, was seen at 1-month post-embolization with a mean decrease of 35.5 ± 20.7% (N=12; p = 0.0005). The mean dominant fibroid volume continued to decrease at the 6-month time point, with a mean decrease of 45.9 ± 26.9% (p = 0.0015, N=12). A statistically significant change in fibroid perfusion, relative to baseline, was seen at 1-month post-embolization, with a mean decrease in fibroid perfusion of 64.6% ± 38.6% (p=0.01, N=12). Fibroid perfusion at 6-months post-embolization decreased on average by 50.8 ± 55.5% (p = 0.01, WSRT; N=12).

Subject 007 showed minimal fibroid volume decrease and a return of full fibroid perfusion at 1 month post-embolization, which was maintained at 6-months follow-up. Similar results have been noted in published studies. Campbell et al, 2015 (Efficacy of ovarian artery embolization for uterine fibroids: Clinical and magnetic imaging evalutions. Vascular and Interventional Radiology 2015; 66:164-170) studied the re-treatment of patients that required intervention due to incomplete embolization of uterine fibroids. The study subjects demonstrated ovarian artery blood supply to the uterine fibroids that was not embolized at first treatment. Once recognized, subsequent embolization of the ovarian artery supplying the fibroid(s) resulted in complete symptom resolution in 82.4% of the cases.

The average uterine volume was evaluated, relative to baseline. At 1-month post-embolization the relative uterine volume decreased by 15.4 ± 21.2% (p = 0.11, N=12). The relative uterine volume continued to decrease at 6-months post-embolization; mean decrease = 28.8 ± 19.6% (p = 0.0005, WSRT; N=12).

OCL 504 and OCL 505 microspheres were well tolerated with subjects experiencing low to moderate pain after the procedure. Pain associated with the embolization procedure was considered mild with a mean score for the 12 treated subjects of 2.0 ± 1.6 (range 0 to 4.5; median = 2.0) at the 1-week follow-up visit. The pain scale was 0 to 10, with 10 being the worst pain.

Quality of life and symptom changes were assessed using the the UFS-QoL questionnaire. The mean baseline quality of life score was 39.7 ± 19.9 (N=12). The mean quality of life score at 1-month and 6-months post-embolization was 57.2 ± 21.3. The improvement in quality of life at end of study relative to baseline was statistically significant (p = 0.0001, t-test; N=12). Symptom scores decreased from a mean baseline score of 52.5 ± 15.9 to 34.2 ± 14.8 at 1-month follow-up, and 16.0 ± 13.0 at 6-month follow-up. Symptom improvement at end of study relative to baseline was statistically significant (p = 0.0005, WSRT; N=12).

No safety issues related to administration of the microspheres were identified. Follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels were used to determine the effect of Ekobi™ Embolization Microspheres administration on ovarian function. No clinically significant FSH or LH level findings were noted in the treated subjects. A review by Kaump et al (2013) examined the effect of UAE on ovarian function. The authors identified 24 articles that were subsequently reviewed. Only data from randomized trials or prospective cases were included (15 articles). The data from randomized trials suggest that UAE has similar impact on ovarian reserve as surgical treatment. Several trials reported similar occurances of menopausal symptoms between UAE and surgery. Older subjects had a higher propensity for effects on ovarian reserve and menopausal symptoms or amenorrhea. Of the 12 subjects treated in the present study, 1 subject became menopausal; however, this subject evidenced increased FSH and LH levels preceding the embolization. Menopause was not attributed to treatment using the investigational device.

Based on perfusion results, the optimal volume of contrast agent used to re-suspend a vial of microspheres was ≥ 15 ml. Increased dilution of embolic agent mitigates the potential of proximal vascular occlusion (Vaidya et al, 2008). Adding less contrast agent did not affect microsphere travel through the catheter, but can contribute to a decision to prematurely stop particle infusion. A decrease in fibroid size was not affected by the volume of contrast agent used to suspend the microspheres (refer to Figure 10-1).

Adminstration of OCL 504 or OCL 505 to the uterine vasculature resulted in an increase in the hyper-echogenicity of the fibroid tissue at 1-day post-embolization as demonstrated in previous studies in benign prostatic hypertrophy patients (ITA 238567; final report filed with Health Canada). Hyper-echogenicity was reduced at 1-month post-embolization consistent with the degradation profile of the embolic agent (Owen et al, 2012). Echogenicity associated with the embolic agent was not seen at the 6-month follow-up time point consistent with the degradation profile of the Ekobi™ Microspheres (originally branded as Occlusin® 500 Embolization Microspheres; Owen et al, 2012). The echogenic signal of the Ekobi™ Embolization Microspheres increases as they coalesce through platelet capture and bridging of microspheres.

Real-time assessment of the delivery of Ekobi™ Embolization Microspheres by ultrasound confirms the delivery of the microspheres to the target vasculature, also confirming the requisite vascular occlusion (IMBiotechnologies internal data). Monitoring of non-target vasculature by ultrasound during Ekobi™ Embolization Microspheres delivery allows the treating physician to modify treatment if there is a chance that the embolic agent will travel to non-target tissues.

14.2 Conclusions

The following conclusions were drawn for the studied population of women with symptomatic uterine fibroids treated with Ekobi™ Embolization Microspheres:

- Treatment of women with symptomatic uterine fibroids using OCL 504 or OCL 505 was well tolerated.
- There were no AEs leading to withdrawal from the study.
- There were no SAEs, SADES or UADEs.
- There were no clinically significant findings in vital signs, physical examinations, or clinical laboratory assessments.
- A statistically significant decrease in dominant fibroid volume was observed at 6-month EOS follow-up (p=0.0015) post-embolization.
- A statistically significant decrease in dominant fibroid perfusion was observed at 6-month EOS follow-up (p=0.01) post-embolization.
- A statistically significant decrease in uterine volume was observed at 6-month EOS follow-up (p = 0.0005).
- A statistically significant improvement in symptom scores (p = 0.0005) and quality of life scores (p = 0.0001) was seen at 6-month EOS follow-up.
- Administration of OCL 504 or OCL 505 did not negatively impact ovarian function.
- Administration of OCL 504 or OCL 505 to uterine vasculature caused an increase in hyper-echogenicity of fibroid vasculature as determined by B-mode ultrasound confirming delivery of the embolic agent to the target tissue.

The study results do not raise safety concerns and demonstrate effectiveness of Ekobi™ Embolization Microspheres in women with symptomatic uterine fibroids, as measured by a decrease in dominant fibroid volume, and improvement in symptoms and subject quality of life.

15 TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

Not applicable

16 REFERENCE LIST

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17 APPENDICES

17.1 Appendix 1 - Statistical Assessments

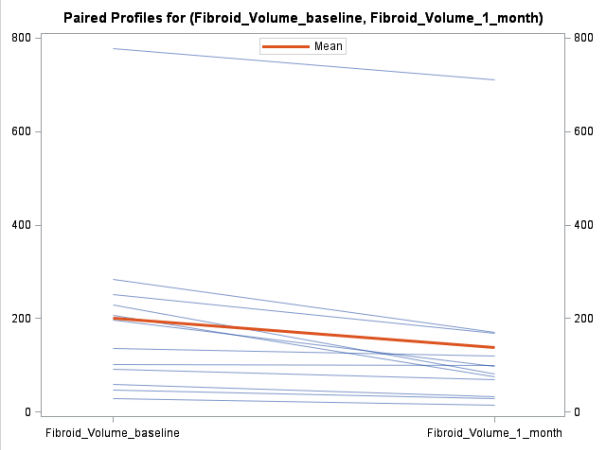
Uterine Fibroid Study
April 11, 2019 Maryna Yaskina

All statistical analyses were performed using SAS Ver. 9.4

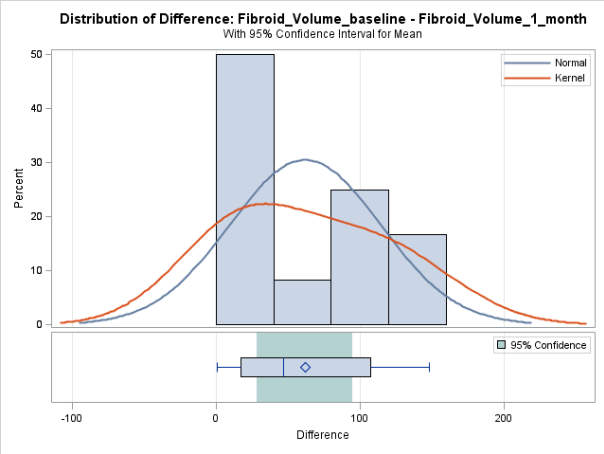
Fibroid Volume – 1 month

Fibroid volume (in cm^3; mls)	***N***	***Mean***	***Std Dev***	***Median***	***25th percentile***	***75th percentile***	***Min***	***Max***	***95% Confidence interval for mean***	
									Lower limit	***Upper limit***
Baseline	12	200.6	200.6	166.2	75.2	239.9	27.7	777.2	73.2	328.0
1 month follow up	12	138.8	186.5	88.8	51.0	143.8	15.3	710.1	20.2	257.3

Individual trajectories for Fibroid volume: baseline (left) and at 1 month follow up (right). Mean change in orange.

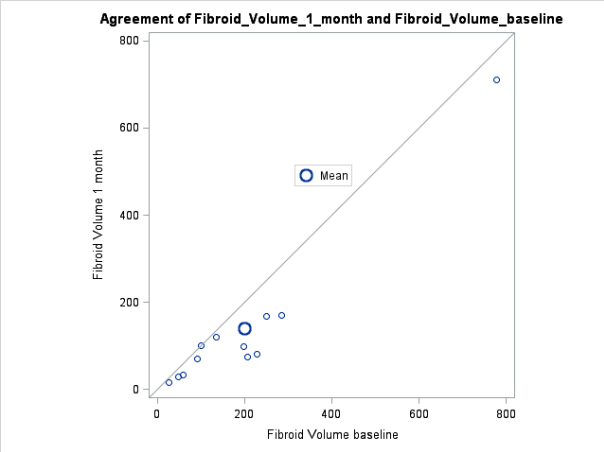


Distribution of the **difference of fibroid volume** (baseline – 1 month follow up) is below. Boxplot shows that both mean and median of the difference lie above 0. Even more, the middle 50% of the score differences (the actual "box" part) also lies above 0.



Difference in fibroid volume (baseline – 1 month)	***N***	***Mean***	***Std Dev***	***Median***	***25th percentile***	***75th percentile***	***Min***	***Max***	***95% Confidence interval for mean***	
									Lower limit	***Upper limit***
	12	61.9	52.4	46.8	17.1	107.6	0.9	148.1	28.6	95.2

Agreement plot: x-axis = fibroid volume at baseline, y-axis = fibroid volume at 1 month. Diagonal line = no change in volume, y=x. It can be seen that only 1 person lies on the line (volume at 1 month is approximately the same as at the baseline) and all other patients lie below the y=x line meaning that their fibroid volume at 1 month is lower than the one at the baseline.



P-values

Fibroid volume	***p-value***	
	t-test	***Wilcoxon sign rank test***
Baseline – 1 month	0.002	0.0005

The difference in fibroid volume between the baseline and 1 month was statistically significantly different from 0, *p*=0.0005 (Wilcoxon sign rank test).
The distribution of the difference in fibroid volume is not normal, so Wilcoxon sign rank test was used for statistical testing. However, it is a good practice to present a t-test *p*-value as well to show that it is also statistically significant.

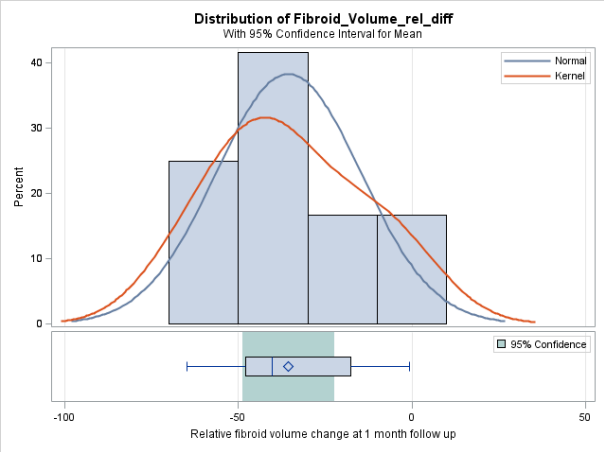
Uterine Fibroid Study
April 18, 2019 Maryna Yaskina

All statistical analyses were performed using SAS Ver. 9.4

Fibroid Relative Volume Change – 1 month

Relative volume change was computed as $\frac{\text{volume at 1 month} - \text{volume at baseline}}{\text{volume at baseline}} * 100\%$

Fibroid relative volume change (%)	***N***	***Mean***	***Std Dev***	***Median***	***25th percentile***	***75th percentile***	***Min***	***Max***	***95% Confidence interval for mean***	
									Lower limit	***Upper limit***
	12	-35.6	20.8	-40.2	-47.8	-17.6	-64.7	-0.9	-48.8	-22.4



Boxplot shows that both mean and median of the relative difference lie well below 0%. Even more, the middle 50% of the score differences (the actual "box" part) also lies well below 0%.

P-values

Fibroid relative volume change (%)	***p-value***	
	t-test	***Wilcoxon sign rank test***
	<0.0001	0.0005

The difference in fibroid relative change in volume at 1 month was statistically significantly different from 0, *p*=0.0005 (Wilcoxon sign rank test).
The distribution of the relative change in volume is not normal, so Wilcoxon sign rank test was used for statistical testing. However, it is a good practice to present a t-test *p*-value as well to show that it is also statistically significant.

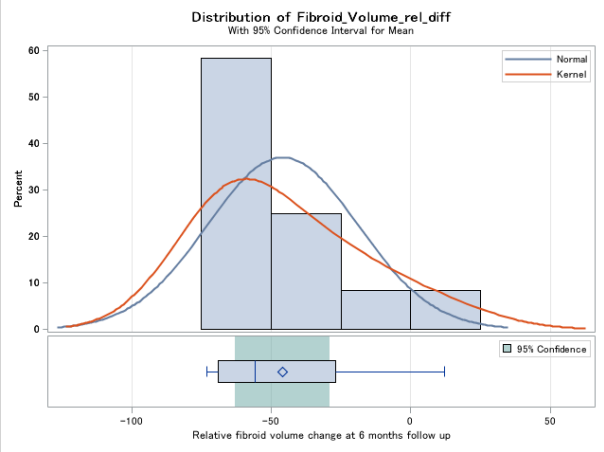
Uterine Fibroid Study
August 23, 2019 Maryna Yaskina

All statistical analyses were performed using SAS Ver. 9.4

Fibroid relative volume change – 6 months

Relative volume change was computed as $\frac{\text{volume at 6 months} - \text{volume at baseline}}{\text{volume at baseline}} * 100\%$

Fibroid relative volume change (%)	***N***	***Mean***	***Std Dev***	***Median***	***25th percentile***	***75th percentile***	***Min***	***Max***	***95% Confidence interval for mean***	
									Lower limit	***Upper limit***
	12	-45.9	26.9	-55.9	-69.1	-27.1	-73.1	12.1	-63.1	-28.8



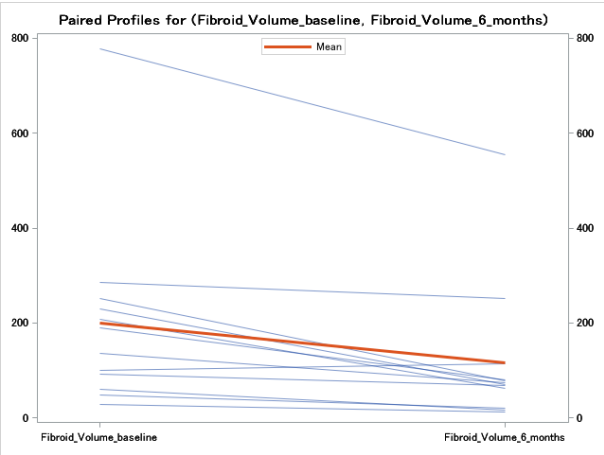
Boxplot shows that both mean and median of the relative difference lie well below 0%. Even more, the middle 50% of all values (the actual "box" part) also lies well below 0%.

P-values

Fibroid relative volume change (%)	***p-value***	
	t-test	***Wilcoxon sign rank test***
	0.0001	0.0015

The difference in fibroid relative change in volume at 6 month was statistically significantly different from 0, *p*=0.0015 (Wilcoxon sign rank test).
The distribution of the relative change in volume is not normal, so Wilcoxon sign rank test was used for statistical testing. However, it is a good practice to present a t-test *p*-value as well to show that it is also statistically significant.

Paired profiles for fibroid volume



As can be seen from profiles, fibroid volume for almost all patients decreased at 6 months compared to the baseline.

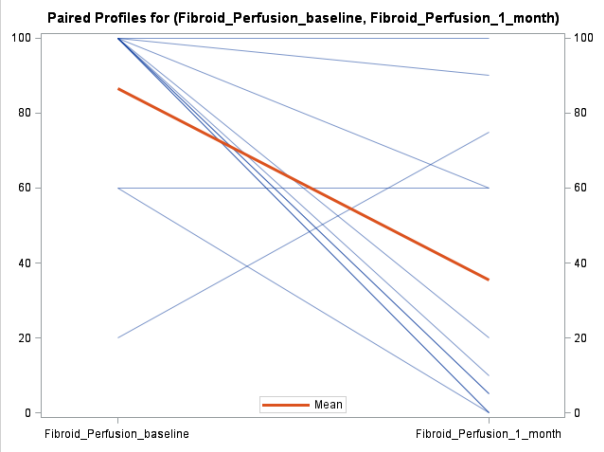
Uterine Fibroid Study
April 15, 2019 Maryna Yaskina

All statistical analyses were performed using SAS Ver. 9.4

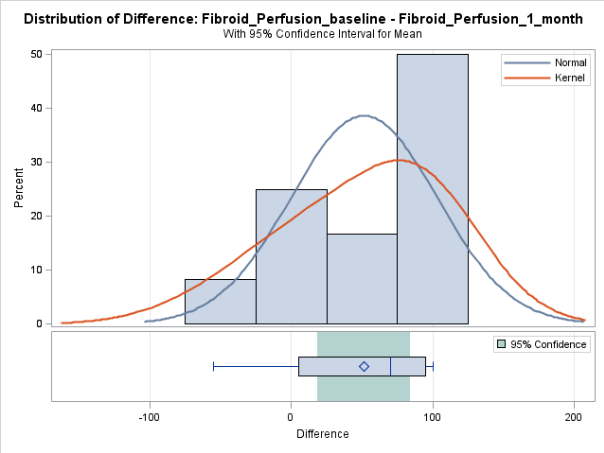
Perfusion Change – 1 month

Fibroid perfusion (%)	***N***	***Mean***	***Std Dev***	***Median***	***25th percentile***	***75th percentile***	***Min***	***Max***	***95% Confidence interval for mean***	
									Lower limit	***Upper limit***
Baseline	12	86.7	26.1	100.0	80.0	100.0	20.0	100.0	70.1	100.0
1 month follow up	12	35.4	38.6	15.0	2.5	67.5	0.0	100.0	10.9	60.0

Individual trajectories for Fibroid perfusion: baseline (left) and at 1 month follow up (right). Mean change in orange.

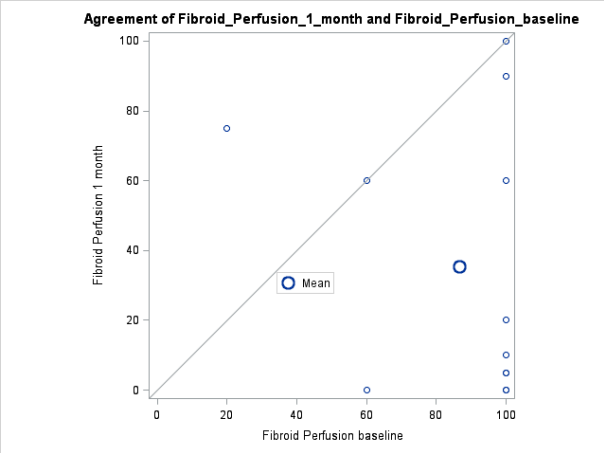


Distribution of the **difference of fibroid perfusion** (baseline – 1 month follow up) is below. Boxplot shows that both mean and median of the difference lie above 0. Even more, the middle 50% of the score differences (the actual "box" part) also lies above 0.



Difference in fibroid perfusion (baseline – 1 month)	***N***	***Mean***	***Std Dev***	***Median***	***25th percentile***	***75th percentile***	***Min***	***Max***	***95% Confidence interval for mean***	
									Lower limit	***Upper limit***
	12	51.3	51.7	70.0	5.0	95.0	-55.0	100.0	18.4	84.1

Agreement plot: x-axis = fibroid perfusion at baseline, y-axis = fibroid perfusion at 1 month. Diagonal line = no change in perfusion, y=x. It can be seen that only 1 person lies above the line (perfusion at 1 month is greater than perfusion at the baseline) and 2 patients lie on the line (perfusion at 1 month is approximately the same as at the baseline), and all other patients lie below the y=x line meaning that their fibroid perfusion at 1 month is lower than the one at the baseline.



P-values

Fibroid perfusion	***p-value***	
	t-test	***Wilcoxon sign rank test***
Baseline – 1 month	0.006	0.01

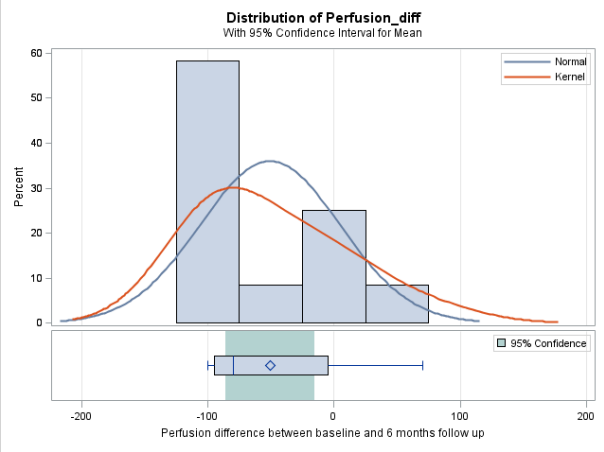
The difference in fibroid perfusion between the baseline and 1 month was statistically significantly different from 0, *p*=0.01 (Wilcoxon sign rank test).
The distribution of the difference in fibroid perfusion is not normal, so Wilcoxon sign rank test was used for statistical testing. However, it is a good practice to present a t-test *p*-value as well to show that it is also statistically significant.

Uterine Fibroid Study
September 01, 2019 Maryna Yaskina

All statistical analyses were performed using SAS Ver. 9.4 (SAS Institute Inc., Cary, NC, USA)

Perfusion Change - 6 months

	N	Mean	Std Dev	Median	25th percentile	75th percentile	Min	Max	95% Confidence interval for mean	
									Lower limit	Upper limit
Perfusion at baseline (%)	12	87.9	24.6	100.0	87.5	100.0	20.0	100.0	72.3	103.6
Perfusion at 6 months follow up (%)	12	37.1	41.2	12.5	2.5	80.0	0.0	100.0	10.9	63.3
Perfusion change (%)	12	-50.8	55.5	-80.0	-95.0	-5.0	-100.0	70.0	-86.1	-15.6



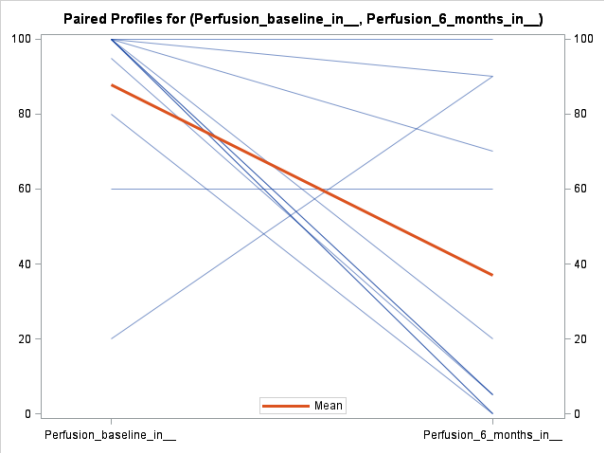
Boxplot shows that both mean and median of the perfusion difference lie well below 0%. Even more, middle 50% of all values (from 25th percentile to 75th percentile – the actual box part in boxplot) lies below 0%.

P-values

Perfusion change at 6 months from the baseline (%)	p-value	
	t-test	Wilcoxon sign rank test
	0.009	0.01

The difference in perfusion change at 6 month was statistically significantly different from 0, p=0.01 (Wilcoxon sign rank test).
The distribution of the perfusion difference is not normal, therefore Wilcoxon sign rank test was used for statistical testing. However, it is a good practice to present a t-test p-value as well to show that it is also statistically significant.

Paired profiles for perfusion



As can be seen from profiles, perfusion at 6 months compared to the baseline decreased for almost all patients. For one patient the values did not change (60% both at 6 months and the baseline), and for one patient perfusion changed from 20% at baseline to 90% at 6 months follow up.

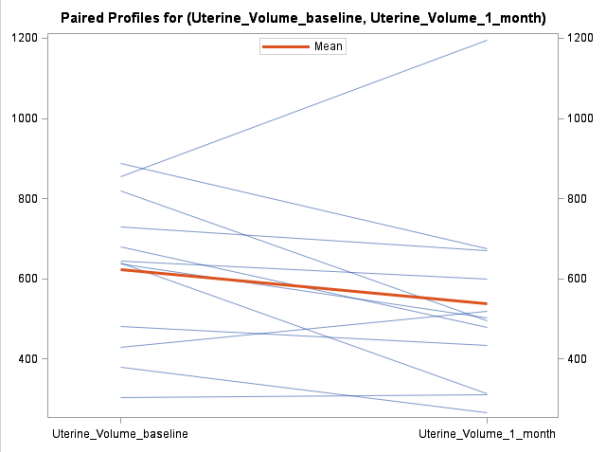
Uterine Fibroid Study
April 16, 2019 Maryna Yaskina

All statistical analyses were performed using SAS Ver. 9.4

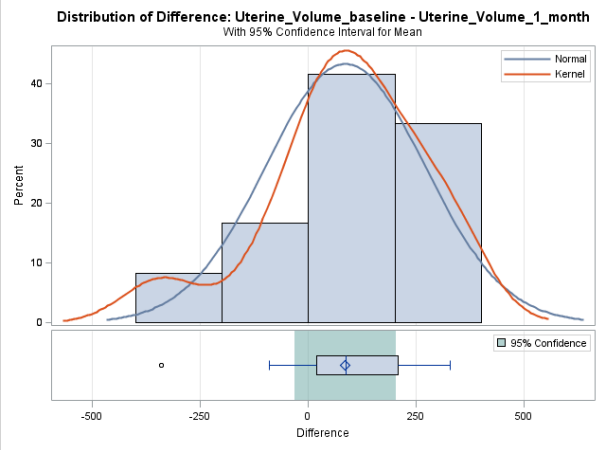
Uterine Volume – 1 month

Uterine volume (in cm^3; mls)	***N***	***Mean***	***Std Dev***	***Median***	***25th percentile***	***75th percentile***	***Min***	***Max***	***95% Confidence interval for mean***	
									Lower limit	***Upper limit***
Baseline	12	623.6	190.3	642.5	454.4	774.9	302.8	887.3	502.7	744.5
1 month follow up	12	538.3	245.7	499.2	373.3	635.3	265.7	1194.0	382.2	694.4

Individual trajectories for Uterine volume: baseline (left) and at 1 month follow up (right). Mean change in orange.

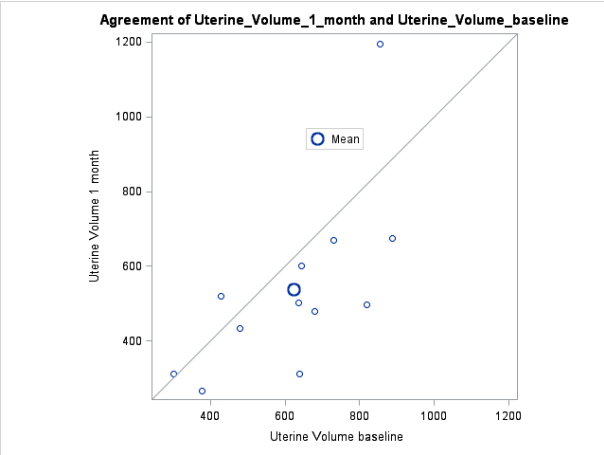


Distribution of the **difference of uterine volume** (baseline – 1 month follow up) is below. Boxplot shows that both mean and median of the difference lie above 0.



Difference in uterine volume (baseline – 1 month)	***N***	***Mean***	***Std Dev***	***Median***	***25th percentile***	***75th percentile***	***Min***	***Max***	***95% Confidence interval for mean***	
									Lower limit	***Upper limit***
	12	85.3	184.1	86.1	18.0	207.0	-339.8	327.7	-31.7	202.3

Agreement plot: x-axis = uterine volume at baseline, y-axis = uterine volume at 1 month. Diagonal line = no change in volume, y=x. It can be seen that 3 patients lie above the line (volume at 1 month is larger than at the baseline) and all other patients lie below the y=x line meaning that their uterine volume at 1 month is lower than the one at the baseline.



P-values

Uterine volume	***p-value***	
	t-test	***Wilcoxon sign rank test***
Baseline – 1 month	0.14	0.11

The difference in uterine volume between the baseline and 1 month was not statistically significantly different from 0, p=0.11 (Wilcoxon sign rank test).
The distribution of the difference in uterine volume is not normal, so Wilcoxon sign rank test was used for statistical testing. However, it is a good practice to present a t-test p-value as well.

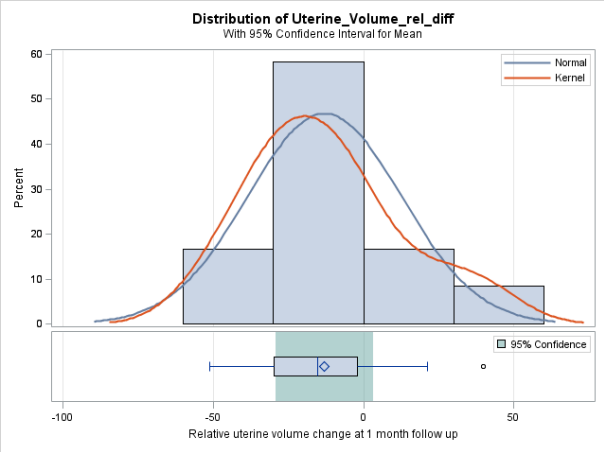
Uterine Fibroid Study
April 18, 2019 Maryna Yaskina

All statistical analyses were performed using SAS Ver. 9.4

Uterine Volume Relative Change – 1 month

Relative volume change was computed as $\frac{\text{volume at 1 month} - \text{volume at baseline}}{\text{volume at baseline}} * 100\%$

Uterine relative volume change (%)	*N*	*Mean*	*Std Dev*	*Median*	*25th percentile*	*75th percentile*	*Min*	*Max*	*95% Confidence interval for mean*	
									Lower limit	*Upper limit*
	12	-13.0	25.6	-15.4	-29.7	-2.0	-51.2	39.8	-29.2	3.2



Boxplot shows that both mean and median of the relative difference, as well as the middle 50% of the score differences (the actual "box" part), lie well below 0%; however, 0% lies inside the 95% CI of the mean.

P-values

Uterine relative volume change (%)	*p-value*	
	t-test	*Wilcoxon sign rank test*
	0.11	0.11

The difference in uterine relative change in volume at 1 month was not statistically significantly different from 0%, *p*=0.11 (Wilcoxon sign rank test).
The distribution of the relative change in volume is not normal, so Wilcoxon sign rank test was used for statistical testing. However, it is a good practice to present a t-test *p*-value as well to show that it agrees with Wilcoxon sign rant test.

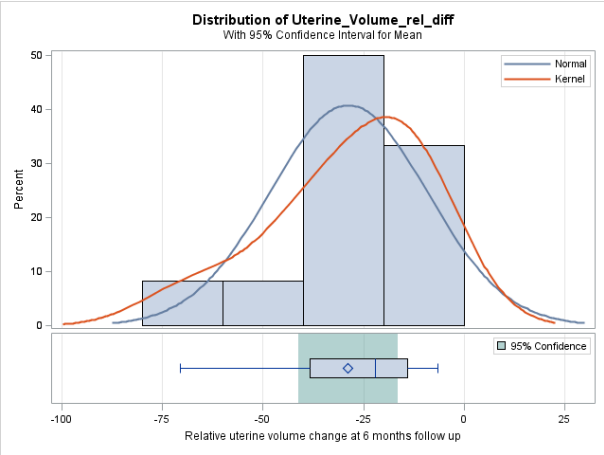
Uterine Fibroid Study
August 31, 2019 Maryna Yaskina

All statistical analyses were performed using SAS Ver. 9.4 (SAS Institute Inc., Cary, NC, USA)

Uterine Volume Relative Change – 6 months

Relative volume change was computed as $\frac{\text{volume at 6 months} - \text{volume at baseline}}{\text{volume at baseline}} * 100\%$

	N	*Mean*	*Std Dev*	*Median*	*25th percentile*	*75th percentile*	*Min*	*Max*	*95% Confidence interval for mean*	
									Lower limit	*Upper limit*
Uterine volume at baseline	12	640.6	221.8	642.5	454.4	774.9	302.8	1070.7	499.6	781.5
Uterine volume at 6 months follow up	12	456.2	232.8	390.5	265.0	555.6	233.9	976.7	308.3	604.1
Uterine volume - relative change (%)	12	-28.8	19.6	-22.0	-38.4	-14.1	-70.7	-6.5	-41.3	-16.4



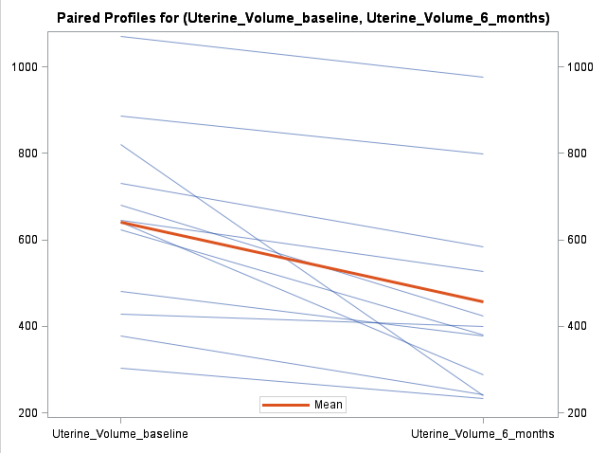
Boxplot shows that both mean and median of the relative change lie well below 0%. Even more, all values lie below 0% which mean that all patients have reduced uterine volume at 6 months compared to the baseline.

P-values

Uterine relative volume change (%)	*p-value*	
	t-test	*Wilcoxon sign rank test*
	0.0003	0.0005

The difference in uterine relative change in volume at 6 month was statistically significantly different from 0, *p*=0.0005 (Wilcoxon sign rank test).
The distribution of the relative change in volume is not normal, therefore Wilcoxon sign rank test was used for statistical testing. However, it is a good practice to present a t-test *p*-value as well to show that it is also statistically significant.

Paired profiles for uterine volume



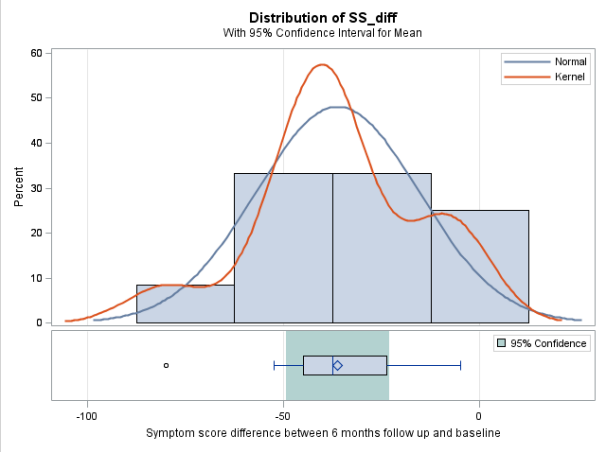
As can be seen from profiles, uterine volume at 6 months compared to the baseline decreased for all patients.

Uterine Fibroid Study
September 03, 2019 Maryna Yaskina

All statistical analyses were performed using SAS Ver. 9.4 (SAS Institute Inc., Cary, NC, USA)

Symptom Score Change - 6 Months

	N	*Mean*	*Std Dev*	*Median*	*25th percentile*	*75th percentile*	*Min*	*Max*	*95% Confidence interval for mean*	
									Lower limit	*Upper limit*
Symptom score at baseline	12	52.3	15.9	50.0	43.8	63.8	22.5	80.0	42.2	62.4
Symptom score at 6 months follow up	12	16.0	13.0	13.8	7.5	22.5	0.0	45.0	7.8	24.3
Symptom score change	12	-36.3	20.7	-37.5	-45.0	-23.8	-80.0	-5.0	-49.4	-23.1



Boxplot shows that both mean and median of the symptom score difference lie well below 0%. Even more, symptom score difference for all patients lies below 0%.

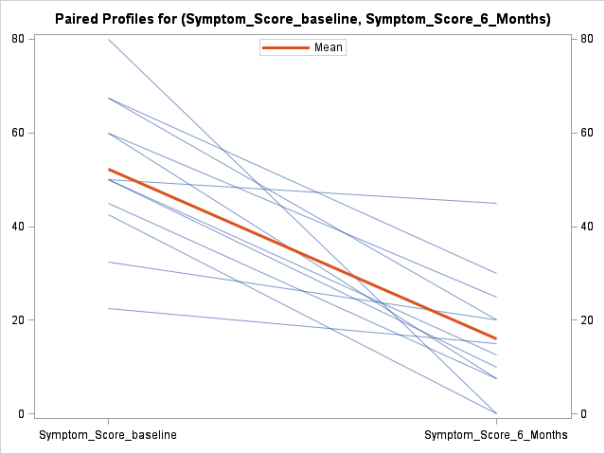
P-values

Symptom score change at 6 months from the baseline (%)	*p-value*	
	t-test	*Wilcoxon sign rank test*
	<0.0001	0.0005

The difference in symptom score change at 6 month was statistically significantly different from 0, *p*=0.0005 (Wilcoxon sign rank test).

The distribution of the symptom score differences is not normal, therefore Wilcoxon sign rank test was used for statistical testing. However, it is a good practice to present a t-test *p*-value as well to show that it is also statistically significant.

Paired profiles for symptom scores



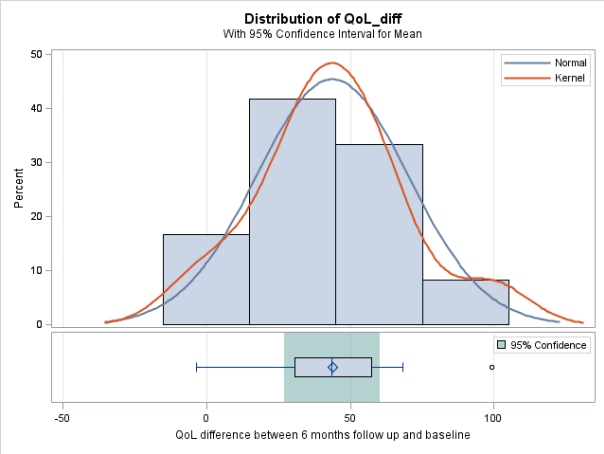
As can be seen from profiles, symptom score at 6 months compared to the baseline decreased for all patients.

Uterine Fibroid Study
September 02, 2019 Maryna Yaskina

All statistical analyses were performed using SAS Ver. 9.4 (SAS Institute Inc., Cary, NC, USA)

Quality of Life Change - 6 Months

	N	*Mean*	*Std Dev*	*Median*	*25th percentile*	*75th percentile*	*Min*	*Max*	*95% Confidence interval for mean*	
									Lower limit	*Upper limit*
QoL at baseline	12	39.7	19.9	38.8	28.0	52.6	0.9	75.9	27.0	52.3
QoL at 6 months follow up	12	83.4	17.5	90.1	71.6	95.7	46.6	100.0	72.3	94.5
QoL change	12	43.7	26.4	43.5	30.6	57.3	-3.4	99.1	27.0	60.5



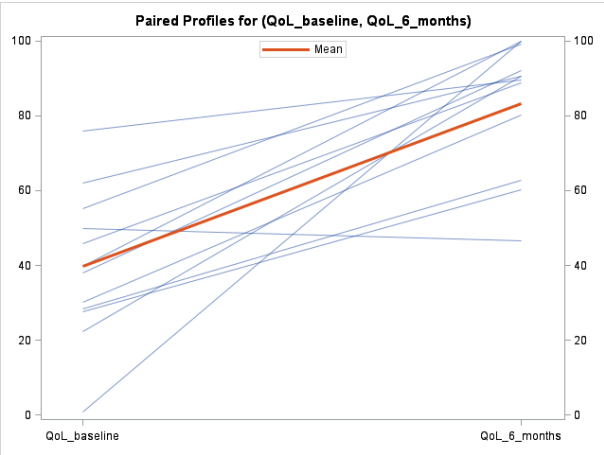
Boxplot shows that both mean and median of the symptom score difference lie well below 0%. Even more, QoL score difference for the middle 50% of all patients (from 25th percentile to 75th percentile, the actual box part in the boxplot) lies below 0%.

P-values

QoL change at 6 months from the baseline (%)	*p-value*
	t-test
	0.0001

The difference in QoL score change at 6 month was statistically significantly different from 0, *p*=0.0001 (t-test). The distribution of the QoL score differences is approximately normal, therefore t- test was used for statistical testing.

Paired profiles for QoL scores



As can be seen from profiles, QoL score at 6 months compared to the baseline increased for almost all patients. For one patient (ID S3) it decreased slightly.