1 TITLE PAGE

Clinical Study Report

An Open Label, Single Center, Pilot Study to Evaluate the Safety and Effectiveness of OCL 503 in the Treatment of Women with Leiomyomata Scheduled for Hysterectomy

Test Product:	OCL 503 (vascular embolization device)
Indication:	Leiomyomata (uterine fibroids) in patients scheduled for hysterectomy
Sponsor/Sponsor Signatory:	Michael W. Stewart, President and Chief Executive Officer *IM*Biotechnologies Ltd. Suite 215, Advanced Technology Centre 9650 20th Avenue, NW Edmonton, Alberta T6N 1G1 Canada Tel: +1-780-945-6609 Fax: +1-780-987-0941
Protocol No.:	OCL503-P1-UFE-01
Development Phase:	Pilot
Study Initiation Date:	08 April 2015
Study Completion Date:	25 March 2016
Principal Investigator:	Dr. Gary Siskin
Medical Monitor:	Sarah Chennoufi, MD
Medical Review:	Maria Gasior, MD

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

Date of the Report: **31 August 2016**

APPROVAL SIGNATURE(S)

An Open Label, Single Center, Pilot Study to Evaluate the Safety and Effectiveness of OCL 503 in the Treatment of Women with Leiomyomata Scheduled for Hysterectomy

Protocol No. OCL503-P1-UFE-01

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 Signatory:

....

Michael W. Stewart, MSc Date
President and Chief Executive Officer
*IM*Biotechnologies Ltd.

Sponsor Signatory:

....

Maria Gasior, MD Date
Medical Reviewer
*IM*Biotechnologies Ltd.

Investigator Signature:

....

Gary Siskin, MD Date
Principal Investigator
Albany Medical Center

APPROVAL SIGNATURE(S)

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Michael W. Stewart, MSc — Date
President and Chief Executive Officer
*IM*Biotechnologies Ltd.

Sponsor Signatory:

....

Maria Gasior, MD — Date
Medical Reviewer
*IM*Biotechnologies Ltd.

Investigator Signature:

..... 9/7/16

Gary Siskin, MD — Date
Principal Investigator
Albany Medical Center

APPROVAL SIGNATURE(S)

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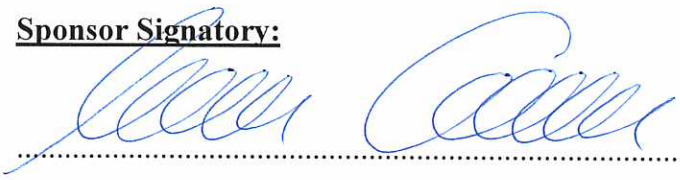
Michael W. Stewart, MSc
President and Chief Executive Officer
*IM*Biotechnologies Ltd.

Date

Sponsor Signatory:



..... SEP 8, 2016

Maria Gasior, MD
Medical Reviewer
*IM*Biotechnologies Ltd.

Date

Investigator Signature:

....

Gary Siskin, MD
Principal Investigator
Albany Medical Center

Date

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Protocol No. OCL503-P1-UFE-01

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Sponsor Signatory:

M.W. Stewart ..... 6 Sept 2016

Michael W. Stewart, MSc
President and Chief Executive Officer
*IM*Biotechnologies Ltd.

Date

Sponsor Signatory:

.....

Maria Gasior, MD
Medical Reviewer
*IM*Biotechnologies Ltd.

Date

Investigator Signature:

.....

Gary Siskin, MD
Principal Investigator
Albany Medical Center

Date

2 SYNOPSIS

Name of Company: *IM*Biotechnologies Ltd.	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use only)*
Name of Finished Product: OCL 503		
Name of Active Ingredient: Not applicable		

Title of Study: An Open Label, Single Center, Pilot Study to Evaluate the Safety and Effectiveness of OCL 503 in the Treatment of Women with Leiomyomata Scheduled for Hysterectomy

Principal Investigator:
Dr. Gary Siskin

Study Center:
It was planned that 1 center would be initiated in the USA.

Publication (reference): None.

Study Period:
08 April 2015 to 25 March 2016

Phase of Development:
Pilot

Objectives:

Primary Objectives:

- Evaluate the short-term safety of OCL 503 for treatment of women with leiomyomata by uterine artery embolization (UAE).
- Evaluate the effect of OCL 503 on fibroid perfusion.

Secondary Objectives:

- Evaluate the macroscopic and microscopic pathologic changes of uterine tissue after treatment of women with leiomyomata by UAE.
- Evaluate the inflammatory response to OCL 503 after treatment of women with leiomyomata by UAE.

Methodology:
This was a single center, open label pilot study. After screening and baseline testing, eligible patients underwent transarterial embolization of the uterine arteries before proceeding to standard of care hysterectomy. The first 2 patients were to be enrolled into Cohort 1. After completion of treatment, surgery, and a review of follow-up assessments to ensure no safety concerns had arisen, subsequent patients were to be allocated to Cohort 2 or Cohort 1 until 8 additional evaluable patients had undergone treatment and surgery. Patients underwent hysterectomy 1 week after embolization (Cohort 1) or 4 weeks after embolization (Cohort 2). The patients underwent magnetic resonance imaging (MRI)/magnetic resonance angiography (MRA) prior to embolization and again prior to hysterectomy. Uterine tissues removed during hysterectomy underwent histopathological assessment.

Number of Patients (Planned and Analyzed):
It was planned that 15 patients would be enrolled to ensure 10 evaluable patients were enrolled into 2 cohorts. Three patients were actually enrolled, of whom 2 patients were enrolled in Cohort 1 and 1 patient was enrolled in Cohort 2. All 3 patients completed the study.

Diagnosis and Main Criteria for Inclusion:
Presence of leiomyomata (uterine fibroids) in patients scheduled for hysterectomy.

Name of Company: *IM*Biotechnologies Ltd.	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use only)*
Name of Finished Product: OCL 503		
Name of Active Ingredient: Not applicable		

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

OCL 503 is a vascular embolization device designated as Class II under special guidance controls by the United States Food and Drug Administration. OCL 503 was provided in a sealed glass vial as 400 mg of sterile dry microspheres. Sufficient vials of OCL 503 vials were administered to achieve near stasis in the target vasculature. No more than 10 vials of OCL 503 were to be administered per treatment.

Infusion of embolic material was transarterial via catheter, following the Instructions For Use and hospital's clinical practice. 400 mg OCL 503 microspheres, re-suspended by the physician in saline, were diluted with a contrast agent to achieve an iso-buoyant suspension. The suspension was drawn into a 1 mL or 3 mL sterile plastic syringe, and slowly delivered by microcatheter to the uterine artery(ies) and monitored by fluoroscopy. OCL 503 was delivered to near stasis in the target vasculature. Near stasis embolization was defined as retention of contrast agent in the target vasculature for 3 to 5 cardiac beats.

The following batch numbers were used in the study: C6831 (expiry 28 December 2015); D2773 (expiry 28 September 2016).

Duration of Study Drug Treatment:

OCL 503 was delivered into the uterine vasculature until near stasis in the target vasculature was achieved. Each patient was to undergo one embolization treatment only.

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

Not applicable.

Criteria for Evaluation:

Safety:

- MRI of uterus and uterine vasculature.
- Histopathological analysis of the excised uterus.
- Laboratory studies.
- Occurrence of unanticipated adverse device effects (UADEs) and serious adverse events (SAEs).

Effectiveness:

- MRI/MRA of uterine vasculature and histological analysis of uterine vasculature to determine the efficiency of embolization by evaluating the degree of fibroid devascularization. Successful embolization of the vascular feeding a fibroid(s) was demonstrated by an absence of contrast enhancement of the fibroid tissue as assessed by MRA. Enhancement of fibroid tissue with MRA indicated perfusion of the fibroid tissue and a potential of fibroid regrowth.

Other:

- Uterine Fibroid Syndrome and Quality of Life Assessment.

Statistical Methods:

An analysis of the safety and effectiveness data collected in this study was performed. As only 3 patients were enrolled, no summary analyses were performed. The analysis of the data derived from this study was primarily descriptive.

Summary of Results:

All 3 patients were Black or African American, ranging in age from 41 to 55 years. Patients 002 and 003 had comparable body mass index (BMI), while Patient 001 had a higher BMI. The Transformed Severity Scores from the uterine fibroid symptom QoL questionnaire carried out at Screening were comparable for Patients 002 and 003, while Patient 001 had a lower score.

The results from the Pap smear, pelvic examination, and endometrial biopsy were normal for all 3 patients. Uterine

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Name of Finished Product: OCL 503		
Name of Active Ingredient: Not applicable		

fibroids were confirmed in all 3 patients by MRI; no other abnormal findings were observed as determined by laboratory assessment, MRI assessment, and physical examination. Successful embolization of the arterial vasculature of the fibroids(s) was demonstrated by an absence of contrast enhancement of the fibroid tissue as assessed by MRI. Enhancement of fibroid tissue with MRI indicates perfusion of the fibroid after embolization, which indicates the potential for future fibroid growth.

Effectiveness Results:

Magnetic Resonance Imaging Assessment

For Cohort 1 (Patients 001 and 002), MRI assessments were carried out at Screening and Visit 3. Visit 3 occurred at 5 days and 3 days post-embolization for Patients 001 and 002, respectively. For Patient 003 (Cohort 2), assessments were carried out at Screening and Visit 4 (26 days post-embolization).

MRI/MRA Assessment Results

	Patient 001		**Patient 002**		**Patient 003**	
	Screening	**Visit 3**	**Screening**	**Visit 3**	**Screening**	**Visit 4**
Enhancement of each dominant fibroid	Yes	Yes	Yes	No	Yes	No
Uterine volume (mL)	562.6	617.6	178.9	140.4	540.9	509.1
Volume of 3 dominant fibroids (mL)	128.8	132.4	24.7	20.8	74.0	56.5
Uterine arteries	Patent	Patent	Patent	Patent	Patent	Patent
Anomalous blood supply	Absent	Absent	Absent	Absent	Absent	Absent

Enhancement of each dominant fibroid was observed for all patients at the Screening assessment, and at Visit 3 for Patient 001. There was no enhancement of each dominant fibroid for Patients 002 and 003 at Visits 3 and 4, respectively. Patient 001 displayed no reduction in either uterine or fibroid volume, whereas reductions in volume were observed for Patients 002 and 003 at 3 days and 26 days post-embolization, respectively.

Histological Assessment

Incomplete necrotic changes were seen in fibroid tissue in all 3 patients, 20% necrosis within all fibroids for Patients 001 and 002, and 80% necrosis for Patient 003. There were 6 days between the embolization procedure and SOC hysterectomy for Patients 001 and 002, and 27 days between embolization and hysterectomy for Patient 003.

A mild inflammatory response was observed for all 3 patients (low grade cellular response of perivascular inflammation and extrauterine necrosis was observed in Patients 001 and 002.

Safety and Tolerability Results:

A total of 7 adverse events (AEs) were reported by the 3 patients. All AEs were mild or moderate in severity, with onset occurring post-embolization, and were regarded by the Investigator as probably related to the test device. No SAEs or AEs leading to withdrawal were reported during the study. All 3 patients reported abdominal pain and cramping, while nausea and vaginal discharge were reported by Patients 002 and 003.

There were no clinically significant findings in vital sign, physical examination, or clinical laboratory assessments.

Name of Company: *IM*Biotechnologies Ltd.	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use only)*
Name of Finished Product: OCL 503		
Name of Active Ingredient: Not applicable		

Conclusions:

In the studied population of women with symptomatic uterine fibroids scheduled for hysterectomy:

- OCL 503 was generally well tolerated with all patients experiencing an expected post-embolization syndrome; no new safety patterns or trends were identified.
- There were no SAEs or AEs leading to withdrawal from the study, and no clinically significant findings in vital sign, physical examination, or clinical laboratory assessments.
- Fibroid perfusion was noted on MRI in 1 of the 3 patients.
- Reduction in uterine and fibroid volume was observed in 2 of the 3 patients following embolization with OCL 503.
- Incomplete necrotic changes were seen in fibroid tissue for all 3 patients.
- Extrauterine necrosis was observed in 1 patient, while endometrial necrosis was noted in 2 patients.

Date of Report: 31 August 2016

3 TABLE OF CONTENTS

3.1 List of In-text Tables

4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADE	Adverse device effect
AE	Adverse event
BMI	Body mass index
CFR	Code of Federal Regulations
eCRF	Electronic case report form
FDA	Food and Drug Administration
GnRH	Gonadotropin releasing hormone
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IRB	Institutional review board
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
PLGA	Poly-DL-lactide-co-glycolic acid
QoL	Quality of life
SADE	Serious adverse device effect
SAE	Serious adverse event
SOC	Standard of care
UADE	Unanticipated adverse device effect
UAE	Uterine artery embolization
UFE	Uterine fibroid embolization
VAS	Visual Analog Scale

5 ETHICS

5.1 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 institutional review board (IRB) prior to study initiation.

A list of all IRBs consulted is presented in Appendix 16.1.3.

5.2 Ethical Conduct of the Study

This study was conducted in accordance with current applicable regulations, International Conference on Harmonisation (ICH) and Good Clinical Practice guidelines, FDA regulations relating to investigational devices (21 Code of Federal Regulations [CFR] 812) and local legal requirements. It complies with the ethical principles described in the Declaration of Helsinki World Medical Association, 2002.

5.3 Patient Information and Consent

The Patient Informed Consent Form (ICF) and consent process were in compliance with the requirements of 21 CFR 50. The Investigator 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 *IM*Biotechnologies 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. A copy was kept on file by the Investigator and another given to the patient for her reference.

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 Investigator 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.

Representative written information for the patient and a sample patient consent form is presented in Appendix 16.1.3.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Role in Study	**Name and Contact Details**
Sponsor	Michael Stewart President and Chief Executive Officer, *IM*Biotechnologies Ltd. Suite 215, Advanced Technology Centre 9650 20th Avenue, NW Edmonton, Alberta T6N 1G1 Canada
USA Investigational Device Exemption Sponsor	Robert Lally Senior Vice President, Regulatory Affairs BTG International Inc. Five Tower Bridge, Suite 800 300 Barr Harbor Drive West Conshohocken, Pennsylvania 19428-2998 USA
Medical Monitor	Dr. Sarah Chennoufi (on behalf of BTG International Inc.) Medical Director Oncology
Principal Investigator	Dr. Gary Siskin Albany Medical Center Chair, Department of Radiology 43 New Scotland Avenue Albany, New York 12208 USA
Obstetrics/Gynecology (surgeon)	Dr. Peter Cole Albany Medical Center
Pathologist (histological review)	Dr. Ann Boguniewicz Albany Medical Center
Central Laboratory	Albany Medical Center
Clinical Research Organization	ICON Clinical Research LLC 62 Forrest Street, Suite 300 Marlborough, Maryland 01752 USA
Data Management and Biostatistics	ICON Clinical Research LLC

Medical Writing	Andrew Senior ICON Clinical Research Ltd. Concept House, 6 Stoneycroft Rise, Chandler's Ford, Eastleigh SO53 3LD United Kingdom
Provision of study device	DSM Biomedical 735 Pennsylvania Drive Exton, Pennsylvania 19341 USA

7 INTRODUCTION

7.1 Background

Uterine leiomyomata or uterine fibroids are a common benign tumor of the uterine muscle in pre-menopausal women. Up to 40% of women aged ≥35 years are believed to have uterine fibroids of a significant size, however, they are generally asymptomatic with some studies estimating that 60% to 90% of such tumors fail to cause any symptoms.[1] In some women, fibroids can cause bleeding, pelvic pain, and pressure, which can lead to affected women requiring major surgery for the removal of the fibroids. Common treatments for uterine fibroids include medical therapy, hysterectomy, and myomectomy.

Uterine fibroids are generally diagnosed during a physical examination by the finding of an enlarged or irregularly shaped uterus in the absence of other abnormalities suggesting another diagnosis. Imaging studies such as transvaginal ultrasound, magnetic resonance imaging (MRI) and sonohysterography or hysteroscopy are used to confirm diagnosis.

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 non-steroidal anti-inflammatory drugs 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. Hysterectomy is the predominant invasive treatment for uterine fibroids in the USA [2,3] and is a major surgical procedure with a substantial recovery period. Furthermore, hysterectomy removes an organ that plays a role in sexual function, guarantees infertility, produces immediate menopause and has psychological implications for many women.

Myomectomy may provide relief from symptoms without some of the adverse effects of hysterectomy. Since the uterus is conserved, future childbearing may be possible and the sexual and psychological implications of hysterectomy may also be avoided.

Uterine artery embolization (UAE) is a minimally invasive technology for reducing symptoms from uterine fibroids and has been demonstrated to be a less invasive alternative to surgical treatment of these common, benign uterine tumors. Evaluation of embolic particles in the treatment of uterine fibroids is recommended prior to routine clinical use.[4,5] Successful embolization of the vascular feeding a fibroid(s) is demonstrated by an absence of contrast enhancement of the fibroid tissue as assessed by magnetic resonance angiography (MRA). Enhancement of fibroid tissue with MRA indicates perfusion of the fibroid tissue and a potential for fibroid regrowth.[4] Since gynecologists in the USA perform more than 150,000 hysterectomies and 35,000 myomectomies each year to relieve symptoms of uterine fibroids,

UAE has the potential to benefit many patients. Reduction in uterine and fibroid volumes is evident several weeks after embolization.[6]

OCL 500 is a collagen-coated poly-DL-lactide-co-glycolic acid (PLGA) microsphere. The primary mechanism of action of OCL 500 as an embolization agent is based on physical blockade of the target blood vessel(s), leading to blood stasis and subsequent clot formation. In addition to its primary mode of action, OCL 500 also promotes vascular occlusion by consolidating clot formation by capturing platelets. Platelets bind to OCL 500 by means of collagen covalently bound to the surface of the OCL 500 particles. Preclinical studies and animal testing demonstrate that OCL 500 promotes vascular occlusion. The United States Food and Drug Administration (FDA) have cleared OCL 500 as a Class II artificial embolization device for the treatment of unresectable and inoperable hypervascularized tumors. In this study, OCL 500 was provided in a single size range, 150 to 212 µm (OCL 503).

7.2 Rationale

This study was designed to collect data on safety, as well as on the ability of OCL 503 to act as an embolization agent and to promote vascular occlusion in women with leiomyomata scheduled for hysterectomy.

8 STUDY OBJECTIVES

8.1 Primary Objectives

The primary objectives of this study were to:

- Evaluate the short-term safety of OCL 503 for treatment of women with leiomyomata by UAE.
- Evaluate the effect of OCL 503 on fibroid perfusion.

8.2 Secondary Objectives

The secondary objectives of this study were to:

- Evaluate the macroscopic and microscopic pathologic changes of uterine tissue after treatment of women with leiomyomata by UAE.
- Evaluate the inflammatory response to OCL 503 after treatment of women with leiomyomata by UAE.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan - Description

This was a prospective, pilot, open label, uncontrolled safety and effectiveness study of uterine fibroid embolization (UFE) with OCL 503 in women with fibroids who were scheduled for hysterectomy. All patients were to be treated with OCL 503 on Day 1. OCL 503 was only to be administered to the patient in the study site by properly trained and qualified study personnel.

Prior to entering the study, all patients underwent pre-study assessments, including compliance with inclusion and exclusion criteria, laboratory assessments, MRI/ MRA pelvic imaging, and a quality of life (QoL) questionnaire. A negative urine pregnancy test was obtained immediately prior to the UAE procedure at Visit 2.

The first 2 patients were to be enrolled into Cohort 1. After completion of treatment, surgery, and a review of follow-up assessments to ensure no safety concerns had arisen, 8 additional evaluable patients were to be allocated into Cohort 2 or Cohort 1.

Following angiography to delineate the uterine vasculature, each patient underwent embolization with OCL 503. OCL 503 was administered intra-arterially until there was persistent visualization under fluoroscopy of contrast within the target uterine artery for 3 to 5 cardiac beats. Following the embolization, standard of care (SOC) supportive therapy was given to ameliorate the effects of the post-embolization syndrome. Patients in Cohort 1 underwent a hysterectomy 1 week after treatment with OCL 503. Patients in Cohort 2 underwent a hysterectomy 4 weeks after treatment with OCL 503. The hysterectomy was to be conducted according to the study center SOC and was not considered part of this study.

Patient assessments, including laboratory assessments, MRI/MRA, and patient interviews were conducted prior to the hysterectomy. Follow-up (End of Study) patient interviews were conducted approximately 1 month post-hysterectomy. Safety, as assessed by the reporting of adverse events (AEs), clinical laboratory assessments, vital signs, physical examinations, and Visual Analog Scale (VAS) scores for pain, was evaluated throughout the study.

The duration of patient involvement in the study and duration of the study period, including pre-study assessment and enrolment (enrolment was defined as the time at which a patient had signed and dated the consent form), was approximately 70 days (Cohort 1) to 90 days (Cohort 2). This time included pre-study visits through to post-hysterectomy follow-up. Total study duration was approximately 5 months.

The timing of all study procedures is shown in Table 9–1 and Table 9–2 for Cohorts 1 and 2, respectively.

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

The assessments and procedures used in this study are typical for the treatment of women with uterine fibroids and have been selected to maximize patient safety and minimize risks.

OCL 500 comprises a series of microsphere diameters, manufactured in specific size ranges. The various size ranges are OCL 501 (40 to 100 µm), OCL 503 (150 to 212 µm), OCL 505 (300 to 425 µm) and OCL 507 (500 to 800 µm). OCL 500 was demonstrated to be non-toxic and biocompatible in *in vitro* and in preclinical *in vivo* studies. OCL 500 has 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 and pigs, respectively.

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

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

1. Had received a diagnosis of symptomatic uterine fibroids, 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 were attributed to uterine fibroids (bulk-related symptoms included pelvic pressure, abdominal distension, abdominal bloating, constipation, backache, urinary frequency, urinary retention, ureteral dilation, and rectal pressure), and
    b) the intensity of the uterine fibroid-related symptoms, which were sufficiently severe to warrant hysterectomy, and
    c) the patient's medical history, physical examination, and the results of imaging by ultrasound or MRI.
2. Were between the ages of 30 and 55 years old, inclusive.
3. Had a pelvic examination by a gynecologist within the previous 6 months.
4. Had a normal Pap smear within the last 12 months.
5. Had an endometrial biopsy within the previous 3 to 6 months, as appropriate to patient history.
6. Were premenopausal with menstrual cycles lasting between 22 and 35 days, which was documented. A follicle stimulating hormone value obtained within 3 months prior to the procedure was < 40 IU/L.
7. Were scheduled for a total abdominal hysterectomy.
8. Were willing and able to provide written informed consent.

9.3.2 Exclusion Criteria

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

1. Had been treated with GnRH agonists within the previous 12 weeks.
2. Had an American Society of Anesthesiologists score ≥ 3 (see protocol Attachment B [Appendix 16.1.1]).
3. Had abnormally large ovarian arteries, as assessed by MRA and determined by the Investigator.
4. Had an undiagnosed pelvic mass outside of the uterus.
5. Had claustrophobia or other contraindications to the performance of the pre- and post-procedure MRI studies, including the presence of metal implants, metal plates, bone pins, bone screws, neurostimulators, cardiac pacemakers, aneurysm clips, cochlear or retinal implants, permanent hearing aids, or permanent eye-liner.
6. Had pedunculated subserosal fibroids with an attachment to the uterus less than one third of the greatest diameter of the fibroid.
7. Did not agree to use contraceptives from Visit 1 until undergoing total abdominal hysterectomy.
8. Had compromised hematopoietic function (hemoglobin < 100 g/L; lymphocyte count < 500×10^6/L; neutrophil count < 1.5×10^9/L; platelet count < 50×10^9/L).
9. Had hepatic dysfunction defined as liver function tests 30% above the upper limit of normal.
10. Had an active gynecologic or systemic infection.
11. Had renal dysfunction as defined by a serum creatinine > 1.5 mg/dL.
12. Had a history of gynecologic malignancy.
13. Had a documented anaphylactic reaction to a drug or anesthetic, or an allergic reaction to iodine contrast media not controlled by antihistamines or steroids.
14. Had received other investigational drugs or who had had experimental therapy within the past 4 weeks or were participating in any other concurrent experimental therapy.
15. Had a uterine volume < 250 mL or approximating > 24 weeks gestation.
16. Had known endometrial hyperplasia, adenomyosis, or pelvic inflammatory disease.
17. Had abnormal coagulation profiles.
18. Were allergic to bovine collagen.
19. Wished to become pregnant in the future.

9.3.3 Removal of Patients from Treatment or Assessment

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

1. The patient withdrew consent.

2. The patient elected not to proceed with hysterectomy after treatment with OCL 503.
3. The Investigator determined that it was not in the best interests of the patient to continue in the study.
4. The patient experienced an adverse reaction that, in the opinion of the Investigator, necessitated the removal of the patient from the study, including any unresolved serious adverse event (SAE).
5. Intercurrent illness or other reasons that would, in the opinion of the Investigator, affect assessment of clinical status or conduct of the study to a significant degree.

The reasons for withdrawing the patient were to be documented in the electronic case report form (eCRF). Patients who had been withdrawn from the study were followed up, where possible.

Patients who withdrew consent before being treated with OCL 503 were not followed up and were to be replaced. Patients who were treated with OCL 503 but did not proceed with hysterectomy were to be followed up at 5 weeks ± 1 week post scheduled hysterectomy and were not to be replaced.

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.

9.3.4 Study Stopping Criteria

The Investigator 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 OCL 503 agent.

9.4 Investigational Device

9.4.1 Administration of OCL 503

OCL 503 was administered during a UAE procedure, a minimally invasive technology for reducing symptoms from uterine fibroids by inducing fibroid infarction. Following a pelvic angiogram to delineate the uterine vasculature, embolization procedures of the left and right uterine arteries (as required) were performed on each patient. OCL 503 (150 to 212 μm diameter) microspheres were delivered by microcatheter, with a starting dose of approximately 400 mg of OCL 503. OCL 503 particles were to be administered slowly, and evenly intra-arterially. Additional vials of OCL 503 consisting of 400 mg/vial were to be 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. A maximum of 10 vials of OCL 503 were to be administered per treatment.

MRI/MRA were used to assess fibroid infarction. Histological analysis of excised tissue was used to evaluate local tissue response to embolization and fibroid infarction.

Symptomatic treatment of the post-embolization syndrome was to be given per center SOC to ameliorate the effects of the post-embolization syndrome.

9.4.2 Identification of Investigational Device

For this study, OCL 500 was provided in a single size range, 150 to 212 μm (OCL 503). OCL 503 is compatible for use with microcatheters. OCL 503 microspheres have a density of approximately 1.3 g/mL.

OCL 503 was provided in a sealed glass vial as 400 mg of sterile dry microspheres to be reconstituted and administered via microcatheter to the uterine artery/arteries. Instructions for Use were provided with each vial.

As is true for other vascular embolization devices, at the time/point of use, the OCL 503 particles 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™ (not included with the product). The bolus of contrast agent elutes from the vascular bed to leave a radiolucent, embolized vessel.

OCL 503 was manufactured for *IM*Biotechnologies by DSM Biomedical (Exton, PA) in compliance with Good Manufacturing Practice. The following batch numbers were used in the study: C6831 (expiry 28 December 2015); D2773 (expiry 28 September 2016).

OCL 503 was 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 503 was shipped to the study facility in an insulated container containing cold packs. Upon arrival, the vials were transferred to a cool, dry storage location, protected from light. After reconstitution, OCL 503 is stable at room temperature for several hours.

Vials of OCL 503 were stored in a locked, temperature-controlled room or cabinet until required for administration as part of this protocol. OCL 503 was stored in a cool dry location, at room temperature, protected from light.

The Research Coordinator was responsible for storage of OCL 503 in the Department of Radiology, Albany Medical Center.

9.4.3 Method of Assigning Patients to Treatment Groups

The first 2 patients were to be enrolled into Cohort 1. After completion of treatment, surgery, and follow-up assessments to ensure that no safety concerns had arisen, subsequent patients were to be allocated to Cohort 2 or Cohort 1 until 8 additional evaluable patients had undergone treatment and surgery. Allocation was to be at the physician's discretion, considering the urgency for treatment on a per-patient basis.

9.4.4 Selection of Doses in the Study

The starting dose of OCL 503 particles was approximately 400 mg, administered intra-arterially. Additional vials of OCL 503 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. A maximum of 10 vials of OCL 503 were to be administered per treatment.

9.4.5 Selection and Timing of Dose for Each Patient

See Section 9.4.1.

9.4.6 Blinding

This was an open label study.

9.4.7 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 SOC treatment for symptoms, including:

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

Any treatments administered were to be documented on the eCRF.

9.4.8 Treatment Compliance

Administration of the investigational device (OCL 503) was only to be performed under the supervision of the Investigator or qualified delegate; therefore measures to ensure patient compliance were not required. However, 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 ensure compliance with protocol scheduled study visits.

9.5 Effectiveness and Safety Variables

9.5.1 Effectiveness and Safety Measurements Assessed and Flow Chart

The schedule of assessments is presented in Table 9–1.

Table 9–1 Schedule of Assessments: Cohort 1 (SOC Hysterectomy at 1 Week Post-embolization)

	Pre-Study			Study			End of Study	Unscheduled Visits
TIME (weeks)	**Within 1 year of study start**	**Within 6 months of study start**	**Within 1 month of study start**	**1**		**2**	**7**	
TIME (calendar days)	**-365**	**-180**	**-28**	**1**	**7 ± 2[1]**	**8 + 3[1]**	**43 ± 7**	
VISIT NO.			**1**	**2**	**3**	**4**	**5**	
PRE-STUDY ASSESSMENTS								
Pap smear	X							
Pelvic examination		X						
Biopsy/bacterial cultures[2]		X						
Informed consent			X					
History (medical, surgical)			X					
Cohort assignment			X					
STUDY ASSESSMENTS								
Physical examination, vital signs			X	X				X
MRI/MRA[3] imaging of pelvis			X	X[3]	X[3]			
Patient interview					X		X	X
Administration of OCL 503/UAE				X				
Complete abdominal hysterectomy (SOC)						X		
LABORATORY EXAMINATIONS								
Pregnancy test				X[4]				
Hematology			X	X		X		
Blood chemistry			X	X		X		
Coagulation profile			X	X		X		
Histopathology of uterus						X		
QUALITY OF LIFE								
Uterine fibroid symptom – QoL instrument			X					
SAFETY								
Adverse event				X	X	X	X	X
Chart review and concomitant medications				X	X	X	X	X

Abbreviations: MRA=magnetic resonance angiography; MRI=magnetic resonance imaging; QoL=quality of life; SOC=standard of care; UAE=uterine artery embolization.

1 Day 7 and Day 8 procedures could be performed on the same day.

2 Cultures as appropriate to patient history.

3 MRI/MRA performed at Visit 2 within 48 hours prior to the UAE procedure and at Visit 3 prior to hysterectomy.

4 Urine pregnancy test prior to UAE procedure.

Table 9–2 Schedule of Assessments: Cohort 2 (SOC Hysterectomy at 4 Weeks Post-embolization)

	Pre-Study			Study				End of Study	Unscheduled Visits
TIME (weeks)	**Within 1 year of study start**	**Within 6 months of study start**	**Within 1 month of study start**	**1**		**4**	**5**	**10**	
TIME (calendar days)	**-365**	**-180**	**-28**	**1**	**7 ± 2**	**28 ± 2[1]**	**29 + 3[1]**	**64 ± 7**	
VISIT NO.			**1**	**2**	**3**	**4**	**5**	**6**	
PRE-STUDY ASSESSMENTS									
Pap smear	X								
Pelvic examination		X							
Biopsy/bacterial cultures[2]		X							
Informed consent			X						
History (medical, surgical)			X						
Cohort assignment			X						
STUDY ASSESSMENTS									
Physical examination, vital signs			X	X					X
MRI/MRA[3] imaging of pelvis			X	X[3]		X[3]			
Patient interview					X	X		X	X
Administration of OCL 503/UAE				X					
Complete abdominal hysterectomy (SOC)							X		
LABORATORY EXAMINATIONS									
Pregnancy test				X[4]					
Hematology			X	X			X		
Blood chemistry			X	X			X		
Coagulation profile			X	X			X		
Histopathology of uterus							X		
QUALITY OF LIFE									
Uterine fibroid symptom – QoL instrument			X						
SAFETY									
Adverse event				X	X	X	X	X	X
Chart review and concomitant medications				X	X	X	X	X	X

Abbreviations: MRA=magnetic resonance angiography; MRI=magnetic resonance imaging; QoL=quality of life; SOC=standard of care; UAE=uterine artery embolization.

[1] Day 28 and Day 29 procedures could be performed on the same day.

[2] Cultures as appropriate to patient history.

[3] MRI/MRA performed at Visit 2 within 48 hours prior to the UAE procedure and at Visit 4 prior to hysterectomy.

[4] Urine pregnancy test prior to UAE procedure.

9.5.1.1 Effectiveness Assessments

9.5.1.1.1 Magnetic Resonance Imaging/Magnetic Resonance Angiography

Tumor response was measured by changes in fibroid size and perfusion, as measured by MRI and MRA. Successful embolization was demonstrated by an absence of contrast enhancement of the fibroid tissue. Enhancement of fibroid tissue indicated perfusion of the fibroid tissue and a potential for fibroid regrowth.

A blinded radiologist was responsible for review and documentation of MRI images.

The MRI protocol included the following sequences:

- Pre-contrast T2-weighted SSFSE (axial, sagittal, and short axis uterus).
- Pre-contrast T1 GRE, in and out phase (axial).
- Pre-contrast T1 GRE, Fat Sat (axial, sagittal).
- Pre-contrast MRA of pelvic vasculature.
- Post-contrast T1 GRE, Fat Sat (axial, sagittal).
- Post-contrast MRA of pelvic vasculature.

A standard gadolinium contrast agent was used for the imaging studies (gadopentetic acid – Magnevist, or equivalent). The studies were conducted with and without contrast and included the measurement of the length, width, and depth of the uterus and the dimensions of the dominant fibroids and all identifiable fibroids > 5 cm, and for determination of any ovarian arterial contribution to uterine blood flow. Patients with confirmed arterial contribution were excluded from the study.

The studies must have been of sufficient quality to allow determination of arterial blood flow and to show adequate detail of the fibroids and the endometrium and arterial blood flow. The change in size of the uterus and the uterine fibroids was calculated relative to measurements taken at baseline.

9.5.1.1.2 Histological Assessment

After total abdominal hysterectomy on either Study Day 8 (Cohort 1) or Study Day 29 (Cohort 2), the pathohistologic assessment of uterine tissues was conducted by the institution's pathologist to determine the following:

- Percentage of necrosis within all fibroids present within the uterus.
- Extent of mural penetration (vascular discontinuity caused by the embolic agent), vessel wall necrosis, and aneurysmal change within the uterine arteries and its branches.
- Graded cellular response (low, moderate, high) of intraluminal and perivascular inflammation with characterization of the various cell types involved in the inflammatory

response (e.g., polymorphonuclear leukocytes, lymphocytes, eosinophils, macrophages, and giant cells).

- Estimates of the percentage of internal elastic lamina, external elastic lamina, and media remaining in circumferential and longitudinal sections of occluded arterial segments.
- Graded extent (1=mild, 4=severe) of thrombosis, organization, neovascularization, proteoglycan production, smooth muscle cell and collagen deposition within the treated vessels and perivascular tissue.
- Quantitation of recanalization at 7 days (Cohort 1) and 28 days (Cohort 2)
- Selected vessels were evaluated to determine the estimated normal vascular diameter at the point of occlusion, the size of the occluding microspheres at the point of occlusion, and the approximate proportion of occluding plugs that were thrombus versus embolic material.

9.5.1.2 Safety Assessments

9.5.1.2.1 Adverse Events

Safety was assessed throughout the study, and documented at every study visit from Day 1 (Study Visit 2; day of UAE 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 (Appendix 16.1.1).

9.5.1.2.2 Laboratory Safety Assessments

Standard laboratory tests, conducted at the local laboratory were performed at the times specified in Table 9–1 and Table 9–2. Laboratory tests for hematology and blood chemistry were performed to assess effects of the study treatment. The results of all laboratory tests were assessed by the Investigator as to their clinical significance. Any post-baseline laboratory value that was found to be clinically significant was evaluated by the Investigator 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 (Appendix 16.1.1).

The laboratory safety assessments performed during the study are presented in Table 9–3.

Table 9–3 Laboratory Safety Assessments

Hematology: Complete blood count	**Coagulation:** Prothrombin time Activated partial thromboplastin time
Serum chemistry:	
Liver function tests	Metabolic function tests
Albumin	Calcium
Alkaline phosphatase	Phosphate
Aspartate aminotransferase	Glucose
Alanine aminotransferase	Uric acid
Bilirubin (total)	Electrolytes
Lactate dehydrogenase	Bicarbonate
Total Protein	Chloride
α-fetoprotein	Potassium
Kidney function tests	Sodium
Creatinine	Hormone levels
Urea	Follicle stimulating hormone

9.5.1.2.3 Physical Examination

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

9.5.1.2.4 Vital Signs

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

9.5.1.2.5 Pregnancy Test

A negative urine pregnancy test was to be obtained on the day of the UAE, prior to the UAE procedure.

9.5.1.3 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 (see protocol Attachment C: Uterine Fibroid Symptom and Health-related Quality of Life Questionnaire [Appendix 16.1.1]).

Patient interviews were conducted per the Investigator's usual procedure with UAE patients, according to the questionnaire and VAS for pain[6] (see protocol Attachment D [Appendix 16.1.1]).

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

9.5.1.4 (Standard of Care) Abdominal Hysterectomy

Approximately 1 week (Cohort 1, Study Visit 4) or 4 weeks (Cohort 2, Study Visit 5) post-embolization and post MRI/MRA assessment, patients underwent abdominal hysterectomy.

The complete abdominal hysterectomy was performed per study center SOC, and was not considered part of this study for any patient.

Criteria for histological assessment of uterine tissue are provided in Section 9.5.1.1.2.

9.5.2 Appropriateness of Measurements

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

9.6 Data Quality Assurance

Documentation of inter-laboratory standardization methods and quality assurance procedures are presented in Appendix 16.1.10.

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 documented completion of site preparation and training. Training necessary to ensure compliance with the protocol is detailed in Section 15 of the protocol (Appendix 16.1.1).

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 Investigator permitted and assisted the Monitor to carry out verification of completed eCRFs against data in the source documents.

The Monitor was to inform 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 Investigator and for convening with the investigational site personnel to conduct timely corrective actions.

The Monitor was to submit written reports to the Sponsor, after each visit or contact with the Investigator or investigational site personnel.

9.7 Statistical Methods Planned and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

No statistical analysis plan was produced for this study.

9.7.1.1 Study Populations

Not applicable.

9.7.1.2 Statistical Methods

An analysis of the safety and effectiveness data collected in this study was performed. As only 3 patients were enrolled, no summary analyses were performed. The analysis of the data derived from this study was primarily descriptive.

Patient data are presented in the individual eCRFs (Appendix 16.2).

9.7.1.2.1 Demographic and Baseline Characteristics

Demographic and baseline data collected at Screening are presented in the individual eCRFs.

9.7.1.2.2 Concomitant Medication

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

9.7.1.2.3 Extent of Exposure and Compliance

The amount of OCL 503 administered and the duration of embolization procedure were listed in the individual patient eCRFs.

9.7.1.2.4 Effectiveness Analysis

Effectiveness analyses were based on the MRI/MRA assessments at Screening and post-embolization, and the results of the histopathological analysis of the excised uterus. The analyses were primarily descriptive.

9.7.1.2.5 Safety Analysis

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

9.7.2 Determination of Sample Size

Enrollment in this study was planned to continue until 10 women with leiomyomata had been treated with OCL 503. Allowing for a 50% drop out rate, the total enrollment was to be up to 15 patients to ensure that 10 evaluable patients were available for statistical analysis.

9.8 Changes in the Conduct of the Study or Planned Analyses

The study was terminated early due to difficulty in recruiting patients. Discussions with the Investigator and study coordinator identified the following issues:

- Patient's time commitment – In addition to the SOC hysterectomy requiring a surgical procedure and hospital stay, patients needed to allocate time for the embolization procedure.

- Patient's discomfort – Patients were required to undergo 2 separate procedures; SOC hysterectomy and the embolization procedure. The embolization procedure occurred prior to hysterectomy.

10 STUDY PATIENTS

Patient disposition and protocol deviation data are presented in the individual patient eCRFs (Appendix 16.2).

10.1 Disposition of Patients

The study was terminated early due to difficulty in recruiting patients. Overall, 3 patients were enrolled and all 3 patients completed the study. Patient 001 and Patient 002 were enrolled into Cohort 1 (both patients underwent hysterectomy 1 week after treatment with OCL 503) and Patient 003 was enrolled into Cohort 2 (hysterectomy 4 weeks after treatment with OCL 503).

10.2 Protocol Deviations

Minor protocol deviations relating to unperformed clinical laboratory assessments and the timing of visits were noted for all 3 patients.

11 EFFECTIVENESS EVALUATION

11.1 Data Sets Analyzed

Not applicable.

11.2 Demographic and Other baseline Characteristics

Demographic data and medical and surgical history are presented in the individual patient eCRFs (Appendix 16.2).

11.2.1 Demographic Characteristics

Demographic characteristics for all enrolled patients are presented in Table 11–1.

Table 11–1 Demographic and Baseline Characteristics

Statistic	Patient		
	001	**002**	**003**
Age (years)	47	41	55
Race	Black or African American	Black or African American	Black or African American
Ethnicity	Not Hispanic or Latino	Not Hispanic or Latino	Not Hispanic or Latino
Height (cm)	167.6	172.1	160.0
Weight (kg)	123.0	82.3	72.6
BMI (kg/m^2)	43.8	27.8	28.3
Uterine Fibroid Symptom - QoL Transformed Severity Score	56.25	81.25	71.88

Abbreviations: BMI=body mass index; QoL=quality of life

All 3 patients were Black or African American, ranging in age from 41 to 55 years. Patients 002 and 003 had comparable BMI, while Patient 001 had a higher BMI. The Transformed Severity Scores from the uterine fibroid symptom QoL questionnaire carried out at Screening were comparable for Patients 002 and 003, while Patient 001 had a lower score.

The results from the Pap smear, pelvic examination, and endometrial biopsy were normal for all 3 patients. Uterine fibroids were confirmed in all 3 patients by MRI/MRA; no other abnormal findings were observed as determined by laboratory assessment, MRI/MRA assessment, and physical examination..

11.2.2 Medical and Surgical History

Medical and surgical history for all enrolled patients is presented in Table 11–2.

Table 11–2 Medical History

Patient	Disease	Start Date	Stop Date	Ongoing Prior Medication
001	Abnormal uterine bleeding	15-Jan-2008	Ongoing	
	Uterine fibroids	Unknown	Ongoing	
	Iron deficiency anemia	Unknown	Ongoing	Ferrous sulphate
	Depression	01-Jan-2007	Ongoing	Mirtazapine
	Knee pain/osteoarthritis	Unknown	Ongoing	Hydrocodone
	Cocaine abuse	01-Jan-1989	01-Jan-2010	
	HIV	01-Jan-2008	Ongoing	Altripla
	Asthma	01-Jan-2011	Ongoing	Flovent HFA Proventil
	Hypertension	Unknown	Ongoing	Metoprolol
002	Uterine fibroids	Unknown	Ongoing	
	Chronic constipation	Unknown	Ongoing	
	Lupus	Unknown	Ongoing	Hydrochloroquine
	Hiatal hernia	Unknown	Ongoing	
	Gastroesophageal reflux disease	Unknown	Ongoing	Pantoprazole Zofran
	Asthma	Unknown	Ongoing	Budesonide
	Anemia	Unknown	Ongoing	
	Rheumatoid arthritis	Unknown	Ongoing	Hydrochloroquine Ibuprofen
	Genital herpes	Unknown	Ongoing	
	Retroversion of uterus	Unknown	Ongoing	
	Cesarean section	Unknown	Unknown	
003	Leiomyoma uterus	2012	Ongoing	
	Benign essential hypertension	2011	Ongoing	Amlodipine Lisinopril
	Anxiety	Unknown	Ongoing	
	Hyperthyroidism	2011	Ongoing	
	Benign mass right breast	2011	Unknown	
	Iron deficiency	2011	Unknown	Iron
	Anemia	2011	Ongoing	
	Palpitations	2011	Ongoing	
	Menorrhagia	Unknown	Ongoing	Ibuprofen Norethindrone Acetate

11.3 Measurements of Treatment Compliance

Not applicable.

11.4 Effectiveness Results and Tabulations of Individual Patient Data

Efficacy data are presented in the individual patient eCRFs and histopathology reports (Appendix 16.2).

11.4.1 Effectiveness Analysis

11.4.1.1 Magnetic Resonance Imaging/Magnetic Resonance Angiography Assessment

The results for the MRI/MRA assessments for each patient are presented in Table 11–3. For Cohort 1 (Patients 001 and 002), MRI/MRA assessments were carried out at Screening and Visit 3. Visit 3 occurred at 5 days and 3 days post-embolization for Patients 001 and 002, respectively. For Patient 003 (Cohort 2), assessments were carried out at Screening and Visit 4 (26 days post-embolization).

Table 11–3 MRI/MRA Assessment Results

	Patient 001		Patient 002		Patient 003	
	Screening	**Visit 3**	**Screening**	**Visit 3**	**Screening**	**Visit 4**
Enhancement of each dominant fibroid	Yes	Yes	Yes	No	Yes	No
Uterine volume (mL)	562.6	617.6	178.9	140.4	540.9	509.1
Volume of 3 dominant fibroids (mL)	128.8	132.4	24.7	20.8	74.0	56.5
Uterine arteries	Patent	Patent	Patent	Patent	Patent	Patent
Anomalous blood supply	Absent	Absent	Absent	Absent	Absent	Absent

Enhancement of each dominant fibroid was observed for all patients at the Screening assessment, and at Visit 3 for Patient 001. There was no enhancement of each dominant fibroid for Patients 002 and 003 at Visits 3 and 4, respectively. Patient 001 displayed no reduction in either uterine or fibroid volume, whereas reductions in volume were observed for Patients 002 and 003 at 3 days and 26 days post-embolization, respectively.

11.4.1.2 Histological Assessment

The results of the histopathologic assessment of uterine tissue for each patient are presented in Table 11–4.

Table 11–4 Histopathology Results

	Patient 001 (Cohort 1; hysterectomy 1 week after treatment with OCL 503)	**Patient 002 (Cohort 1; hysterectomy 1 week after treatment with OCL 503)**	**Patient 003 (Cohort 2; hysterectomy 4 weeks after treatment with OCL 503)**
Percentage of necrosis within all fibroid present within uterus			
Percentage of necrosis within all fibroids present within the uterus	20%	20%	80%
Extent of mural penetration			
Extent of mural penetration	No penetration of muscle around leiomyomata. Focal necrosis of overlying endometrium	80%	None
Extent of necrosis of the vessel wall	None	None in viable tissue, 100% in necrotic tissue	None
Extent of aneurysmal change within the uterine arteries and its branches	None	None	None
Graded cellular inflammatory response			
Graded cellular response of intraluminal inflammation	Low	None	None
Graded cellular response of perivascular inflammation	Low	Low	Low
Types of cells involved in inflammatory response	Eosinophils, lymphocytes	Lymphocytes, eosinophils, neutrophils	Lymphocytes, eosinophils, neutrophils
Percentage of lamina involvement			
Percentage of internal elastic lamina	0	0	0
Percentage of external elastic lamina	0	0	0
Percentage of media remaining in circumferential and longitudinal sections of occluded arterial segments	100%	100%	100%
Graded extent of thrombosis, organization, neovascularization, proteoglycan production, smooth muscle cell, and collagen deposition within treated vessels and perivascular tissue			
Graded extent of thrombosis	Mild	Mild	Mild
Organization	Yes	No	Yes
Neovascularization	No	No	Yes
Proteoglycan production	No	No	No
Smooth muscle cell	No	No	No
Collagen deposition within the treated vessels	No	No	No
Collagen deposition within the perivascular tissue	No	No	No
Quantitation of recanalization			
Quantitation of recanalization at 7 days (Cohort 1) and 28 days (Cohort 2)	None	None	10%
Point of occlusion estimations: normal vessel diameter/microsphere size/proportion of occluding plug			
Diameter of occluded arteries	Small, medium, and large	0.5 to 2.5 mm	2.5 mm
Size of the occluding embolic agent at the point of occlusion	0.1 to 0.2 mm	0.2 mm	0.2 mm

Portion of the occluding plug that represented thrombus vs. embolic material	20%	10%	< 5%
Other histological findings			
Other histological findings	Unremarkable cervix. Unremarkable bilateral fallopian tubes. Focal necrosis of overlying secretory endometrium	Cervix with ischemic necrosis. Endometrium with extensive necrosis. Bilateral fallopian tubes with extensive ischemic necrosis.	Unremarkable cervix. Left ovary and fallopian tubes with ischemic changes. Right ovary with surface adhesions and unremarkable right fallopian tube.

11.4.2 Statistical/Analytical Issues

11.4.2.1 Adjustments for Covariates

Not applicable.

11.4.2.2 Handling of Dropouts or Missing Data

Not applicable.

11.4.2.3 Interim Analyses and Data Monitoring

No interim analysis was performed for this study.

11.4.2.4 Multicenter Studies

This was a single-center study.

11.4.2.5 Multiple Comparisons/Multiplicity

Not applicable.

11.4.2.6 Use of an Effectiveness Subset of Patients

Not applicable.

11.4.2.7 Active Control Studies Intended to Show Equivalence

Not applicable.

11.4.2.8 Examination of Subgroups

Not applicable.

11.4.3 Tabulation of Individual Response Data

Not applicable.

11.4.4 Drug Dose, Drug Concentration and Relationships to Response

Not applicable.

11.4.5 Drug-Drug and Drug-Disease Interactions

Not applicable.

11.4.6 By Patient Displays

Effectiveness data for each patient are presented in the individual patient eCRFs (Appendix 16.2).

11.4.7 Effectiveness Conclusions

In the studied population of women with symptomatic uterine fibroids scheduled for hysterectomy:

- Fibroid perfusion was noted on MRI in 1 of the 3 patients.
- Reduction in uterine and fibroid volume was observed in 2 of the 3 patients following embolization with OCL 503.
- Incomplete necrotic changes were seen in fibroid tissue for all 3 patients.
- Extrauterine necrosis was observed in 1 patient, while endometrial necrosis was noted in 2 patients.

12 SAFETY EVALUATION

The dose of OCL 503 administered, duration of procedure, and safety data are presented in the individual patient eCRFs (Appendix 16.2).

12.1 Extent of Exposure

The dose of OCL 503 administered, duration of embolization procedure, and outcome (whether near stasis was achieved for the target vasculature) for all 3 patients are presented in Table 12–1. Near stasis embolization was defined as retention of contrast agent in the target vasculature for 3 to 5 cardiac beats.

Table 12–1 Exposure to OCL 503

	Patient		
	001	**002**	**003**
Dose of OCL 503	4000 mg (10 vials)	3200 mg (8 vials)	4000 mg (10 vials)
Duration of embolization procedure (time taken to administer OCL 503)	1 hour 25 minutes	1 hour 11 minutes	1 hour 8 minutes
Outcome	Did not achieve near stasis	Near stasis achieved	Near stasis achieved

12.2 Adverse Events

A total of 7 AEs were reported by the 3 patients. All AEs were mild or moderate in severity, with onset occurring post-embolization, and were regarded by the Investigator as probably related to the test device. No SAEs were reported during the study.

Adverse events for all 3 patients are presented in Table 12–2.

Table 12–2 Display of Adverse Events

Patient	Adverse Event	Duration	Relationship to Test Device	Severity	Required Concomitant Medication?	Outcome
001	Abdominal pain and cramping	4 days	Probably related	Moderate	Yes	Recovered/ resolved
002	Nausea	2 days	Probably related	Mild	Yes	Recovered/ resolved
	Abdominal pain with cramping	5 days	Probably related	Moderate	Yes	Recovered/ resolved
	Vaginal discharge	3 days	Probably related	Mild	No	Recovered/ resolved
003	Abdominal pain and cramping	8 days	Probably related	Moderate	Yes	Recovered/ resolved
	Nausea	1 day	Probably related	Mild	Yes	Recovered/ resolved
	Vaginal discharge	6 days	Probably related	Mild	No	Recovered/ resolved

All 3 patients reported abdominal pain and cramping, while nausea and vaginal discharge were reported by Patients 002 and 003.

All AEs of abdominal pain and nausea required treatment with concomitant medication. For Patient 001, abdominal pain was treated with ibuprofen, oxycodone, and morphine. Patient 002 received ketorolac (Toradol) and oxycodone for the treatment of abdominal pain and ondansetron (Zofran) for the treatment of nausea, while Patient 003 received ketorolac (Toradol), morphine, and oxycodone for abdominal pain and ondansetron (Zofran) for the treatment of nausea.

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

There were no deaths, SAEs, or other significant AEs during the study.

12.4 Clinical Laboratory Evaluation

No clinically significant laboratory assessments were observed at all assessed time points for all patients in the study.

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

12.5.1 Vital Signs

No clinically significant vital sign results were observed at all assessed time points for all patients in the study.

12.6 Physical Examination

No abnormal, clinically significant physical examination results were observed for any patient at all assessed time points.

12.6.1 Patient Interviews and Visual Analog Scale Pain Scores

The responses to the patient interviews and the VAS scores for pain for all 3 patients are presented in Table 12–3.

Table 12–3 Patient Interview and Visual Analog Scale for Pain Results

	Patient 001		Patient 002		Patient 003	
Question	**Visit 3**	**Visit 5**	**Visit 3**	**Visit 5**	**Visit 4**	**Visit 6**
Pain in abdominal or pelvic regions since the procedure?	Yes	No	Yes	Yes	Yes	Yes
Experienced fever since the procedure?	No	No	No	No	No	No
Experienced cramping since the procedure?	Yes	No	Yes	No	Yes	No
Experienced vaginal discharge since the procedure?	No	No	Yes	No	Yes	Yes
Experienced nausea since the procedure?	No	No	Yes	No	Yes	Yes
VAS for pain	Moderate	No pain	Moderate	Moderate	Moderate	Moderate
VAS score for pain	5	0	5	1	4	3

Abbreviations: VAS=visual analog scale

Visit 3 occurred at 5 days and 3 days post-embolization for Patients 001 and 002, respectively. Abdominal pain and cramping were reported by both patients at Visit 3 with Patient 002 also reporting pain at visit 5 and vaginal discharge. No pain, cramping, or discharge was reported by Patient 001 at Visit 5 (42 days post-embolization). Both patients VAS score for pain was 5 (moderate) at Visit 3 and had decreased to 0 (no pain) and 1 (moderate) for Patients 001 and 002, respectively.

For Patient 003, abdominal pain, cramping, vaginal discharge, and nausea were reported at Visit 4 (26 days post-embolization) and abdominal pain, vaginal discharge, and nausea reported at Visit 6 (56 days post-embolization). VAS pain score decreased for 4 (Moderate) to 3 (moderate) between Visit 4 and Visit 6.

12.7 Safety Conclusions

In the studied population of women with symptomatic uterine fibroids scheduled for hysterectomy:

- OCL 503 was generally well tolerated with all patients experiencing an expected post-embolization syndrome; no new safety patterns or trends were identified.
- There were no SAEs or AEs leading to withdrawal from the study, and no clinically significant findings in vital sign, physical examination, or clinical laboratory assessments.

13 DISCUSSION AND OVERALL CONCLUSIONS

13.1 Discussion

This prospective, pilot, open label, uncontrolled study was assessed the safety and effectiveness of UFE with OCL 503 in women with fibroids who were scheduled for hysterectomy. It was planned that 10 evaluable patients were to be enrolled into 2 cohorts; however, only 3 patients were enrolled, of whom 2 patients were enrolled in Cohort 1 and 1 patient was enrolled in Cohort 2. All patients completed the study. The main issues for low recruitment were identified as the extra time commitment and discomfort from undergoing 2 separate procedures (embolization and SOC hysterectomy).

The embolization procedures utilizing OCL 503 in all 3 patients required more fluoroscopy time (and subsequent radiation exposure) and the volume of contrast used were both higher than anticipated. This can potentially be attributed to the amount of OCL 503 microspheres in the vial, and the small size of the OCL 503 microspheres. The procedure itself was generally well tolerated by all 3 patients, with each patient experiencing an expected post-embolization syndrome consisting of abdominal pain, cramping, nausea, and vaginal discharge. Importantly, no new safety patterns or trends were observed in any of the 3 patients.

Fibroid perfusion was noted for 1 patient post-embolization. Enhancement of each dominant fibroid was observed for all 3 patients at Screening; only Patient 001 showed enhancement of each dominant fibroid post-embolization. Patient 001 also showed no tumor response, while a reduction in uterine and fibroid volume was observed in Patients 002 and 003 following embolization with OCL 503.

Incomplete necrosis was observed for all patients, ranging from 20% necrosis within all fibroids for Patients 001 and 002 to 80% for Patient 003. The impact of this finding on long-term symptom control is unknown since all patients had a hysterectomy within 27 days after embolization. In addition, all patients displayed a mild inflammatory response (low grade of perivascular inflammation). Extrauterine necrosis was observed in Patient 002 (fallopian tube necrosis) and endometrial necrosis was seen in Patients 001 and 002; these findings may be attributed to the small size of the OCL 503 microspheres utilized as well as the volume of embolic utilized to achieve embolization of the target vasculature.

Although fibroid necrosis was achieved, treatment could be improved by increasing the size of the embolic agent, thereby decreasing procedure time and minimizing extrauterine effects. A further limitation was the relatively short time-frame to observe the changes occurring post-embolization. Given the results of this study in a limited population, more clinical studies are warranted to fully investigate the efficacy and safety of OCL 503.

13.2 Conclusions

In the studied population of women with symptomatic uterine fibroids scheduled for hysterectomy:

- OCL 503 was generally well tolerated with all patients experiencing an expected post-embolization syndrome; no new safety patterns or trends were identified.
- There were no SAEs or AEs leading to withdrawal from the study, and no clinically significant findings in vital sign, physical examination, or clinical laboratory assessments.
- Fibroid perfusion was noted on MRI in 1 of the 3 patients.
- Reduction in uterine and fibroid volume was observed in 2 of the 3 patients following embolization with OCL 503.
- Incomplete necrotic changes were seen in fibroid tissue for all 3 patients.
- Extrauterine necrosis was observed in 1 patient, while endometrial necrosis was noted in 2 patients.

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

Not applicable.

15 REFERENCE LIST

1. American College of Obstetricians and Gynecologists Technical Bulletin: An Educational Aid to Obstetrician-Gynecologists. Uterine Leiomyomata. 1994;192:863-870.
2. Lepine LA, Hillis SD, Marchbanks PA, Koonin LM, Morrow B and Kieke BA et al. Hysterectomy Surveillance - United States, 1980-1993. Morbidity and Mortality Weekly Reports. 1997;46:1-16.
3. National Center for Health Statistics. Ambulatory and Inpatient Procedures in the United States, 1996. Hyattsville, Maryland: Public Health Service, 1998; DHHS Publication No. (PHS) 99-1710.
4. Spies JB. What evidence should we demand before accepting a new embolic material for uterine artery embolization. Journal of Vascular and Interventional Radiology. 2009;20:567-570.
5. Worthington-Kirsch R, Siskin GP, Hegener P and Chesnick R. Comparison of the efficacy of the embolic agents acrylamido polyvinyl alcohol microspheres and tris-acryl gelatin microspheres for uterine artery embolization for leiomyomas: a prospective randomized controlled trial. Cardiovascular and Interventional Radiology. 2011;34:493-501.
6. Stokes L, Wallace M, Godwin R, Kundu S and Cardella J. Quality improvement guidelines for uterine artery embolization for symptomatic leiomyomas. Journal of Vascular and Interventional Radiology. 2010;21:1153-1163.
7. Jensen M, Karoly P and Braver S. The measurement of clinical pain intensity: a comparison of six methods. Pain. 1986;27:117-126.

16 APPENDICES

16.1 Study Information

16.1.1 Protocol and protocol amendments

16.1.2 Sample case report form (unique pages only)

16.1.3 List of institutional review boards (plus the name of the committee Chair if required by the regulatory authority) - representative written information for patient and sample consent forms

16.1.4 List and description of investigators and other important participants in the study, including brief (1 page) curriculum vitae or equivalent summaries of training and experience relevant to the performance of the clinical study

16.1.5 Signatures of principal or coordinating investigator(s) or sponsor's responsible medical safety officer, depending on the regulatory authority's requirement

16.1.6 Listing of patients receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used

16.1.7 Randomization scheme and codes (patient identification and treatment assigned) (not applicable)

16.1.8 Audit certificate (not applicable)

16.1.9 Documentation of statistical methods (not applicable)

16.1.10 Documentation of inter-laboratory standardization methods and quality assurance procedures if used (not applicable)

16.1.11 Publications based on the study (not applicable)

16.1.12 Important publications referenced in the report (not applicable)

16.2 Patient Data Listings

Case report form – Patient 001

Case report form – Patient 002

Case report form – Patient 003

Pathology report – Patient 001

Pathology report – Patient 002

Pathology report – Patient 003

16.3 Case Report Forms

16.3.1 Case report forms of deaths, other serious adverse events and withdrawals for adverse events (not applicable)

16.3.2 Other case report forms submitted (not applicable)

16.4 Individual Patient Data Listings (US Archival Listings) (not applicable)

Original Report Date: 31 August 2016

REVISIONS

Date	Comments	Initials
15 Nov 2016	Changes to the report: 1 ▪ Table 12-3 was amended to correct typographical errors a. Patient 002 / Visit 3 / Experienced nausea since the procedure changed from "no" to "yes" b. Patient 002 / Visit 5 / Pain in abdominal or pelvic regions since the procedure changed from "no" to "yes" 2 ▪ Page 42 – paragraph following Table 12-3 – verbiage corrected to address typographical errors in Table 12-3	15 NOV 2016