1 TITLE PAGE

Prostate Artery Embolization (PAE) Report

(Protocol OCL503-P2-PAE-01)

Test Product:	Occlusin® 500 Artificial Embolization Device
Indication:	Prostate Artery Embolization (PAE) for Benign Prostatic Hypertrophy (BPH)
Report Number:	OCL-500-CLN-003.0
Study Initiation Date:	11 September 2015
Study Completion Date:	27 February 2018
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: **17 April 2018**

APPROVAL SIGNATURE(S)

An Open Label, Single Center, Pilot Study to Evaluate the Safety and Effectiveness of OCL 503 in Prostate Artery Embolization for the Treatment of Men with Benign Prostatic Hypertrophy

Protocol No. OCL503-P2-PAE-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:

M.W. Stewart 19 April 2018

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

Date

Quality Assurance:

19 Apr 2018

Irwin Griffith, PhD
Management Representative, IMBiotechnologies Ltd

Date

Investigator Signature:

Richard Owen Apr/18 2018

Richard Owen, MD
Principal Investigator
University of Alberta Hospitals

Date

2 SYNOPSIS

Name of Company: *IM*Biotechnologies Ltd.	
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 Men with Benign Prostatic Hypertrophy (BPH)	
Principal Investigator: Dr. Richard Owen	
Study Center: University of Alberta Hospitals, Edmonton, Alberta, Canada.	
Publication (reference): None.	
Study Period: 11 September 2015 to 27 February 2018	
Objectives: <u>Primary Objectives:</u> • Evaluate the safety of OCL 503 for treatment of BPH in men with moderate to severe Lower Urinary Tract Symptoms (LUTS). • Evaluate the effect of OCL 503 on International Prostate Symptom Score (IPSS). <u>Secondary Objectives:</u> • Evaluate the effect of OCL 503 on uroflowmetry, International Index of Erectile Function (IIEF), prostate specific antigen (PSA) in men with BPH who have moderate to severe LUTS. • Evaluate the change in prostate volume following treatment with OCL 503.	
Methodology: This is a single center, open label pilot study. After screening and baseline testing, eligible patients underwent transarterial embolization of the prostate vasculature. After completion of treatment in the first 2 patients and review of follow-up assessments after 7 days, no safety concerns were identified. Subsequent patients were enrolled. All subjects were followed at 3 months, 6 months, and 12 months (end of study) post-embolization.	
Number of Patients (Planned and Analyzed): It was planned that 15 patients be treated. Ten (10) patients with BPH and moderate to severe LUTS have undergone PAE.	
Diagnosis and Main Criteria for Inclusion: Presence of enlarged prostate (benign prostatic hypertrophy; BPH) with moderate to severe LUTS.	

Name of Company: *IM*Biotechnologies Ltd.	
Name of Finished Product: OCL 503	
Name of Active Ingredient: Not applicable	

Test Product, Dose and Mode of Administration, Lot 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 and class IV by Health Canada. 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.

Infusion of embolic material was transarterial via catheter, following the Instructions For Use (IFU) and hospital's clinical practice. 400 mg OCL 503 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 1 mL sterile plastic syringe, and slowly delivered by microcatheter to the prostatic artery(ies) and monitored by fluoroscopy. OCL 503 was delivered to near stasis in the target vasculature. Near stasis embolization was defined as stasis of contrast agent in the main prostatic artery for 3 to 5 cardiac beats.

The following lot numbers were used in the study: C6832 (expiry date 28 December 2015), C7123 (expiry 28 December 2015); D2775 (expiry 28 June 2017).

Duration of Study Drug Treatment:

OCL 503 was delivered into the prostatic 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, prostate specific antigen [PSA])
- Occurrence of unanticipated adverse device effects (UADEs) and serious adverse events (SAEs).

Effectiveness:

- IPSS (primary)
- Uroflowmetry (Qmax, voiding time, voiding volume, post-void residual; secondary)
- MRI of prostate (secondary)

Other:

- IIEF
- Quality of Life

Statistical Methods:

Statistical analysis was conducted for the primary end-point efficacy assessment of IPSS, including Quality of Life (QoL) using SAS software. Change in IPSS, including QoL, was evaluated relative to baseline measurements. Non-parametric analysis was conducted using the Wilcoxon signed rank test.

Summary of Results:

Fifteen subjects were screened, 5 subjects failed screening, and 10 subjects were treated with OCL 503. All 10 treated subjects were Caucasian men ranging in age from 56 to 78 years.

Effectiveness:

Ten treated subjects were followed for 12 months post-embolization. Eight of 10 patients showing a decreased IPSS (decrease range 28.6% to 92.3%). The mean change in IPSS for all subjects at 12 months post-embolization in comparison to baseline was -37.6%, demonstrating an overall improvement in IPSS ($p = 0.01$).

In 9 of 10 subjects, QoL improved by 40.8% (95% confidence interval [CI] 0.7 to 3.3; 7-point scale) at 12 months.

Name of Company: *IM*Biotechnologies Ltd.	
Name of Finished Product: OCL 503	
Name of Active Ingredient: Not applicable	
Safety and Tolerability Results: There were 10 treated subjects. One subject experienced two adverse events (AEs) considered unrelated to administration of the test device (vertigo, hypokalemia). A second subject experienced fever, post-embolization, considered unrelated to administration of the test device. A third patient experienced nausea, typical of post embolization syndrome seen with other embolic agents. No subject experienced pain post-embolization. There were no clinically significant findings in vital signs, physical examination, or clinical laboratory assessments in any of the patients. No subject withdrew from the study. No ADEs, SADEs or UADEs were reported during the study.	
Date of Report: 17 April 2018	

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADE	Adverse device effect
AE	Adverse event
BPH	Benign prostatic hypertrophy
CA	Competent authority
CBC	Complete blood count
CI	Confidence interval
CSR	Clinical Study Report
CT	Computerized tomography
eCRF	Electronic case report form
GCP	Good clinical practice
GLP	Good laboratory practice
ICF	Informed consent form
ICH	International conference on harmonization
IFU	Instructions for use
IIEF	International index of erectile function
INR	International normalized ratio
IPSS	International prostate symptom score
IRB	Institutional review board
MRI	Magnetic resonance imaging
PAE	Prostatic artery embolization
PLGA	Poly-DL-lactide-co-glycolic acid
PT	Prothrombin time
PVR	Post void residual
QoL	Quality of life
SADE	Serious adverse device effect
SAE	Serious adverse event
SD	Standard deviation
SOC	Standard of care
TURP	Transurethral resection of the prostate
UADE	Unanticipated adverse device effect
VAS	Visual analog scale

4 REPORT CONTENTS

This report provides a summary of results obtained from study protocol OCL503-P2-PAE-01. Clinical study data including a full report are maintained at IMBiotechnologies in compliance with GCP guidelines and IMBiotechnologies Quality Management System.

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 University of Alberta institutional review board (IRB) prior to study initiation.

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 (GCP) guidelines and local legal requirements. The study complied 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 Health Canada guidelines. 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 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. A patient signed the approved ICF once the patient agreed to participate in the study. The original signed ICF was placed in the patient's permanent file. The Investigator 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. Any revision to the patient information or ICF required Sponsor and IRB approval in advance of use. 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 sign the revised form.

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

6 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. Maria Gasior (on behalf of BTG International Inc.)
Principal Investigator	Dr. Richard Owen Site Leader, Radiology and Imaging University of Alberta Hospital Edmonton, Alberta Canada
Urology	Dr. Ronald Moore and Dr. Shubha De Department of Urology University of Alberta Hospital
Central Laboratory	University of Alberta Hospital
Clinical Research Organization	ICON Clinical Research LLC 62 Forrest Street, Suite 300 Marlborough, Maryland 01752 USA
Data Management and Biostatistics	ICON Clinical Research LLC 62 Forrest Street, Suite 300 Marlborough, MA 01752 USA
Provision of study device	DSM Biomedical 735 Pennsylvania Drive Exton, Pennsylvania 19341 USA

7 INTRODUCTION

7.1 Background

Benign prostatic hyperplasia (BPH) with LUTS affects a large proportion of the male population. Symptoms include bladder-filling symptoms (urinary frequency, urgency, dysuria, nocturia), voiding symptoms (poor stream, hesitancy, terminal dribbling, incomplete voiding, overflow incontinence) as well as hematuria, acute urinary retention and sexual/erectile difficulties. The prevalence of BPH with LUTS increases with age, seen in approximately half of men over 80 years of age (McVary, 2006).

Treatment of moderate to severe LUTS due to BPH involves the medical control of symptoms with the use of 5-alpha reductase inhibitors, at times in combination with an alpha blocker (Juliao et al, 2012). A review of patient data conducted by Stroup et al (2012) showed that BPH-associated adverse events (AEs) including acute renal failure, urinary retention, bladder stones and urinary tract infections of hospitalized patients is increasing. The prevalence of acute renal failure increased by > 400% from 1998 to 2008.

In addition to age and androgen levels, other factors may contribute to hyperplasia of the prostate including metabolic syndrome, lifestyle, inflammation, and growth factor production (Yoo and Cho, 2012).

LUTS associated with BPH affect the patient's quality of life (QoL). Objective measures do not correlate well with the severity of symptoms (Priest et al, 2012). Symptom severity can be estimated using the international prostate symptom score (IPSS), prostate size, and uroflowmetry including measurement of maximum urine flow rate (Qmax) and post-void residual volume (PVR). The IPSS provides a severity measure of 7 key LUTS providing an overall assessment of QoL (Dias, 2012).

BPH patients, with moderate to severe LUTS who do not respond to medical therapy, can be treated using surgical procedures. Transurethral resection of the prostate (TURP) is performed on smaller prostates (60-80 cm^3), while prostatectomy is performed if patients present with larger prostates. Other techniques involve the use of intraprostatic stents, transurethral needle ablation, transurethral microwave therapy and laser vaporization (O'Donova et al, 2015; review).

Severe prostatic hemorrhage due to prostate cancer or BPH has been treated by embolization of branches of the internal iliac arteries, paving the way to purposeful treatment of BPH by PAE (O'Donova et al, 2015; review). Over the past several years, PAE has been studied as an alternative to TURP in patients that do not respond to medical therapy (Pisco et al, 2011; Carnevale et al, 2014).

PAE is similar to uterine artery embolization (UAE) in its recommended primary point of vascular access. Catheterization of the femoral artery allows access to the iliac arteries and ultimately the prostatic vasculature. Unlike UAE with its relatively predictable uterine vascular structure, the vasculature of the prostate is variable. Recent studies by Bilhim et al (2012) and others (Abele, et al, 2015) have highlighted the complexity of the prostatic vasculature.

PAE technique requires careful consideration of the prostatic vasculature in conjunction with the patient's medical history. Complications identified with PAE include post-embolization syndrome, rectal bleeding, constipation, haematuria and bladder retention. Pisco et al (2011) noted a single case of bladder ischemia requiring surgical intervention. Various groups have refined the PAE technique to improve both safety and efficacy of the procedure (Bagla et al, 2013; Carnevale et al, 2014; Bagla and Sterling, 2014). Embolic agents used in PAE are regulated by the United States Food and Drug Administration as Class II medical devices.

The assessments and procedures used in the study reported in this document are typical for the treatment of this patient population (men with LUTS associated with BPH) and have been selected to maximize patient safety and minimize risks. OCL 503 has been shown to be safe in preclinical studies and has FDA clearance for the treatment of unresectable and inoperable hypervascularized tumors (product code KRD). This investigation has been 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 this patient population.

Occlusin® 500 is a collagen-coated poly-DL-lactide-co-glycolic acid (PLGA) microsphere. The primary mechanism of action of Occlusin® 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, Occlusin® 500 also promotes vascular occlusion by consolidating clot formation by capturing platelets. Platelets bind to Occlusin® 500 by means of collagen covalently bound to the surface of the Occlusin® 500 particles. Preclinical studies and animal testing demonstrate that Occlusin® 500 promotes vascular occlusion. The United States Food and Drug Administration (FDA) has cleared Occlusin® 500 as a Class II artificial embolization device for the treatment of unresectable and inoperable hypervascularized tumors.

Occlusin® 500 microspheres comprise a series of size ranges. In this study, Occlusin® 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 reduce the symptoms of moderate to severe LUTS due to BPH. Primary endpoint measurement of IPSS was chosen based on study design employed by key opinion leaders conducting prostate artery embolization studies.

8 STUDY OBJECTIVES

8.1 Primary Objectives

The primary objectives of this study were to:

- Evaluate the safety of OCL 503 for treatment of BPH in men with moderate to severe LUTS.
- Evaluate the effect of OCL 503 on IPSS in men with moderate to severe LUTS due to BPH.

8.2 Secondary Objectives

The secondary objectives of this study were to:

- Evaluate the effect of OCL 503 on uroflowmetry, IIEF, PSA in men with BPH who have moderate to severe LUTS.
- Evaluate the change in prostate volume following treatment with OCL 503.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan - Description

This was a prospective, open-label, uncontrolled, non-randomized safety and effectiveness study of OCL 503 in men with BPH evidencing moderate to severe LUTS. All patients were treated with OCL 503 on Day 1. Only properly trained and qualified study personnel administered OCL 503 to the patient in the hospital. OCL 503 is a vascular embolization device designated as a Class IV device by Health Canada.

Prior to entering the study, all patients underwent pre-study assessments, including compliance with inclusion and exclusion criteria, laboratory assessments, IPSS, uroflowmetry, IIEF, and MRI pelvic imaging.

Each patient received transarterial embolization with OCL 503 following conventional catheter angiography with cone-beam computerized tomography (CT) to confirm catheter placement and prostate vasculature. OCL 503 was administered intra-arterially via a microcatheter until there was near stasis of blood flow (persistent visualization under fluoroscopy of contrast within the target prostatic 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, IPSS, uroflowmetry, IIEF, MRI and patient interviews were conducted at 3 months, 6 months, and 12 months post embolization.

The first 2 patients were treated and follow-up assessments were reviewed after 7 days. Subsequent patients were enrolled as no safety concerns were observed in the first 2 patients. Safety was assessed throughout the study.

9.2 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 LUTS in men with BPH by PAE and have been selected to maximize patient safety and minimize risks (Bilhim et al, 2016).

Patient's baseline data were used as control in comparison to data collected for each patient at time points specified in the study. Patients with moderate to severe LUTS associated with BPH, who have attempted life style modification experience no change or worsening of symptoms in the absence of intervention (McVary et al, 2010).

Occlusin® 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). Occlusin® 500 was demonstrated to be non-toxic and biocompatible in *in vitro*, preclinical *in vivo* studies, and clinical studies. Occlusin® 500 was shown to be safe in preclinical studies including laboratory studies, biocompatibility assessment, and histological analysis. Preclinical studies showed OCL 503 (150 to 212 μm) and OCL 505 (300 to 425 μm) 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 showed OCL 503 to be a safe and effective artificial

embolization device. OCL 503 (150-212 µm) was chosen as the embolic agent for this PAE study based upon microsphere size (Bilhim et al, 2013).

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

Men diagnosed with BPH with moderate to severe LUTS, who are not considered to be part of a vulnerable population, were eligible for this study if they met the following criteria:

1. Have received a diagnosis of BPH with moderate to severe LUTS, as determined by IPSS
2. Are greater than 50 years of age
3. Have had a pelvic examination by a urologist within the previous 6 months
4. Have been refractory to medical therapy for 6 months, or have refused medical therapy
5. Have a Qmax below 15 mL/s or acute urinary retention
6. Have a prostate larger than 40 cm^3 (IRB allowed a decrease from an initial volume larger than 50 cm^3)
7. Are 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. Have a known malignancy
2. Have a total serum PSA > 10.0 ng/mL at screening
3. Have advanced atherosclerosis and tortuosity of the iliac arteries
4. Have had a prior TURP
5. Have a PVR > 250 mL
6. Chronically use metronidazole
7. Have used phytotherapy for BPH within 2 weeks of the screening visit
8. Have secondary renal insufficiency (due to prostatic obstruction)
9. Have chronic renal failure (glomerular filtration rate < 60)
10. Have large bladder diverticula or bladder stones
11. Have claustrophobia or other contraindications to the performance of the pre- and post-procedure MRI studies, including but not confined to the presence of metal implants, metal plates, bone pins, bone screws, neurostimulators, cardiac pacemakers, aneurysm clips, cochlear or retinal implants, or permanent hearing aids
12. Have compromised hematopoietic function (hemoglobin < 100 g/L; lymphocyte count < 500 $x10^6$/L; neutrophil count < 1.5 x 10^9/L; platelet count < 50 x 10^9/L
13. Have 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. Have received other investigational drugs or who have had experimental therapy within the past 4 weeks or are participating in any other concurrent experimental therapy
15. Have abnormal coagulation profiles

16. Are allergic to bovine collagen
17. Are unable to comply with the follow-up requirements of the study.

9.3.3 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 Investigator 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 Investigator, 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 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 withdraw from the study will 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.

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 PAE procedure, a minimally invasive technology for reducing symptoms of BPH in men with moderate to severe LUTS. Following a pelvic angiogram to delineate the prostatic vasculature and ensure catheter placement with cone-beam CT, embolization procedures of the left and right prostatic arteries (as required) were performed on each patient. OCL 503 (150-212 μm diameter) microspheres were delivered by microcatheter, with a starting dose of approximately 400 mg of OCL 503. OCL 503 particles were 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.

9.4.2 Identification of Investigational Device

For this study, Occlusin® 500 was provided in the single size range of 150 to 212 µm in diameter (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 (IFU) were provided with each shipment of vials.

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.

DSM Biomedical (Exton, PA) manufactured OCL 503 for IMBiotechnologies in compliance with Good Manufacturing Practice. The following lot numbers were used in the study: C6832 (expiry 28 December 2015), C7123 (expiry 28 December 2015), and D2775 (expiry 28 June 2017).

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 with cold packs. Upon arrival, OCL 503 was 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 503 in the Department of Radiology, University of Alberta Hospital.

9.4.3 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 to be administered until there was persistent visualization under fluoroscopy of contrast within the target prostatic vasculature for 3 to 5 cardiac beats.

9.4.4 Selection and Timing of Dose for Each Patient

See 9.4.1.

9.4.5 Blinding

This was an open label study.

9.4.6 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 routinely received 8 mg of dexamethazone prior to the procedure, and anti-inflammatory medications (ibuprofen 400 mg TID or equivalent) and prophylactic antibiotics (Cefazolin 1) following the procedure.

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, analgesics.
- Antipyretics.
- Antiemetics.
- Additional non-steroidal anti-inflammatory drugs.

Any treatments administered were to be documented on the eCRF.

9.4.7 Treatment Compliance

Administration of the investigational device (OCL 503) was performed under the supervision of the Investigator or PI 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 facilitate 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

	Pre-Study		Study				End of Study	Unscheduled Visits
TIME (weeks)	Within 6 months of study start	Within 1 month of study start	1		13	25	53	
TIME (calendar days)		-28	1	7±2	97±7	187+7	372±14	
VISIT NO.		1	2	3	4	5	6	
Informed Consent		X						
History (Medical, Surgical, or Pelvic Exam)	X	X						
Physical Examination, vital signs		X	X		X	X	X	X
MRI Imaging of Pelvis – Prostate Volume		X			X	X	X	
Cone-beam CT			X					
Patient Interview & VAS				X	X	X	X	X
ADMINISTRATION OF OCL 503 /PAE			X					
PSA Test		X			X	X	X	X
Complete Blood Cell Count		X	X		X	X	X	X
Serum Chemistry		X	X		X	X	X	X
Coagulation Profile		X	X		X	X	X	X
Uroflowmetry		X			X	X	X	X
IPSS		X			X	X	X	X
IIEF		X			X	X	X	X
Adverse Events			X	X	X	X	X	X
Chart Review & Concomitant meds				X	X	X	X	X

CT = computerized tomography, IIEF = international index of erectile function, IPSS = international prostate symptom score, OCL = Occlusin® Artificial Embolization Device, PSA = prostate specific antigen

9.5.1.1 Effectiveness Assessments

9.5.1.1.1 IPSS Questionnaire

Changes in symptoms associated with BPH were determined by administering the IPSS questionnaire at baseline, 3 months post-embolization, 6 months post-embolization, and 12 months post-embolization. The IPSS questionnaire was originally developed and validated by Barry et al, 1992. The questionnaire consists of 7 questions with multiple choice answers graded from 0 to 5, with a value of 5 representing the highest symptom score in each question. The questions address frequency of urination, nocturia, strength of voiding, hesitancy during voiding, intermittence of voiding, incomplete emptying of the bladder, and urgency (Barry et al, 1992). The study by Barry et al demonstrated a high correlation between the calculated score and patients' lower urinary tract symptoms. The IPSS questionnaire also contains a quality of life (QoL) component asking the subject to evaluate how they would feel if they were to spend the rest of their life with their current urinary condition. Multiple choice answers are provided with grades of 0 (delighted) through to 6 (terrible).

9.5.1.1.2 Uroflowmetry Assessment

Uroflowmetry studies can assist in the diagnosis of common lower urinary tract dysfunctions (Jarvis et al, 2012). Uroflowmetry measurements were conducted at baseline, 3 months post-embolization, 6 months post-embolization, and 12 months post-embolization. Measurements included maximum urine flow rate (Qmax), urination time, voiding volume, and post-void bladder retention (determined by ultrasound).

9.5.1.1.3 Prostate Volume

Prostate volume measurement using magnetic resonance imaging (MRI) has been shown to be reliable in providing estimates of prostate volume (Paterson et al, 2016). Prostate volume was determined by MRI at baseline, 3 months post-embolization, 6 months post-embolization, and 12 months post-embolization. A blinded radiologist was responsible for review and documentation of the MRI images. The MRI protocol included T2-weighted half-Fourier acquisition single-shot turbo spin echo (HASTE) (axial, sagittal, and coronal), T1 gradient echo (GRE) axial, and 3D volume analysis.

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 PAE 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.

9.5.1.2.2 Laboratory Safety Assessments

Standard laboratory tests, conducted at the local laboratory were performed at the times specified in Table 9-2. Laboratory tests for hematology, coagulation, blood chemistry, and PSA were performed to assess effects of the study treatment. The Investigator 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 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.

The laboratory safety assessments performed during the study are presented in Table 9-2.

Table 9-2 Laboratory Safety Assessment

Hematology: Complete blood count	**Coagulation:** Prothrombin time (PT/INR)
Serum chemistry: Alkaline phosphatase Aspartate aminotransferase Alanine aminotransferase Bilirubin (total) Total Protein Creatinine Prostate specific antigen	

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 International Index of Erectile Function (IIEF) Questionnaire

Non-target embolization of pelvic vasculature can lead to erectile or orgasmic dysfunction (Rayt et al, 2008). The IIEF questionnaire has been used to assess erectile function to monitor safety and efficacy of various therapies, especially treatment of erectile dysfunction (Rosen et al, 2002). The IIEF was used to assess safety related to non-target embolization of pelvic vasculature. The IIEF was administered at baseline, 3 months post-embolization, 6 months post-embolization, and 12 months post-embolization.

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.

Patient interviews were conducted per the Investigator's usual procedure with therapeutic embolization patients, according to the IIEF and IPSS questionnaires and the Visual Analogue Scale (VAS) for pain (see protocol Attachment D). Patient interview questions assessed pain associated with the procedure and pain which may have occurred since the procedure, non-target embolization indicators such as blood in urine and rectal bleeding, as well as fever and nausea. Interviews were conducted at 7 days, 3 months, 6 months, and 12 months post-embolization. Questioning at 7 days assessed patient well-being from the day of treatment to the 7-day time

point. Study subject interviews at the 3, 6 and 12-month time points assessed patient well-being at the specific time point.

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

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

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.

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 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 Investigator 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 Investigator or investigational site personnel.

9.7 Statistical Analysis

9.7.1 Statistical and Analytical Plans

Statistical analysis was conducted for the primary end-point efficacy assessment of IPSS, including QoL using SAS (version 9.4) software by an independent biostatistician. Change in IPSS and QoL was evaluated relative to baseline for the 3-month, 6-month, and 12-month follow-up visits, post-embolization. Non-parametric analysis was conducted using the Wilcoxon signed rank test. Refer to Appendix 16.1 for statistical analysis.

9.7.1.1 Study Populations

Not applicable.

9.7.1.2 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 primary endpoint analysis of IPSS, including quality of life. Statistical analysis was conducted using the Wilcoxon sign rank method. Any *post hoc* statistical analysis considered to be constructive was exploratory in nature.

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

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. No patients withdrew from the study. There were no reported ADEs, SADEs or UADEs.

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 have been 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.

9.7.1.2.1 Demographic and Baseline Characteristics

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

9.7.1.2.2 Concomitant Medication

Concomitant medications, including any medication used to treat AEs, were 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 the embolization procedure were collected and listed in the individual patient eCRFs.

9.7.1.2.4 Effectiveness Analysis

Effectiveness analyses was conducted based on the primary endpoint IPSS at 12 months post-embolization. IPSS was also analyzed at 3-months and 6-months post embolization, and QoL was assessed at 3, 6, and 12 months post-embolization. Uroflowmetry and MRI assessments at screening and post-embolization were evaluated as secondary objectives. The latter analyses were primarily descriptive.

9.7.1.2.5 Safety Analysis

Safety analyses were based on the clinical and laboratory adverse effects observed in 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 15 men with BPH were treated with OCL 503. Allowing for a 40% drop out rate, the total enrollment was to be up to 25 patients to allow

15 evaluable patients. The study was terminated after treating 10 subjects due to prolonged enrolment. 15 men with BPH were enrolled in the study, with 10 men treated with OCL 503.

9.7.3 Control of Systematic Error/Bias

This is a single center study so there was no bias from over enrollment at 1 site. All patients were treated with the same product so there was no bias introduced from patient treatment. All patients were embolized by the same Interventional Radiologist so there was no intraoperative variability. Investigators 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 films.

10 STUDY PATIENTS

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

10.1 Disposition of Patients

15 patients were enrolled; 5 patients were not treated as they failed to meet all the inclusion/exclusion criteria, and 10 patients were treated with the study product. Table 10-1 provides a summary of screen failures for consented patients.

Table 10-1 Screen Failures

Study Subject	Criterion and Number	Reason for Screen Failure
003	Inclusion 6	Prostate did not meet minimum volume criterion
	Exclusion 5	Post-void urine retention was greater than 250 ml
004	Inclusion 6	Prostate did not meet minimum volume criterion
006	Exclusion 3	Vascular tortuosity
007	Exclusion 3	Vascular tortuosity
009	Exclusion 5	Post-void urine retention was greater than 250 ml

10.2 Protocol Deviations

Study subject 001was not tested for C-reactive protein (CRP) for visit 2 bloodwork. This was not considered a major deviation from the protocol. The principal investigator confirmed that the CRP level at screening was sufficient. Study subject 005 was unable to attend his 12-month follow-up visit as scheduled. This was not considered a major deviation from the protocol, and follow-up testing was conducted 2 weeks beyond the 6-month visit window. Study subject 008 had a Qmax of 15 ml/s at screening which is the cutoff level for enrolment. The subject was enrolled in the study with the approval of the sponsor. This had no impact on patient safety and was not considered a major deviation from the protocol. Study subject 008 was unable to attend his 3-month follow-up visit as scheduled. This was not considered a major deviation from the protocol, and follow-up testing was conducted 5 days earlier than scheduled. Study subject 011 did not have a differential count completed for visit 2 bloodwork due to a laboratory error. The principal investigator confirmed that repeat blood work was not required. This was not considered a major deviation from the protocol. Study subject 12 was unable to attend his 6 month visit as scheduled. This was not considered a major deviation from the protocol, and follow-up testing was conducted 2 days later than the scheduled visit window with sponsor approval. Study subject 14 was unable to attend visit 2 as scheduled. This was not considered a major deviation from the protocol and visit 2 was conducted 1 day later than scheduled. Study subject 0014 was unable to attend his 6-month follow-up visit, as scheduled. This was not considered a major deviation from the protocol, and follow-up testing for this time point was

conducted 2 days past the study visit window with approval of the sponsor. Study subject 015 had Visit 2 blood work collected 2 days before the study window. This was not considered a major deviation from the protocol.

11 EFFECTIVENESS EVALUATION

Data presented was monitored by an independent clinical research organization.

11.1 Data Sets Analyzed

Not applicable.

11.2 Demographic and Other Baseline Characteristics

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

11.2.1 Demographic Characteristics and Screening Results

Demographic characteristics and screening results for all patients enrolled, to date, are presented in Table 11-1. Height, weight and BMI were not determined for patients that failed screening.

Table 11-1 Demographic Baseline Characteristics of Treated Subjects

Parameter	001	002	005	008	010	011	012	013	014	015
Age (years)	73	63	64	56	62	78	59	66	65	59
Race	White	White	White	White	White	White	White	White	White	White
Height (cm)	179	172.1	170	183	184.5	172	178	185.4	178	170
Weight (kg)	98	89	94.2	101.6	86.4	94.5	100	88.6	77	78.5
BMI (kg/m^2)	30.6	26.9	32.6	30.3	25.4	31.9	31.6	25.8	24.3	27.2

Abbreviations: BMI=body mass index

The average age of the subjects treated in the study (n=10) is 64.5 ± 6.7 (sd) years, with an age range of 56 to 78 years (median 63.5).

11.2.2 Medical and Surgical History

Medical and surgical history for all enrolled patients is presented in Table 11-2. All enrolled subjects were diagnosed with BPH with moderate to severe LUTS.

Table 11-2 Medical History of Treated Subjects

Patient	Disease / Procedure	Start Date	Stop Date	Ongoing / Prior Medication
001	Rotator Cuff Repair	1990	1990	
	Vasectomy	1995	1995	
	Hernia Repair	2005	2005	Pantaloc
	Hypertension	2008	2008	Metoprolol, Tiazac, Ramipril
	Angioplasty	2008	2008	Plavix, Aspirin, Ezatrol
	Benign Prostatic Hypertrophy	Unknown	Ongoing	Tamsulosin
002	Acoustic Neuroma	2009	2009	
	Hypertension	2010	Ongoing	Coresyl, Bisoprolol, Perindopril, Amilodipine
	Diabetes – Type 2	2010	Ongoing	Metformin
	Back Surgery	2010	2010	
	Sleep Apnea	2012	Ongoing	
	Hypokalaemia	2015	Ongoing	K-Dur, Potassium Chloride
	Prevention of Heart Attack	Unknown	Ongoing	Prevastatin, Aspirin
	Benign Prostatic Hypertrophy	Unknown	Ongoing	Dutasteride, Tamsulosin
005	Gastric Reflux	2010	Ongoing	Lansoprazole
	Hypertension	2015	Ongoing	Perindopryl
	Benign Prostatic Hypertrophy	Unknown	Ongoing	
008	Tonsillectomy	1969	1969	
	Vasectomy	1992	1992	
	Asthma	2006	Ongoing	Symbicort
	Hypertension	2006	Ongoing	Amilodipine
	Prevention of Gastric Indigestion	Unknown	Ongoing	Tecta
	Benign Prostatic Hypertrophy	Unknown	Ongoing	Flomax, Dutasteride
010	Benign Prostatic Hypertrophy	Unknown	Ongoing	
	Prevention of Swelling	Unknown	2016	Dexamethasone
011	Bowel Resection	1978	1978	
	Right Hip Arthroplasty	2009	2009	
	Left Hip Arthroplasty	2016	2016	
	Hypothyroid	2016	Ongoing	Synthroid
	Benign Prostatic Hypertrophy	Unknown	Ongoing	Flomax

012	Tonsillectomy	1962	1962	
	Left Forearm Fracture	1971	1971	
	Blepharoplasty	2007	2007	
	Laser Eye Surgery (Right Eye)	2012	2012	
	High Blood Pressure	Unknown	Ongoing	Ramapril
	Benign Prostatic Hypertrophy	Unknown	Ongoing	
013	Benign Prostatic Hypertrophy	Unknown	Ongoing	
	Prevention of Heart Attack	Unknown	Ongoing	Rosuvastatin
014	Nail Ablation	2010	2010	
	Cholesterol Lowering	Unknown	2010	Tecta
	Benign Prostatic Hypertrophy	Unknown	2016	Symbacort, Tamulosin, Flomax
015	Tendon Surgery (Right Wrist)	2013	2013	
	Benign Prostatic Hypertrophy	Unknown	Ongoing	Flomax

11.3 Measurements of Treatment Compliance

Not applicable.

11.4 Effectiveness Results and Tabulations of Individual Patient Data

Efficacy data were collected in the individual patient eCRFs.

11.4.1 Effectiveness Analysis

11.4.1.1 IPSS Assessment and QoL

The results for IPSS assessment and QoL for each treated subject are presented in Table 11-3. A high IPSS score is representative of severe LUTS, and a reduced IPSS score as improvement in symptoms. The QoL scale assessing the subject's view of their urinary condition ranged from 0 (delighted) to 6 (terrible).

Table 11-3 IPSS and QoL

Subject Number	Pre-Embolization Baseline	Post-Embolization Follow-up		
		3 Months	6 Months	12 Months (End of Study)
001	IPSS = 26	IPSS = 5 (-80.8%)	IPSS = 5 (-80.8%)	IPSS = 10 (-61.5%)
	QoL = 5	QoL = 0	QoL = 1	QoL = 1
002	IPSS = 26	IPSS = 16 (-38.5%)	IPSS = 18 (-30.8%)	IPSS = 23 (-11.5%)
	QoL = 6	QoL = 3	QoL = 4	QoL = 5
005[1]	IPSS = 21	IPSS = 12 (-42.9%)	IPSS = 14 (-33.3%)	IPSS = 16 (-23.8%)
	QoL = 4	QoL = 2	QoL = 2	QoL = 3
008[2]	IPSS = 21	IPSS = 10 (-52.4%)	IPSS = 29 (38.1%)	IPSS = 21 (0%)
	QoL = 4	QoL = 2	QoL = 5	QoL = 4
010	IPSS = 23	IPSS = 12 (-47.8%)	IPSS = 8 (-65.2%)	IPSS = 27 (17.4%
	QoL = 5	QoL = 0	QoL = 1	QoL = 4
011	IPSS = 18	IPSS = 7 (-61.1%)	IPSS = 15 (-16.7%)	IPSS = 12 (-33.3%)
	QoL = 4	QoL = 3	QoL = 2	QoL = 2
012[3]	IPSS = 28	IPSS = 13 (-53.6%)	IPSS = 13 (-53.6%)	IPSS = 17 (-39.3%)
	QoL = 5	QoL = 3	QoL = 3	QoL = 3
013	IPSS = 25	IPSS = 10 (-60.0%)	IPSS = 9 (-64.0%)	IPSS = 7 (-72.0%)
	QoL = 4	QoL = 3	QoL = 2	QoL = 2
014[4]	IPSS = 26	IPSS = 2 (-92.3%)	IPSS = 3 (-88.5%)	IPSS = 1 (-96.2%)
	QoL = 6	QoL = 0	QoL = 0	QoL = 0
015	IPSS = 28	IPSS = 20 (-28.6%)	IPSS = 20 (-28.6%)	IPSS = 17 (-39.3%)
	QoL = 6	QoL = 5	QoL = 5	QoL = 5

Values in brackets indicate the percentage change from baseline.

[1]End of study assessment for Subject 005 was conducted 2 weeks later than scheduled. [2]Visit 4 for subject 008 occurred 5 days earlier than scheduled. [3]Visit 5 for subject 012 occurred 2 days later than scheduled. [4]Six month assessment for Subject 0014 was conducted 1 day later than scheduled.

Baseline IPSS was determined to be 24.2 ± 3.3 (range 18.0 to 28.0; median = 25.5). A decrease in IPSS score was noted for all patients at the 3-month follow-up visit (mean IPSS = 10.7 ± 5.2; median = 11.0; range = -28.6% to -92.3%) indicating the patients had fewer / less severe lower urinary tract symptoms (95% CI 9.7 to 17.3). QoL improvement was noted in all patients at 3 months (range -1 to -6; 95% CI 1.5 to 4.1).

A decrease in IPSS score was noted for 9 of 10 patients at the 6-month follow-up visit (mean IPSS = 13.4 ± 8.4; median = 13.5; range = 38.1% to -88.5%; mean change of all patients = -42.3%; 95% CI 4.2 to 17.4), in comparison to baseline. QoL improved for 9 of 10 patients at the 6-month follow-up visit, in comparison to baseline (range 0 to -6; 95% CI 1.0 to 3.8).

A decrease in IPSS was noted for 8 of 10 patients at 12 months follow-up over baseline scores, with one patient showing an increase and one patient showing no change (mean IPSS = 15.1 ± 7.8; median = 16.5; range = -11.5% to -61.5%; p = 0.01). QoL improved statistically in 9 of 10 patients followed out to 12 months, in comparison to baseline, with one patient showing no change (range 0 to -6; 95% CI 0.7 to 3.3).

Statistical analysis of IPSS and QoL for the study population is provided in Appendix 16.1.

11.4.1.2 Uroflowmetry Assessment

Uroflowmetry analysis evaluated the strength of the subject's voiding stream (Qmax), the voiding volume, the post-void residual urine in the bladder, and the voiding time. The average volume of urine delivered per unit time was derived from the voiding volume and the time required to complete urination. The results of the uroflowmetry assessment for each patient are presented in Table 11-4.

Table 11-4 Uroflowmetry Results

Subject Number	Parameter	Pre-Embolization Baseline	Post-Embolization Follow-up		
			3 Months	6 Months	12 Months
001	Qmax (ml/s)	9	7	9	8
	Voiding Volume	127	270	171	106
	PVR (ml)	38.9	138	158	36
	Voiding Time (s)	765	733	738	795
	Q-mean (ml/s)	0.17	0.37	0.21	0.13
002	Qmax (ml/s)	8	12	12	8
	Voiding Volume	92	129	295	111
	PVR (ml)	7	8	15.5	11.5
	Voiding Time (s)	780	734	790	705
	Q-mean (ml/s)	0.12	0.18	0.37	0.16
005[1]	Qmax (ml/s)	6	6	5	7
	Voiding Volume	241	457	161	175
	PVR (ml)	217	217	162	175

Subject Number	Parameter	Pre-Embolization Baseline	Post-Embolization Follow-up		
			3 Months	6 Months	12 Months
	Voiding Time (s)	813	718	702	705
	Q-mean (ml/s)	0.30	0.64	0.23	0.25
008[2]	Qmax (ml/s)	15	17	14	10
	Voiding Volume	320	320	144	100
	PVR (ml)	63	26	4	3
	Voiding Time (s)	750	780	720	730
	Q-mean (ml/s)	0.43	0.41	0.20	0.14
010	Qmax (ml/s)	4	5	4	5
	Voiding Volume	96	167	432	90
	PVR (ml)	13.2	12.2	4	5
	Voiding Time (s)	740	835	770	735
	Q-mean (ml/s)	0.13	0.2	0.56	0.12
011	Qmax (ml/s)	11	15	16	8
	Voiding Volume	214	216	183	274
	PVR (ml)	40.5	73.1	91.7	114
	Voiding Time (s)	710	740	720	705
	Q-mean (ml/s)	0.30	0.29	0.25	0.39

Subject Number	Parameter	Pre-Embolization Baseline	Post-Embolization Follow-up		
			3 Months	6 Months	12 Months
012[3]	Qmax (ml/s)	13	20	17	16
	Voiding Volume	179	239	198	225
	PVR (ml)	43.1	17.8	33.8	49.5
	Voiding Time (s)	723	660	720	670
	Q-mean (ml/s)	0.25	0.36	0.28	0.34
013	Qmax (ml/s)	6	6	6	4
	Voiding Volume	127	119	123	104
	PVR (ml)	25	12	35.9	13.7
	Voiding Time (s)	765	720	710	805
	Q-mean (ml/s)	0.17	0.17	0.17	0.13
014[4]	Qmax (ml/s)	4	18	15	11
	Voiding Volume	160	239	250	305
	PVR (ml)	98	4	14.9	33
	Voiding Time (s)	555	725	720	720
	Q-mean (ml/s)	0.29	0.33	0.35	0.42
015	Qmax (ml/s)	12	7	11	7
	Voiding Volume	216	113	227	135
	PVR (ml)	36	33.7	21	5
	Voiding Time (s)	685	780	720	675
	Q-mean (ml/s)	0.31	0.14	0.32	0.2

[1]End of study assessment for Subject 005 was conducted at 13 months post-embolization. [2]Visit 4 for subject 008 occurred 5 days earlier than scheduled. [3]Visit 5 for subject 012 occurred 2 days later than scheduled. [4]Six month assessment for Subject 0014 was conducted 1 day later than scheduled.

Qmax increased in 6 subjects, decreased in 2 subjects, and remained unchanged in 2 subjects at the 3-month follow-up visit. Qmax increased in 4 subjects, decreased in 3 subjects and remained unchanged in the remaining 3 subjects tested at the 6-month follow-up visit. Qmax increased in 4 subjects, decreased in 5 subjects, and was unchanged in 1 subject followed out to 12 months.

Post void retention (PVR), as measured by ultrasound, increased in 3 subjects, decreased in 6 subjects and remained unchanged in 1 subject at the 3-month follow-up visit, in comparison to baseline. PVR increased in 4 subjects and decreased in 6 subjects at the 3-month follow-up visit, in comparison to baseline. PVR increased in 3 subjects and decreased in 7 subjects at the 12-month follow-up visit in comparison to baseline. PVR did not exceed the exclusion criterion maximum of 250 ml in any treated study subject, at any time point. Ultrasound demonstrated hyper-echoic areas in the prostate post-embolization consistent with the hyper-echoic properties of the embolic agent.

Voiding volume increased in 7 subjects, decreased in 2 subjects and was unchanged in 1 subject at the 3-month follow-up visit. Voiding volume increased in 6 subjects and decreased in 4 subjects at the 6-month follow-up visit. Of 10 subjects followed out to 12 months, the voiding volume increased in 4 subjects, decreased in 6 subjects, and remained essentially unchanged in the remaining subject.

Voiding time increased in 5 subjects and decreased in 5 subjects at the 3-month follow-up visit. Voiding time increased in 5 subjects, decreased in 5 subjects at the 6-month follow-up visit. Of 10 subjects followed out to 12 months, the voiding time increased in 3 subjects and decreased in 7 subjects.

The average rate of urination increased in 6 subjects, decreased in 3 subjects, and was unchanged for 1 subject at the 3-month follow-up visit. The average rate of urination increased in 6 subjects, decreased in 3 subjects, and remained unchanged in the remaining subject at the 6-month follow-up visit. Of 10 subjects followed out to 12 months, the average rate of urination increased in 4 subjects and decreased in 6 subjects.

11.4.1.3 Prostate Volume

MRI was used to assess prostate volume. The results of the prostate volume assessment are presented in Table 11-5 for each patient. Prostate volume did not change dramatically at any time point.

Table 11-5 Prostate Volume (ml)

Subject Number	Pre-Embolization Baseline	Post-Embolization Follow-up		
		3 Months	6 Months	12 Months (End of Study)
001	160.0	161.8	158.0	165.3
002	91.0	80.8	107.0	106.4
005[1]	63.5	55.5	55.5	62.8
008[2]	70.1	59.7	68.0	73.6
010	202.4	207.4	201.2	215.0
011	97.7	107.2	99.0	109.0
012[3]	44.5	53.1	54.3	57.0
013	42.9	50.6	35.5	38.7
014[4]	44.5	42.6	45.0	51.2
015	56.6	40.0	55.8	55.0

[1]End of study assessment for Subject 005 was conducted at 13 months post-embolization. [2]Visit 4 for subject 008 occurred 5 days earlier than scheduled. [3]Visit 5 for subject 012 occurred 2 days later than scheduled. [4]Six month assessment for Subject 0014 was conducted 1 day later than scheduled.

The mean prostate volume of the 10 subjects followed to 12 months remained essentially unchanged in comparison to baseline; 93.40 ± 61.20 ml versus 87.87 ± 49.72 ml, respectively.

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 formal 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 Effectiveness Summary – Primary Endpoint

Of the 10 men treated, 6 underwent bilateral prostatic artery embolization and 4 underwent unilateral embolization. In the studied population of men with BPH associated with moderate to severe LUTS treated with Occlusin® Embolization microspheres the following observations were noted:

- IPSS (primary endpoint measurement) improved in all subjects at 3 months (95% CI 9.7 to 17.3), in 9 of 10 subjects at 6 months (95% CI 4.2 to 17.4), and 8 of 10 subjects at 12 months ($p = 0.01$ primary endpoint), post-embolization.
- QoL assessed using a 7-point scale (0 – 6), as part of the IPSS, improved in all subjects at 3 months (95% CI 1.5 to 4.1), and in 9 of 10 subjects at 6 months (95% CI 1.0 to 3.8) and 12 months (95% CI 0.7 to 3.3) post-embolization.
- The mean prostate volume did not change over the study.
- Uroflowmetry parameters in the 10 subjects followed to 12 months were variable over the study period.

12 SAFETY EVALUATION

The dose of OCL 503 administered, duration of procedure, and safety data were collected in the individual patient eCRFs.

12.1 Exposure to Investigational Product

The dose of OCL 503 administered, duration of embolization procedure, and outcome (whether near stasis was achieved for the target vasculature) for treated subjects 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 Administration of Investigational Product

Subject Number	OCL 503 Administered (mg)	OCL 503 Administered (microsphere	Near Stasis Embolization	Embolization	Embolization Time (min)
001	250	107,664	Yes	Bilateral	33
002	150	64,599	Yes	Bilateral	62
005	100	43,066	Yes	Unilateral	58
008	130	55,985	Yes	Bilateral	35
010	340	146,244	Yes	Bilateral	51
011	120	51,679	Yes	Unilateral	34
012	210	90,438	Yes	Bilateral	42
013	70	30,146	Yes	Unilateral	72
014	120	51,569	Yes	Unilateral	110
015	120	51,679	Yes	Bilateral	107

[1]The number of microspheres in a 400 mg vial of OCL 503 = 172,263 (430.66 microspheres per mg)

Near-stasis embolization was achieved in all patients treated (successful embolization). Successful embolization required less than 1 vial of investigational product per procedure. In bilateral embolizations more product was used to embolize the first side in comparison to the second side, regardless of which side was embolized first. Four subjects underwent unilateral embolization. The treating physician was unable to access the contralateral vasculature with a guidewire in the unilateral embolization patients due to vascular tortuosity or due to lack of vascular supply to the contralateral side. The time required for embolization ranged from 33 to 110 minutes.

Investigational product was stored in a secured safe within a secured office. Access to investigational product was limited to the Principal Investigator and the Study Coordinator. Temperature within the secured safe was monitored constantly, with readings recorded weekly. A temperature recording device malfunctioned during a monitoring visit and was replaced the same day. There were no effects on the study product.

12.2 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 12-2.

Table 12-2 Pain Score

Subject Number	Follow-Up			
	7 Days	3 Months	6 Months	12 Months (End of
001	0	0	0	0
002	0	0	0	0
005[1]	0	0	0	0
008[2]	0	0	0	0
010	0	0	0	0
011	0	0	0	0
012[3]	0	0	0	0
013	0	0	0	0
014[4]	0	0	0	0
015	0	0	0	0

[1]End of study assessment for Subject 005 was conducted at 13 months post-embolization. [2]Visit 4 for subject 008 occurred 5 days earlier than scheduled. [3]Visit 5 for subject 012 occurred 2 days later than scheduled. [4]Six month assessment for Subject 0014 was conducted 1 day later than scheduled.

All treated patients reported no pain associated with the embolization procedure, and no pain post-embolization at all follow-up time points recorded.

Response to interview questions at follow-up visits are summarized in Table 12-3.

Table 12-3 Responses to Interview Questions

Subject Number	Question	Post-embolization Follow-up			
		7 Days	3	6	12 Months
001	Have you experienced pain in your abdominal or	N	N	N	N
	Have you experienced fever since the procedure?	N	N	N	N
	Have you experienced blood in your urine since the	N	N	N	N
	Have you experienced rectal bleeding since the	N	N	N	N
	Have you experienced nausea since the procedure?	N	N	N	N
002	Have you experienced pain in your abdominal or	N	N	N	N
	Have you experienced fever since the procedure?	N	N	N	N
	Have you experienced blood in your urine since the	N	N	N	N
	Have you experienced rectal bleeding since the	N	N	N	N
	Have you experienced nausea since the procedure?	N	N	N	N

005	Have you experienced pain in your abdominal or	N	N	N	N
	Have you experienced fever since the procedure?	N	N	N	N
	Have you experienced blood in your urine since the	N	N	N	N
	Have you experienced rectal bleeding since the	N	N	N	N
	Have you experienced nausea since the procedure?	N	N	N	N
008	Have you experienced pain in your abdominal or	N	N	N	N
	Have you experienced fever since the procedure?	N	N	N	N
	Have you experienced blood in your urine since the	N	N	N	N
	Have you experienced rectal bleeding since the	N	N	N	N
	Have you experienced nausea since the procedure?	N	N	N	N
010	Have you experienced pain in your abdominal or	N	N	N	N
	Have you experienced fever since the procedure?	N	N	N	N
	Have you experienced blood in your urine since the	N	N	N	N
	Have you experienced rectal bleeding since the	N	N	N	N
	Have you experienced nausea since the procedure?	Y	N	N	N
011	Have you experienced pain in your abdominal or	N	N	N	N
	Have you experienced fever since the procedure?	N	N	N	N
	Have you experienced blood in your urine since the	N	N	N	N
	Have you experienced rectal bleeding since the	N	N	N	N
	Have you experienced nausea since the procedure?	N	N	N	N
012	Have you experienced pain in your abdominal or	N	N	N	N
	Have you experienced fever since the procedure?	N	N	N	N
	Have you experienced blood in your urine since the	N	N	N	N
	Have you experienced rectal bleeding since the	N	N	N	N
	Have you experienced nausea since the procedure?	N	N	N	N
013	Have you experienced pain in your abdominal or	N	N	N	N
	Have you experienced fever since the procedure?	N	N	N	N
	Have you experienced blood in your urine since the	N	N	N	N
	Have you experienced rectal bleeding since the	N	N	N	N
	Have you experienced nausea since the procedure?	N	N	N	N
014	Have you experienced pain in your abdominal or	N	N	N	N
	Have you experienced fever since the procedure?	N	N	N	N
	Have you experienced blood in your urine since the	N	N	N	N
	Have you experienced rectal bleeding since the	N	N	N	N
	Have you experienced nausea since the procedure?	N	N	N	N
015	Have you experienced pain in your abdominal or	N	N	N	N
	Have you experienced fever since the procedure?	N	N	N	N

	Have you experienced blood in your urine since the	N	N	N	N
	Have you experienced rectal bleeding since the	N	N	N	N
	Have you experienced nausea since the procedure?	N	N	N	N

One patient experienced nausea within 1 week of treatment and not considered an adverse event since it is associated with post-embolization syndrome noted in some patients with other embolic agents.

12.3 IIEF Assessment

The international index of erectile function (IIEF) for each treated patient comparing follow-up to baseline scores is presented in Table 12-4. A higher IIEF score indicates better erectile function.

Table 12-4 IIEF Score

Subject Number	Pre-Embolization Baseline	Post-Embolization Follow-up		
		3 Months	6 Months	12 Months (End of
001	65	69	71	69
002	11	9	10	8
005[1]	23	45	44	19
008[2]	50	47	61	52
010	65	65	71	69
011	8	13	17	34
012[3]	61	69	71	70
013	9	11	15	7
014[4]	63	60	66	69
015	59	65	66	67

[1]End of study assessment for Subject 005 was conducted at 13 months post-embolization. [2]Visit 4 for subject 008 occurred 5 days earlier than scheduled. [3]Visit 5 for subject 012 occurred 2 days later than scheduled. [4]Six month assessment for Subject 0014 was conducted 1 day later than scheduled.

There was no precipitous drop in the IIEF for any patient over the study period that would be indicative of erectile dysfunction. Erectile function remained essentially unchanged or improved for the study subjects over the study period.

12.4 Adverse Events

One patient experienced 2 AEs that were determined to be unrelated to administration of the investigational product (vertigo, hypokalemia). A second patient experienced fever, post-embolization. A third patient experienced nausea typical of post-embolization syndrome, an expected consequence of embolization in some patients. Table 12-5 provides a summary of all AEs observed in the study, to date.

Table 12-5 Adverse Events

Subject Number	Adverse Event
002	Vertigo
	Hypokalemia
012	Fever

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

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

12.6 Clinical Laboratory Evaluation

Hypokalemia was noted in 1 patient and determined to be unrelated to administration of the investigational product. Aside from hypokalemia noted in study subject 1, no clinically significant laboratory results were observed in the study.

12.6.1 Prostate Specific Antigen (PSA)

PSA increased in 4 study subjects and decreased in 6 study subjects at the 3-month visit, in comparison to baseline. PSA increased in 6 study subjects and decreased in 4 study subjects at the 6-month visit, in comparison to baseline. PSA increased in 9 study subjects and did not change in 1 study subject at the 12-month visit, in comparison to baseline. PSA levels did not exceed the exclusion criterion of 10 ng/ml for any study subject at any time point.

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

12.7.1 Vital Signs

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

12.8 Physical Examination

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

12.9 Safety Conclusions

In the studied population of men with BPH associated with moderate to severe LUTS:

- OCL 503 was well tolerated with no pain associated with the procedure in all patients. One patient experienced nausea, post-embolization; typically associated with post embolization syndrome seen with other embolic agents.
- There were no SAEs or AEs leading to withdrawal from the study, and no clinically significant findings in vital signs, physical examination, or clinical laboratory assessments.
- A dramatic decline in IIEF indicative of non-target embolization of penile vasculature was not seen in any of the subjects treated.

13 DISCUSSION AND OVERALL CONCLUSIONS

13.1 Discussion

This prospective, open label, uncontrolled study was designed to assess the safety and effectiveness of PAE with OCL 503 in men with BPH associated with moderate to severe LUTS. Fifteen (15) subjects were to be enrolled in the study. Fifteen (15) subjects were screened and consented with 10 subjects embolized. Five subjects did not meet inclusion/exclusion criteria.

The primary objectives of the study were assessment of safety, as determined by AEs, and effectiveness as determined by change in IPSS, including QoL, associated with administration of OCL 503.

OCL 503 was well tolerated by all treated subjects. Less than 1 vial of investigational product was required to achieve near-stasis embolization in all subjects that underwent embolization.

Baseline IPSS was 24.2 ± 3.3 for the study population. IPSS decreased significantly in all subjects at 3 months (95% CI 9.7 to 17.3), in 9 of 10 subjects at 6 months post-embolization (95% CI 4.2 to 17.4) and in 8 of 10 subjects at 12 months post embolization ($p = 0.01$; primary endpoint). Baseline QoL, measured on a 7-point scale, was 4.9 ± 0.9 for the study population. QoL improved post-embolization in all patients at the 3-month follow-up visit (95% CI 1.5 to 4.1), and in 9 of 10 subjects at the 6-month (95% CI 1.0 to 3.8) and 12-month (95% CI 0.7 to 3.3) follow-up visits.

Secondary objectives of the study involved assessment of uroflowmetry and change in prostate volume. Subject responses varied, with minimal changes noted in the uroflowmetry parameters and in prostate volume. There was no precipitous decline in IIEF over the study period. No new safety patterns or trends were observed in any of the treated subjects.

A recent article published by Bilhim et al, 2016 provided a retrospective analysis of outcome measures collected for BPH patients treated by PAE at a single institution over a 6-year period (n=186). The average age of study subjects treated with spherical embolic agent (Bead Block 300-500 μm, permanent implant) was 65.5 ± 7.7 years, similar to the BPH patients treated in this OCL 503 study (64.5 ± 6.7 years). The average prostate size treated was 88.6 ± 51.3 ml in the Bilhim study and 87.9 ± 53.5 in the current study. Baseline IPSS was 22.4 ± 6.1 and 24.2 ± 3.3 for the Bilhim study and the current study, respectively. On average, IPSS dropped by approximately 11 points and 12 points in the Bilhim study at 6 (n=143) and 12 (n=49) months, respectively, in comparison to an average drop in the IPSS of the current study of approximately 11 points and 9 points at 6 months (n=10) and 12 months (n=10), respectively. Baseline QoL was 4.2 ± 0.7 and 4.9 ± 0.9 for the Bilhim study and the current study, respectively. QoL improved 1.8 points and 2.0 points in the Bilhim study at 6 months (n=142) and 12 months (n=49), respectively; the QoL improved 2.4 points and 2.0 points in the current study at 6 months (n=10) and 12 months (n=10), respectively. The study by Bilhim showed that symptom improvement was not dependent on change in prostate volume. Similarly, the current study showed that symptom improvement was not dependent on change in prostate volume.

13.2 Conclusions

The following conclusions were drawn for the studied population of men with BPH associated with moderate to severe LUTS treated with Occlusin® Embolization microspheres:

- Treatment of men with moderate to severe LUTS due to BPH using OCL 503 was well tolerated.
- 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.
- Symptom improvement in the study population, as assessed by IPSS, was statistically significant at 3 months and 6 months post-embolization.
- Primary endpoint IPSS assessment at 12 months post-embolization compared to baseline was statistically significant ($p = 0.01$)
- QoL improvement, in the study population, was statistically significant at 3 months, 6 months and 12 months, post-embolization.

The study results did not raise safety concerns and are suggestive of symptom improvement as measured by IPSS and QoL.

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

Not applicable

15 REFERENCE LIST

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16 APPENDICES

16.1 Appendix 1 - Statistical Assessments

Prostate Artery Embolization Study

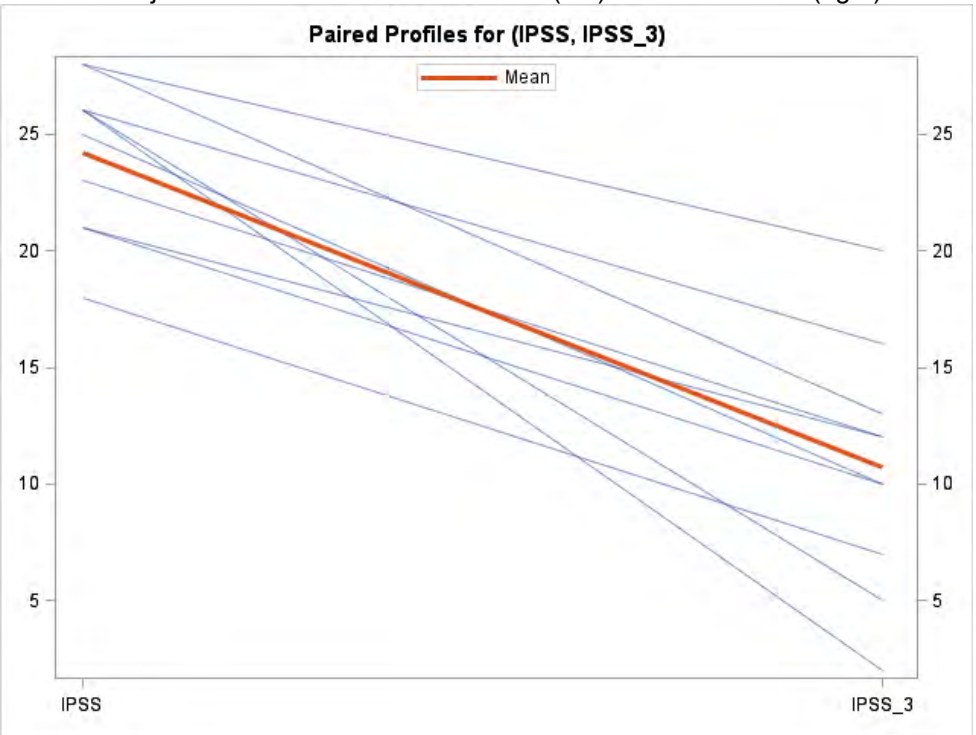
March 21, 2018 Maryna Yaskina

All statistical analyses were performed using SAS Ver. 9.4

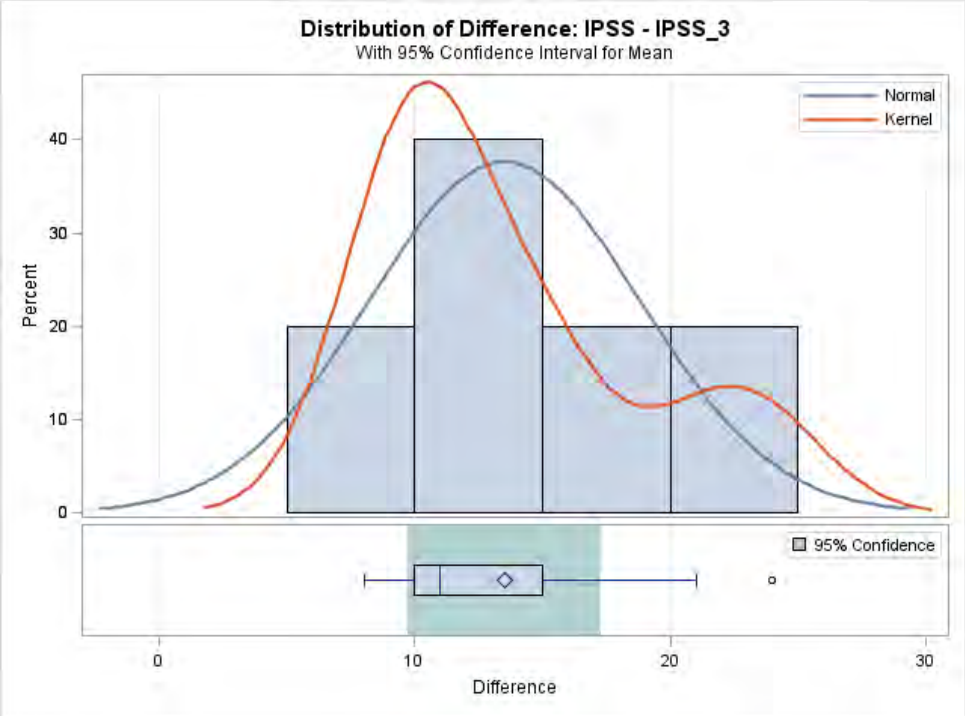
IPSS score change at 3 months from baseline

IPSS	*N*	*Mean*	*Std Dev*	*Median*	*IQR*	*Min*	*Max*	*95% Confidence interval for mean*	
								Lower limit	*Upper limit*
Baseline	10	24.2	3.3	25.5	5.0	18.0	28.0	21.8	26.6
3 months	10	10.7	5.2	11.0	6.0	2.0	20.0	7.0	14.4

Individual trajectories for IPSS score: baseline (left) and at 3 months (right). Mean change in orange.

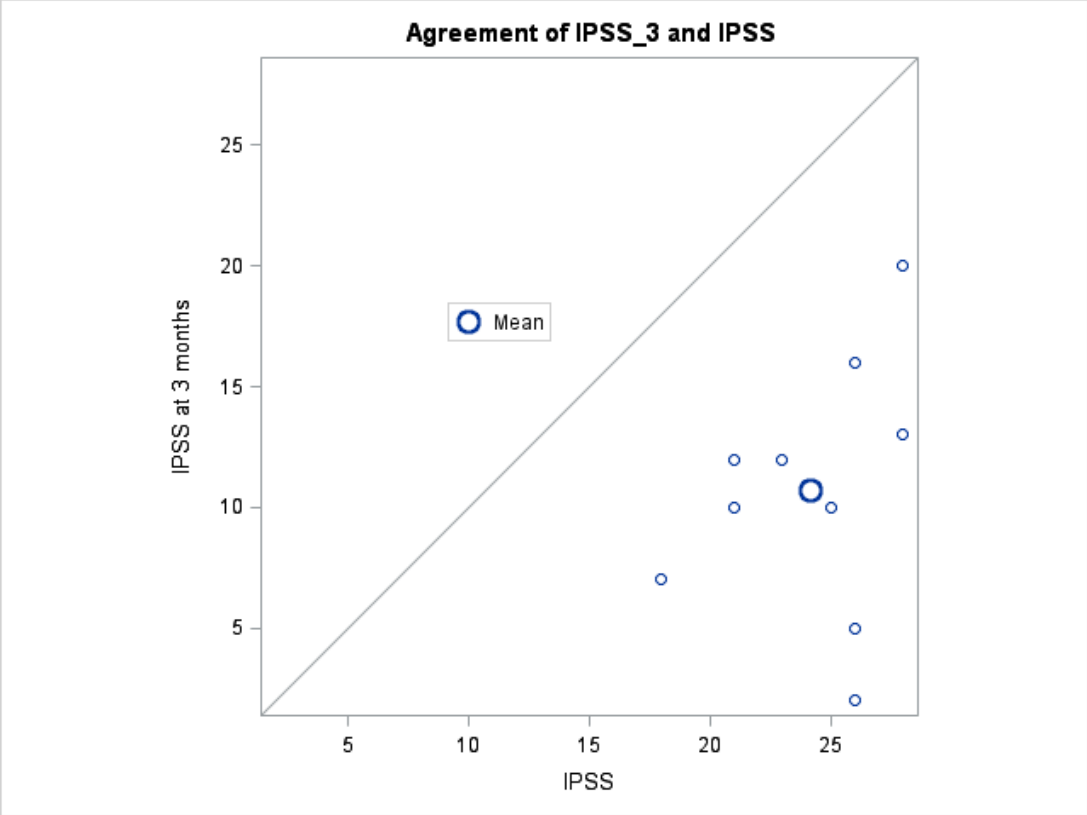


Distribution of the **difference of scores** (baseline – 3 months). Boxplot shows that both mean and median of the difference lie well above 0. Even more, the whole range of the difference also lies above 0.



IPSS change between baseline and 3 months	***N***	***Mean***	***Std Dev***	***Median***	***IQR***	***Min***	***Max***	***95% Confidence interval for mean***	
								Lower limit	***Upper limit***
	10	13.5	5.3	11.0	5.0	8.0	24.0	9.7	17.3

Agreement plot: x-axis = baseline, y-axis = 3 months. Diagonal line = no change in score, y=x. It can be seen that all patients lie below the y=x line meaning that their 3 months score is lower than the one at the baseline.



Prostate Artery Embolization Study

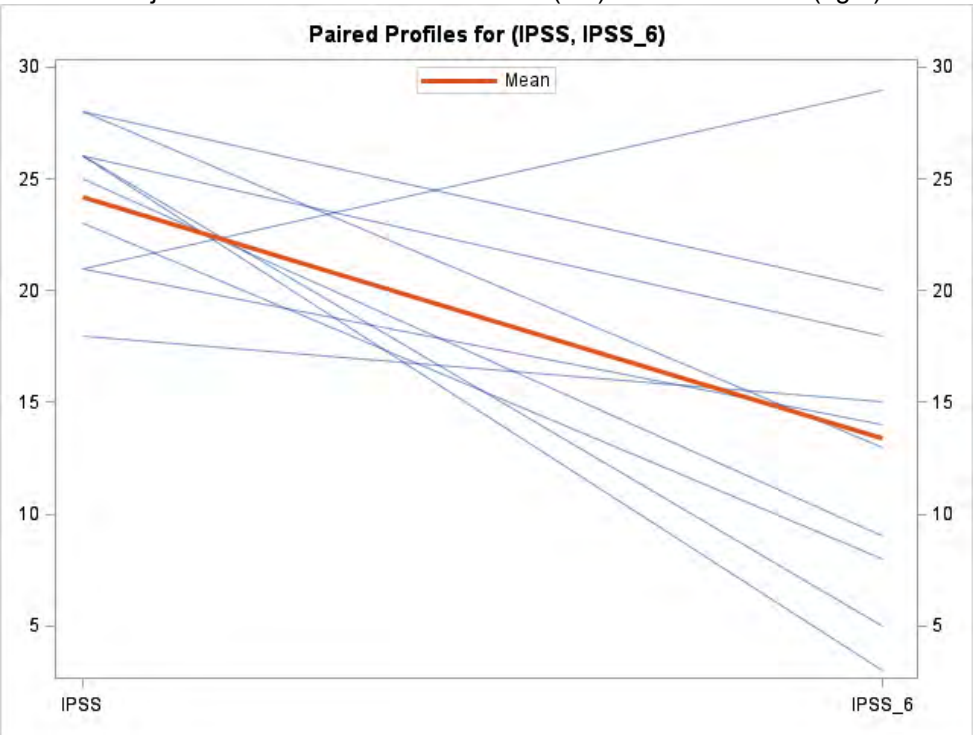
March 21, 2018 Maryna Yaskina

All statistical analyses were performed using SAS Ver. 9.4

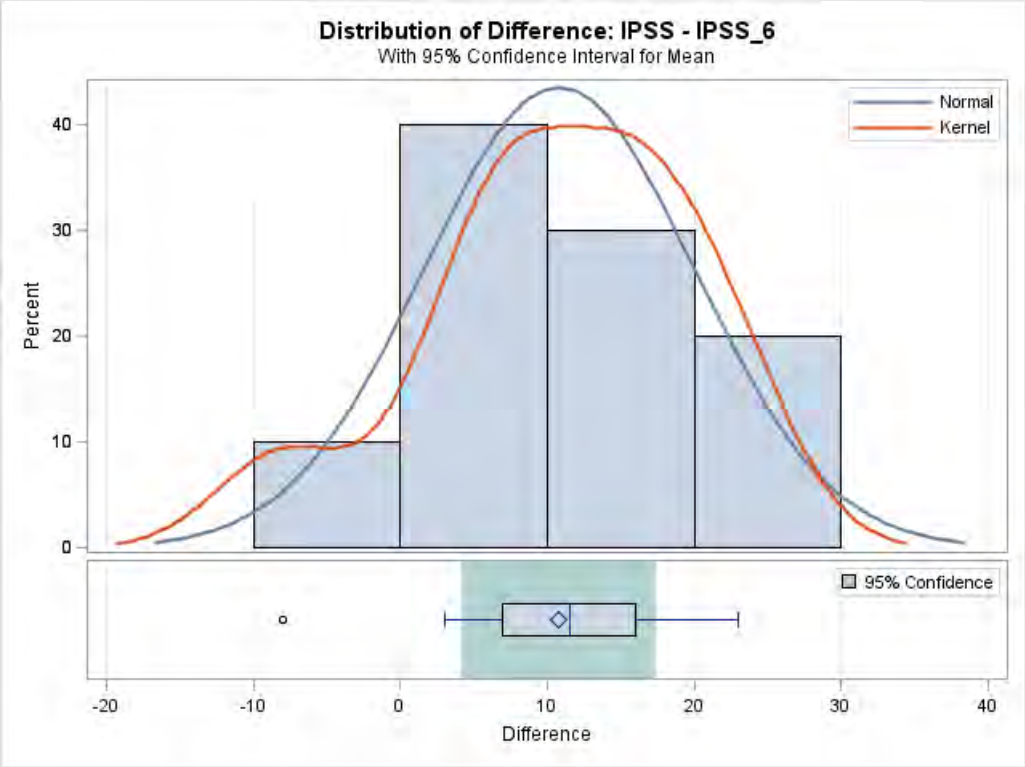
IPSS score change at 6 months from baseline

IPSS	*N*	*Mean*	*Std Dev*	*Median*	*IQR*	*Min*	*Max*	*95% Confidence interval for mean*	
								Lower limit	*Upper limit*
Baseline	10	24.2	3.3	25.5	5.0	18.0	28.0	21.8	26.6
6 months	10	13.4	7.7	13.5	10.0	3.0	29.0	7.9	18.9

Individual trajectories for IPSS score: baseline (left) and at 6 months (right). Mean change in orange.

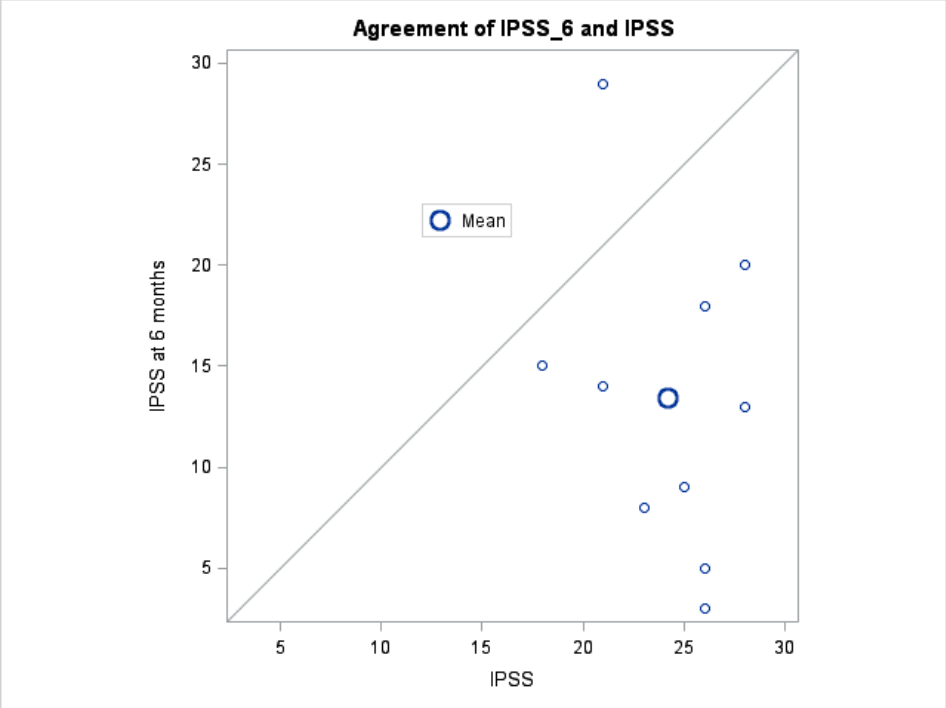


Distribution of the **difference of scores** (baseline – 6 months). Boxplot shows that both mean and median of the difference lie well above 0. Even more, only 1 outlier (a dot on the boxplot) lies below 0, for all others the score change is above 0.



IPSS change between baseline and 3 months	N	Mean	Std Dev	Median	IQR	Min	Max	95% Confidence interval for mean	
								Lower limit	Upper limit
	10	10.8	9.2	11.5	9.0	-8.0	23.0	4.2	17.4

Agreement plot: x-axis = baseline, y-axis = 6 months. Diagonal line = no change in score, y=x. It can be seen that all patients except one lie below the y=x line meaning that their 6 months score is lower than the one at the baseline.



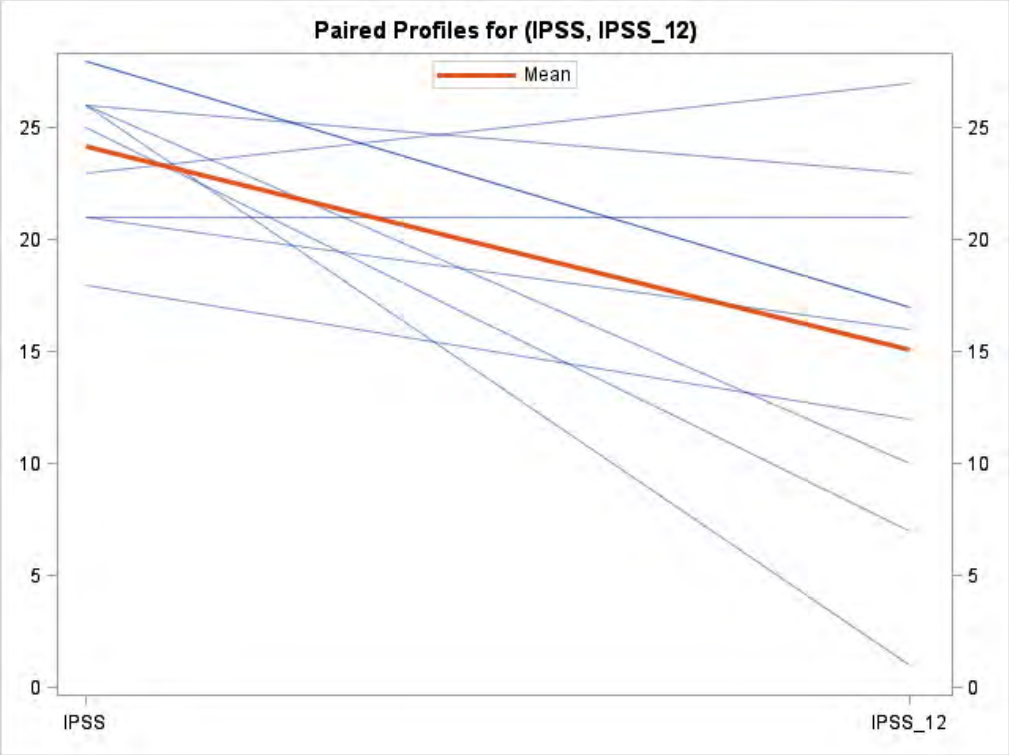
Prostate Artery Embolization Study

March 14, 2018 Maryna Yaskina

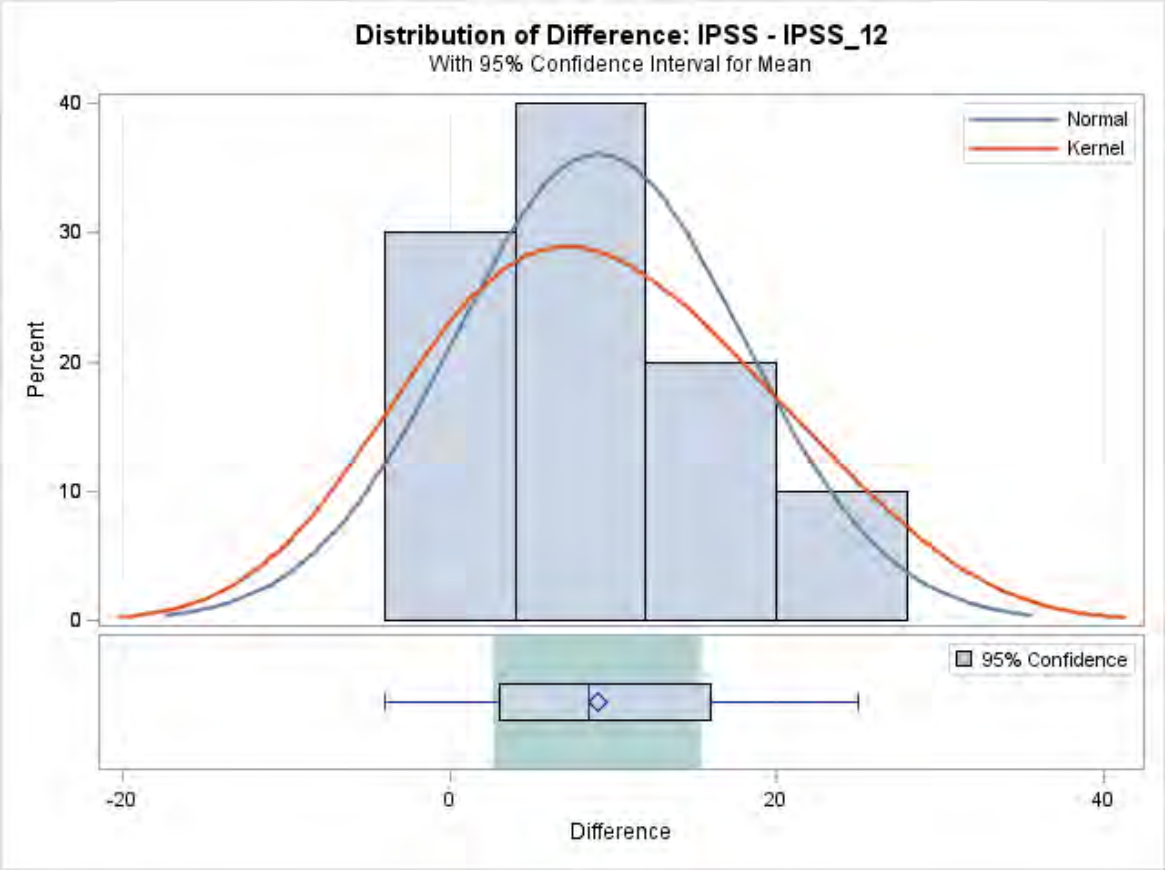
All statistical analyses were performed using SAS Ver. 9.4

IPSS	***N***	***Mean***	***Std Dev***	***Median***	***IQR***	***Min***	***Max***	***95% Confidence interval for mean***	
								Lower limit	***Upper limit***
Baseline	10	24.2	3.3	25.5	5.0	18.0	28.0	21.8	26.6
12 months	10	15.1	7.8	16.5	11.0	1.0	27.0	9.5	20.7

Individual trajectories for IPSS score: baseline (left) and at 12 months (right). Mean change in orange.

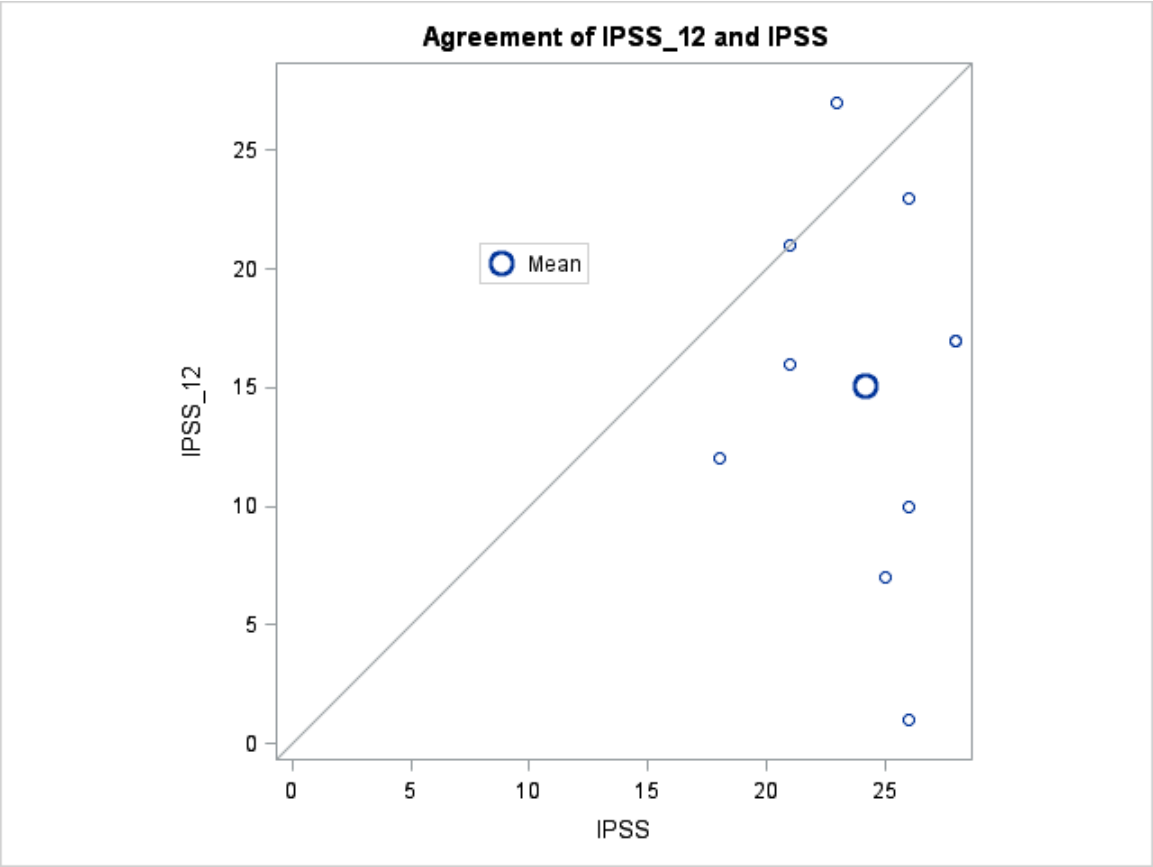


Distribution of the **difference of scores** (baseline – 12 months). Boxplot shows that both mean and median of the difference lie above 0. Even more, the middle 50% of the score differences (the actual "box" part) also lies above 0.



IPSS change between baseline and 12 months	***N***	***Mean***	***Std Dev***	***Median***	***IQR***	***Min***	***Max***	***95% Confidence interval for mean***	
								Lower limit	***Upper limit***
	10	9.1	8.8	8.5	13.0	-4.0	25.0	2.8	15.4

Agreement plot: x-axis = baseline, y-axis = 12 months. Diagonal line = no change in score, y=x. It can be seen that only 1 person lies above the line (score at 12 months is worse than at the baseline), 1 lies on the line and all other patients lie below the y=x line meaning that their 12 months score is lower than the one at the baseline.



P-values

IPSS	***p-value***	
	t-test	***Wilcoxon sign rank test***
Baseline – 12 months	0.01	0.01

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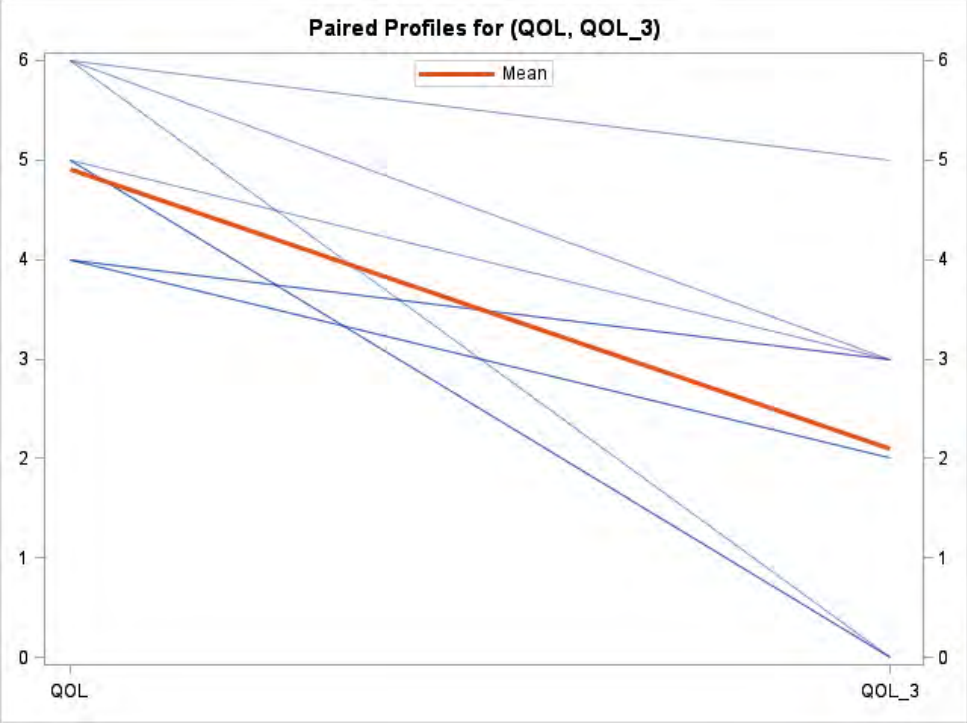
All statistical analyses were performed using SAS Ver. 9.4

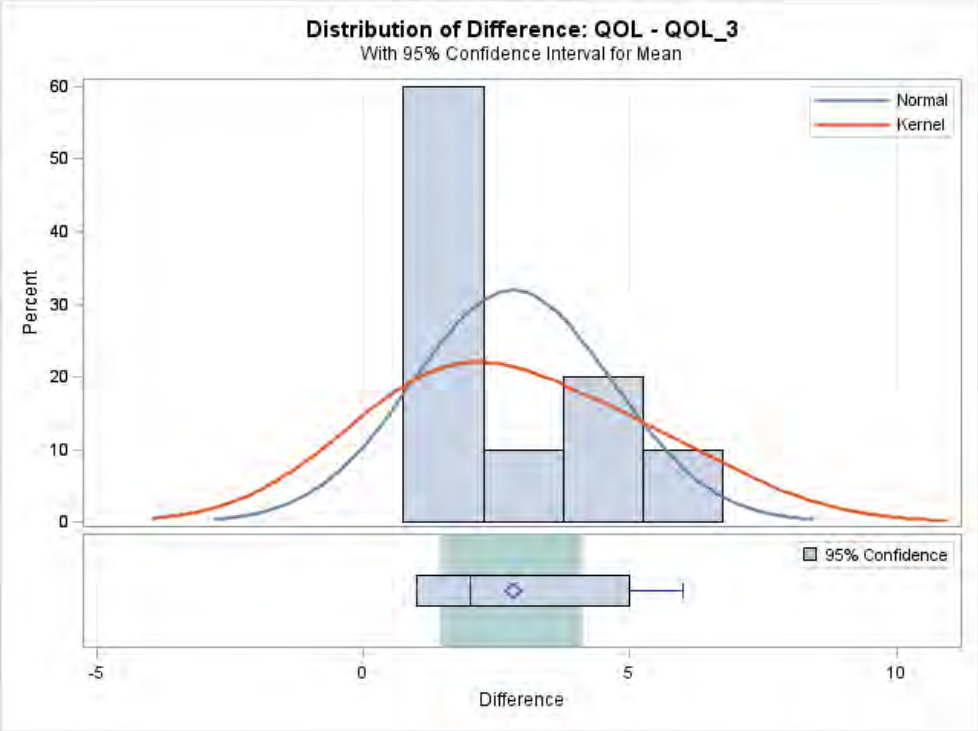
QOL score change at 3 months from baseline

QOL	*N*	*Mean*	*Std Dev*	*Median*	*IQR*	*Min*	*Max*	*95% Confidence interval for mean*	
								Lower limit	*Upper limit*
Baseline	10	4.9	0.9	5.0	2.0	4.0	6.0	4.3	5.5
3 months	10	2.1	1.7	2.5	3.0	0.0	5.0	0.9	3.3

Individual trajectories for QOL score: baseline (left) and at 3 months (right). Mean change in orange.

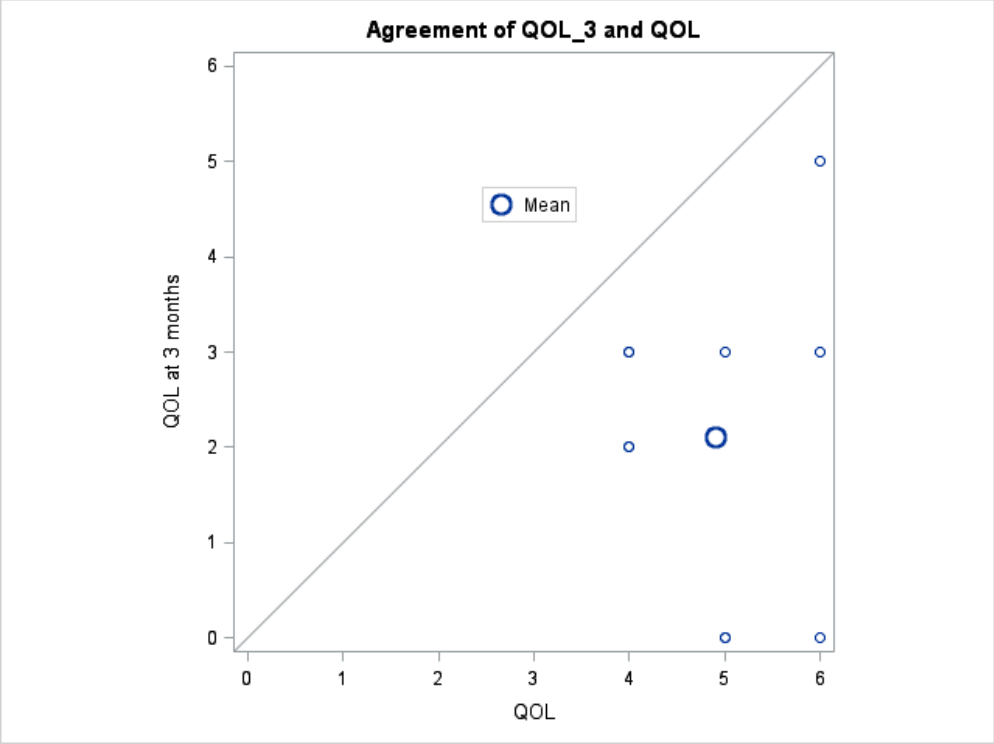


Distribution of the **difference of scores in QOL** (baseline – 3 months). Boxplot shows that both mean and median of the difference lie above 0. Even more, the whole range lies above 0.



QOL change between baseline and 3 months	***N***	***Mean***	***Std Dev***	***Median***	***IQR***	***Min***	***Max***	***95% Confidence interval for mean***	
								Lower limit	***Upper limit***
	10	2.8	1.9	2.0	4.0	1.0	6.0	1.5	4.1

Agreement plot: x-axis = baseline, y-axis = 3 months. Diagonal line = no change in score, y=x. It can be seen that everyone lies below the y=x line meaning that their 3 months score is lower than the one at the baseline.



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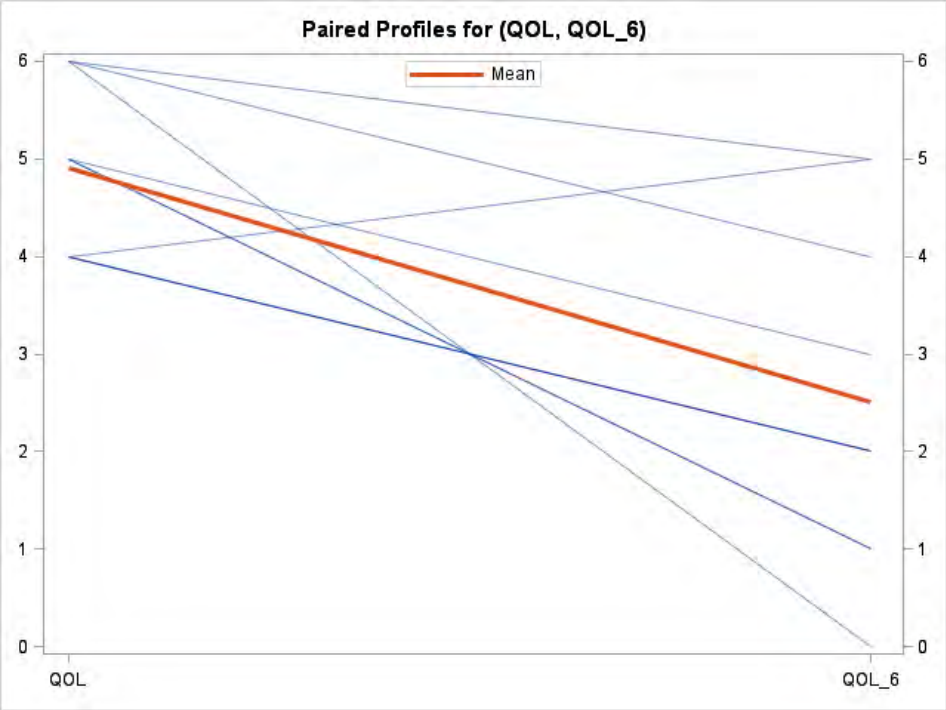
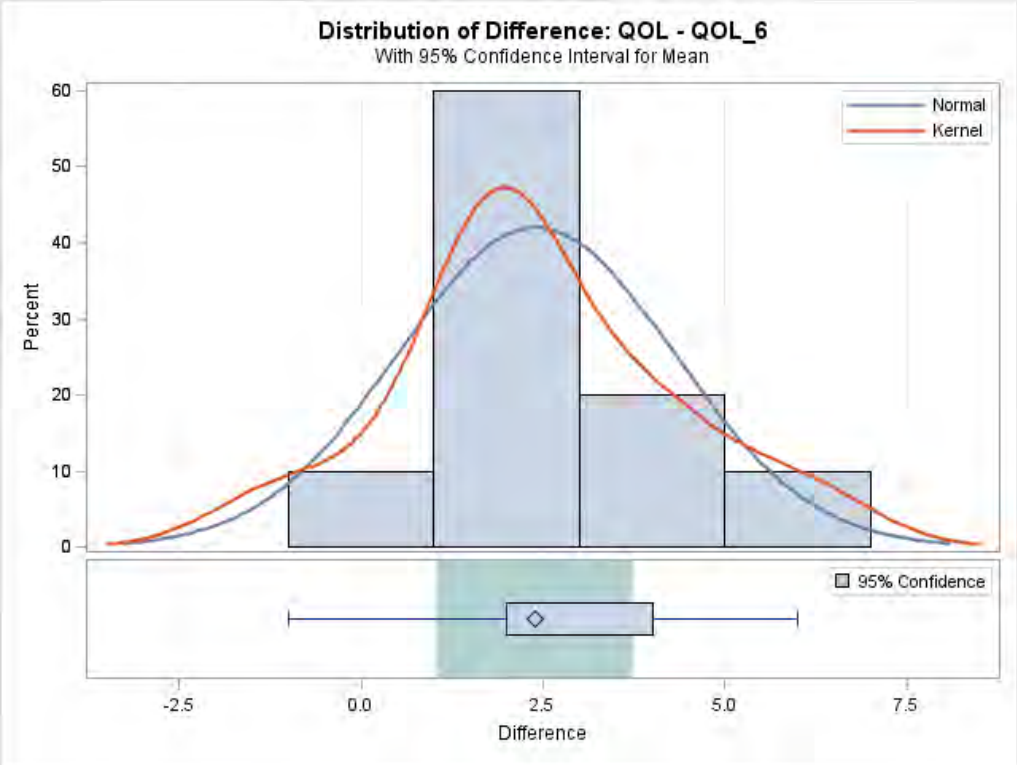
QOL score change at 6 months from baseline

QOL	*N*	*Mean*	*Std Dev*	*Median*	*IQR*	*Min*	*Max*	*95% Confidence interval for mean*	
								Lower limit	*Upper limit*
Baseline	10	4.9	0.9	5.0	2.0	4.0	6.0	4.3	5.5
6 months	10	2.5	1.7	2.0	3.0	0.0	5.0	1.3	3.7

Individual trajectories for QOL score: baseline (left) and at 6 months (right). Mean change in orange.

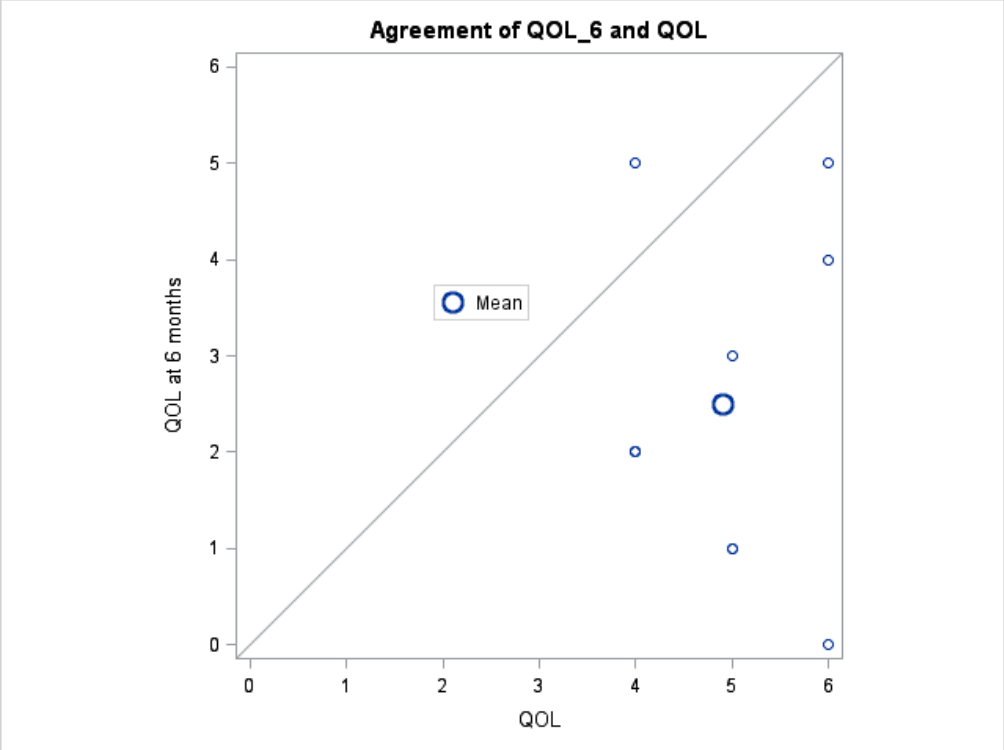


Distribution of the **difference of scores in QOL** (baseline – 6 months). Boxplot shows that both mean and median of the difference lie above 0. Moreower, the middle 50% of the score differences (the actual "box" part) also lies above 0.



QOL change between baseline and 6 months	N	Mean	Std Dev	Median	IQR	Min	Max	95% Confidence interval for mean	
								Lower limit	Upper limit
	10	2.4	1.9	2.0	2.0	-1.0	6.0	1.0	3.8

Agreement plot: x-axis = baseline, y-axis = 6 months. Diagonal line = no change in score, y=x. It can be seen that only 1 person lies above the line, while all other patients lie below the y=x line meaning that their 6 months score is lower than the one at the baseline.



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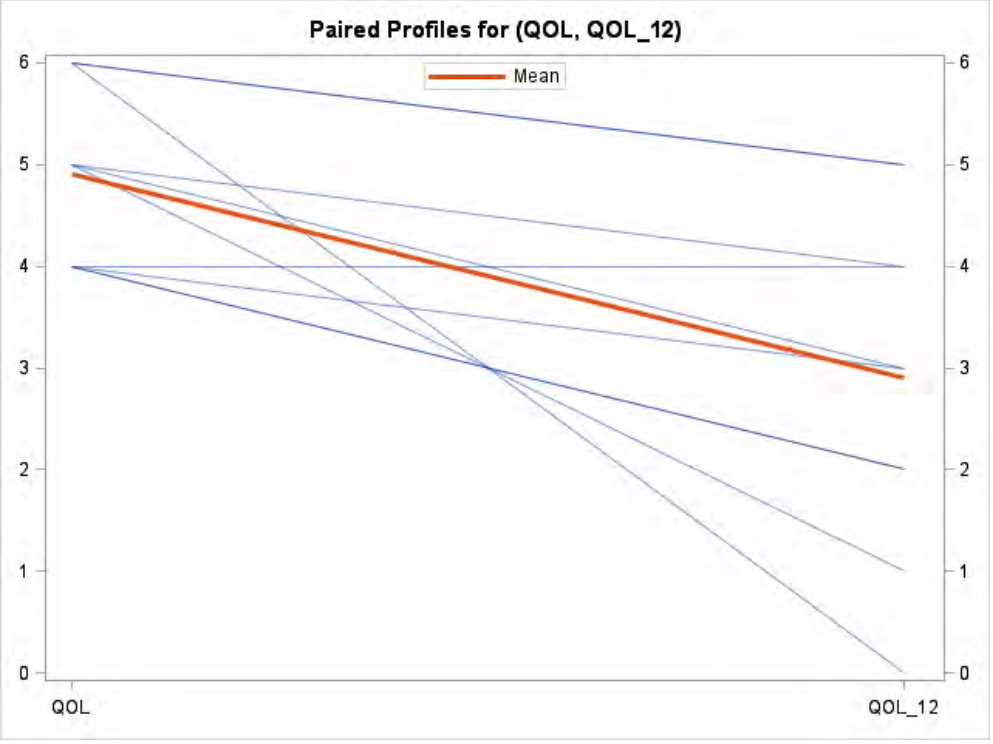
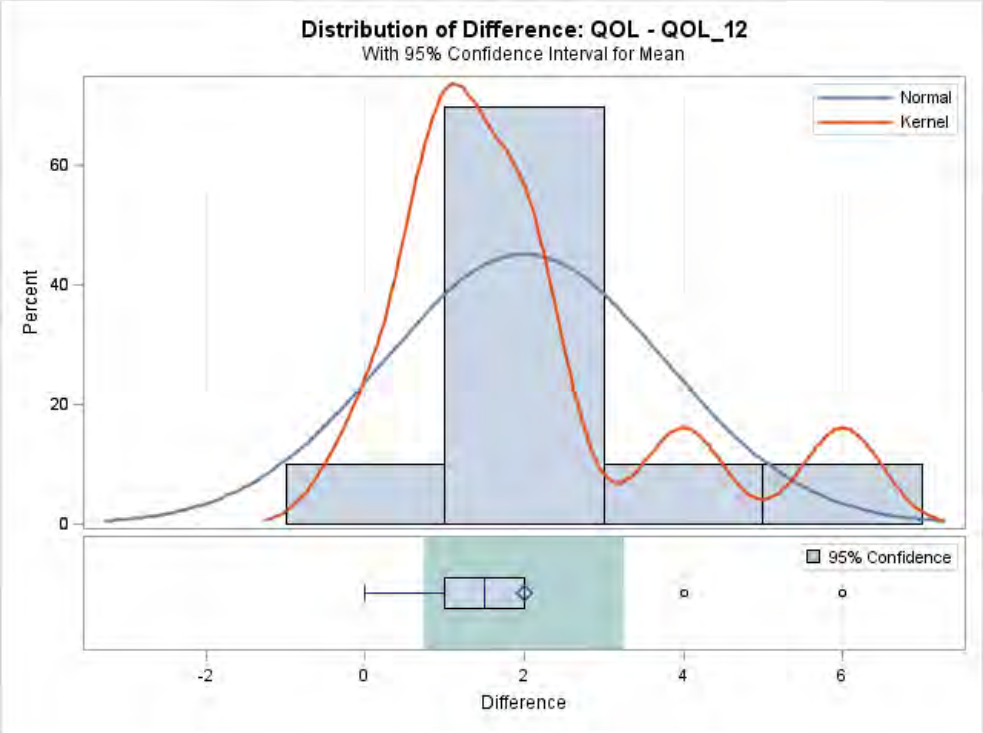
QOL score change at 12 months from baseline

QOL	*N*	*Mean*	*Std Dev*	*Median*	*IQR*	*Min*	*Max*	*95% Confidence interval for mean*	
								Lower limit	*Upper limit*
Baseline	10	4.9	0.9	5.0	2.0	4.0	6.0	4.3	5.5
12 months	10	2.9	1.7	3.0	2.0	0.0	5.0	1.7	4.1

Individual trajectories for QOL score: baseline (left) and at 12 months (right). Mean change in orange.



Distribution of the **difference of scores in QOL** (baseline – 12 months). Boxplot shows that both mean and median of the difference lie above 0. Even more, the whole range lies above or on 0.



QOL change between baseline and 12 months	N	Mean	Std Dev	Median	IQR	Min	Max	95% Confidence interval for mean	
								Lower limit	Upper limit
	10	2.0	1.8	1.5	1.0	0.0	6.0	0.7	3.3

Agreement plot: x-axis = baseline, y-axis = 12 months. Diagonal line = no change in score, y=x. It can be seen that only 1 person lies on the line (his score did not change) and all other patients lie below the y=x line meaning that their 12 months score is lower than the one at the baseline.