DE NOVO CLASSIFICATION REQUEST FOR AQUABEAM SYSTEM

REGULATORY INFORMATION

FDA identifies this generic type of device as:

> **Fluid jet system for prostate tissue removal.** A fluid jet system for prostate tissue removal is a prescription device intended for the resection and removal of prostatic tissue for the treatment of benign prostatic hyperplasia (BPH). The device cuts tissue by using a pressurized jet of fluid delivered to the prostatic urethra. The device is able to image the treatment area, or pairs with an imaging modality, to monitor treatment progress.

NEW REGULATION NUMBER: 21 CFR 876.4350

CLASSIFICATION: II

PRODUCT CODE: PZP

BACKGROUND

DEVICE NAME: AQUABEAM System

SUBMISSION NUMBER: DEN170024

DATE DE NOVO RECEIVED: April 17, 2017

SPONSOR INFORMATION:

PROCEPT BioRobotics Corporation
900 Island Drive Suite 101
Redwood Shores, California 94065

INDICATIONS FOR USE

The AQUABEAM System is indicated as follows:

> The AQUABEAM System is intended for the resection and removal of prostate tissue in males suffering from lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia.

LIMITATIONS

The sale, distribution, and use of the AQUABEAM System is restricted to prescription use in accordance with 21 CFR 801.109.

Use of the AQUABEAM System must be prescribed and administered under the direct supervision of a qualified and trained physician, after appropriate urologic patient evaluation. Limitations on device use are also achieved through the following statements included in the Instructions for Use:

Contraindications:
Do not use the AQUABEAM System in patients with:

- Active urinary tract or systemic infection
- Known allergy to device materials
- Inability to safely stop anticoagulants or antiplatelet agents perioperatively
- Diagnosed or suspected cancer of the prostate

Warnings:

- A thorough understanding of the technical principles, clinical application and risks associated with the AQUABEAM System is necessary before using this product. Read the entire User Manual and Instruction for Use prior to using the AQUABEAM System. Completion of PROCEPT's training program is required prior to use of the AQUABEAM System
- The AQUABEAM Handpiece is designed for use ONLY with the AQUABEAM Console, Motorpack, and Conformal Planning Unit
- Do not place assembled Roll Stand on a plane inclined at an angle greater than 5° from the horizontal plane during normal use or while unattended
- To avoid injury, do not transport assembled Roll Stand on ramps greater than 9° incline. Do not leave unattended on ramps with greater than 9° incline
- This device is not suitable for use in the presence of a flammable anesthetic mixture with air or oxygen
- Each AQUABEAM Handpiece is designed for Single Use Only. DO NOT attempt to re-sterilize or reuse the Handpiece. Discard each AQUABEAM Handpiece after use. Neither the sterility nor the functionality of a reused Handpiece can be guaranteed and injury to the subject may occur
- The AQUABEAM Scope must be cleaned and sterilized prior to each procedure. To minimize the risk of transmitting disease from one patient to another, after each procedure the Scope must be cleaned and sterilized as described in Scope Reprocessing instructions
- To minimize the risk of transmitting disease from one patient to another, the AQUABEAM Console, Conformal Planning Unit, Foot Pedal, Power Cord, Handpiece Articulating Arm, TRUS Articulating Arm, Motorpack and Roll Stand must be properly cleaned after each procedure. Failure to properly clean after each procedure may compromise patient safety
- To avoid potential contamination of the AQUABEAM Handpiece Articulting Arm, Motorpack and TRUS Articulating Arm, they must be draped with new sterile drapes for each procedure
- Failure to drape the AQUABEAM Console on all sides may result in fluid ingress from Aquablation saline supply into the Console

PLEASE REFER TO THE LABELING FOR A COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

The AQUABEAM System is a personalized image-guided prostate tissue removal system that uses a high-velocity water jet to resect and remove a predetermined volume of tissue.

The AQUABEAM System (**Figure 1**) is comprised of nine main components along with accessories. The main components are as follows:

- AQUABEAM Conformal Planning Unit
- AQUABEAM Console
- AQUABEAM Motorpack
- AQUABEAM Roll Stand
- AQUABEAM Foot Pedal
- AQUABEAM Handpiece Articulating Arm
- AQUABEAM TRUS Articulating Arm
- AQUABEAM Handpiece
- AQUABEAM Scope

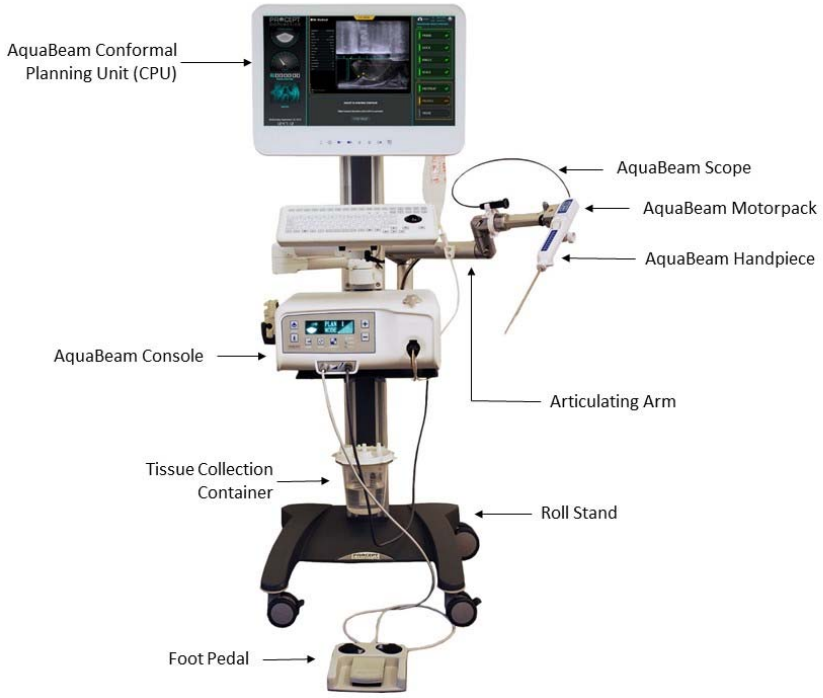

Figure 1 AQUABEAM System

AQUABEAM Conformal Planning Unit (CPU)

The Conformal Planning Unit serves as the primary user interface of the AQUABEAM System. The CPU performs the following functions:

- Displays live transrectal ultrasound (TRUS) video
- Allows the user to visualize and identify key anatomical markers (e.g. the prostatic capsule, verumontanum and bladder/bladder neck). These key markers optimize the

placement and positioning of the AQUABEAM Handpiece and select target area for treatment
- Allows the user to plan the procedure by selecting the resection angles and calibrating the width and resection depth
- Records planned resection angles and treatment profile and transmit to the Console in order to initiate the procedure
- Provides the user with real time progress of the prostatic tissue resection
- Provides hazard and advisory notifications
- Records and stores procedure data

AQUABEAM Console

The AQUABEAM Console performs the following functions:

- controls the functionality of the high-velocity waterjet delivered by the Handpiece
- accepts planned resection angles and treatment profile from the CPU to allow the initiation of the procedure
- displays the status of the procedure modes
- displays pump level during the procedure
- provides an interface with the Motorpack, Foot Pedal and CPU

AQUABEAM Handpiece

The AQUABEAM Handpiece, a sterile single use component of the system, emits saline at high velocity to resect target prostate tissues. The Handpiece integrates with the Scope to provide live cystoscopic visualization of the prostatic urethra and bladder during insertion and treatment.

AQUABEAM Motorpack

The Motorpack docks with the Handpiece and provides power to the Handpiece by means of DC motors, which enable both rotational and longitudinal movement of the Handpiece probe providing controlled and precise resection of the prostatic tissue in accordance with the CPU treatment plan. The Motorpack additionally has user controls that signal the system to increment or decrement the High-Pressure Pump power when pressed. The Motorpack/Handpiece assembly is secured to the Handpiece Articulating Arm.

AQUABEAM Scope

The AQUABEAM Scope, a re-usable component of the AQUABEAM System, consists of a semi-flexible stainless steel hypotube at the distal end and a flexible Pebax sheath connected to a proximal eye piece. The Scope is inserted into the central lumen of the AQUABEAM Handpiece enabling direct visualization within the prostatic urethra during treatment.

AQUABEAM Foot Pedal

The AQUABEAM Foot Pedal contains three foot-activated buttons and is connected to the Console with a flexible cable. The surgeon depresses the buttons to begin the waterjet resection. Additional buttons control Handpiece priming and aspiration of fluid.

AQUABEAM Roll Stand

The AQUABEAM Roll Stand serves as the chassis for various AQUABEAM System components and is the main power source for the system.

AQUABEAM Handpiece Articulating Arm

The AQUABEAM Handpiece Articulating Arm connects to standard bedrails and rigidly fixes the Handpiece and Motorpack in position relative to the patient. The Handpiece Articulating Arm has a release trigger that enables freedom of movement and locking of the arm. The arm allows ±20° of Handpiece rotation with 2° discrete locking points.

AQUABEAM TRUS Articulating Arm

The AQUABEAM TRUS Articulating Arm (Figure 2) connects to standard bedrails and fixes the TRUS probe and stepper in position relative to the patient. The TRUS Articulating Arm has a release trigger that enables freedom of movement and locking of the arm.

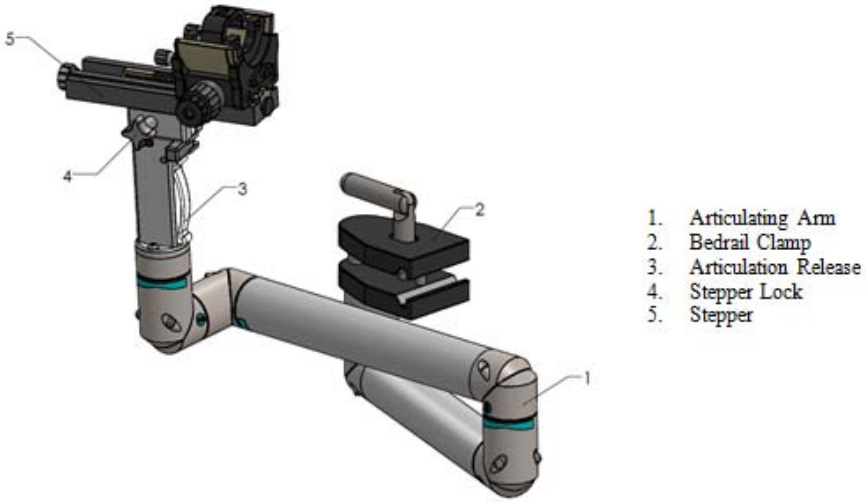

Figure 2 TRUS Articulating Arm

SUMMARY OF NONCLINICAL/BENCH STUDIES

BIOCOMPATIBILITY/MATERIALS

The AQUABEAM Handpiece and AQUABEAM Scope are the only components of the AQUABEAM System that have direct or indirect patient contact. These components were tested as per "external communicating device, tissue/bone/dentin with limited exposure (<24 hours)" device category using the following tests:

- Cytotoxicity
- Sensitization
- Irritation/intracutaneous reactivity
- Acute systemic toxicity
- Material-mediated pyrogenicity
- Hemolysis

All tests passed. Only components of the Handpiece and Scope that have direct/indirect contact with the patient were used to perform the biocompatibility evaluation.

SHELF LIFE/STERILITY

The AQUABEAM Handpiece is provided sterile. The Handpiece is sterilized using 100% Ethylene Oxide (EO) gas sterilization process. The Handpiece is packaged on a HDPE backer card in a pouch. The sealed pouches are then placed into shelf cartons and sterilized using 100% EO to a sterility assurance level (SAL) of 10^{-6}. Other device components are provided non-sterile for reuse.

The Handpiece was shelf-life tested using 2-year accelerated aging in accordance with ASTM F1980 - Standard Guide for Accelerated Aging of sterile medical device packages. In addition to testing the packaging integrity, design verification testing was performed. All test samples were sterilized twice prior to accelerated aging.

REUSABLE COMPONENTS/REPROCESSING

The system's reusable components are the Console, Motorpack, Foot Pedal, Conformal Planning Unit, Roll Stand and Scope. The Scope has a use life of eight months. The remaining reusable components have a use life of 3 years.

The following device components must be sterilized prior to reuse:

- AQUABEAM Scope

Other reusable system parts require only high-level disinfection. Instructions can be found in the AQUABEAM Instruction for Use.

Reprocessing for reusable components was validated in accordance with AAMI TIR30, the FDA guidance document "Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling – Guidance for Industry and Food and Drug Administration Staff" (March 17, 2015), and ISO 17664. The AQUABEAM scope reprocessing involves the following steps:

1. Disassembly and pre-cleaning
2. Manual cleaning
3. Rinsing after manual cleaning
4. Ethylene oxide sterilization
5. Inspection and function testing prior to use

The full reprocessing instructions can be found in the AQUABEAM Scope Reprocessing Instructions.

ELECTROMAGNETIC CAPABILITY & ELECTROMAGNETIC SAFETY

The AQUABEAM system was evaluated and confirmed for conformance to IEC 60601-1-2.

The AQUABEAM system was evaluated and confirmed for conformance to IEC 60601-1 (general requirements) and IEC 60601-2-37 (particular requirements for ultrasonic diagnostic and monitoring equipment).

MAGNETIC RESONANCE (MR) COMPATIBILITY

The AQUABEAM System is MR unsafe. A warning is included in the user manual which states that the AQUABEAM system should not be used near MR technology, including Stereotaxis systems.

SOFTWARE

The AQUABEAM System software was developed in accordance with FDA, the FDA guidance document "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices," dated May 11, 2005 and IEC 62304, Medical device software – Software life cycle processes. The AQUABEAM System Software consists three software components: Console FPGA firmware, Motorpack FPGA firmware, and CPU Software.

The console controls user operations, the Console front panel and Foot Pedal. It communicates with the CPI and Motorpack. It also controls system-related pumps. The Motorpack FPGA firmware controls the Motorpack operation, including controlling the R (rotational) and Z (distance) motion. The CPU software provides user workflow control, generates treatment profile per user input and communicates with the Console and ultrasound video devices.

The following software documentation was provided and is adequate:

Version: 2.6.1	
Software description	x
Device hazard analysis	x
Software requirements specifications	x
Architecture design chart	x
Software design specification	x
Traceability analysis/matrix	x
Development	x
Verification and validation testing	x
Revision level history	x
Unresolved anomalies	x
Cyber and information security	N/A
Run-time error detection	x

The software is a Major Level of Concern (LOC).

PERFORMANCE TESTING - BENCH

Table 1 summarizes the design verification tests performed for the AQUABEAM system that were used to support a reasonable assurance of safety and effectiveness.

Table 1. Design verification test summary.

Test Description	Objective	Results
Console, Visual, Checklist Verification	To provide guidance to setting up the AQUABEAM System and providing a checklist of items to verify activities/components	Pass
Motorpack-Handpiece Set-up Initialization Verification	To verify the AQUABEAM Motorpack and Handpiece functions as intended	Pass
Handpiece-Scope Set-up Verification	To verify the AQUABEAM Handpiece and Scope function as intended	Pass
Probe Longitudinal Stroke Verification	To verify the accuracy of the longitudinal stroke (Z direction) of the AQUABEAM Handpiece, Motorpack, and Console	Pass
Probe Longitudinal Velocity Verification	To verify the velocity of the longitudinal movement (Z direction) of the AQUABEAM System and Handpiece	Pass
Simulated-Use, Pump Power/Flow Testing	To verify the pump performance of the PROCEPT AQUABEAM System	Pass
Simulated-Use, Aspiration Flow Rate Testing	To verify the performance of the aspiration pump of the AQUABEAM System	Pass
Simulated-Use, AQUABEAM Sweep Angle Verification and Probe Centering Verification Testing	To verify the accuracy of the sweep angle of the AQUABEAM Console and Handpiece when the procedure begins at different center positions	Pass
Simulated-Use, Irrigation Flow Rate	To verify the ability of the AQUABEAM system to supply irrigation via the Handpiece during the procedure	Pass
Simulated-Use, PLAN Mode Verification	To verify the set-up of the AQUABEAM Console within the PLAN mode configuration	Pass
Simulated-Use, CUT Mode, Pre-Treat Cut, Veru Cut, and Treatment Cut Verification	To verify the set-up of the PROCEPT AQUABEAM System within the CUT mode configuration	Pass
Simulated Use Testing (Potato Cutting)	To verify the performance of the AQUABEAM System using a potato as a tissue analogue to simulate tissue cutting	Pass
Post Simulated-Use Testing Verification	To verify the integrity of the AQUABEAM System following completion of simulated use testing	Pass
Probe Angular Velocity Verification	To verify the accuracy of the angular velocity of the AQUABEAM Console and Handpiece	Pass
Ingress Protection Testing	To verify the ability of the Handpiece shell to protect the electronics from fluid ingress.	Pass
Resolving Power	To verify the resolving power/resolution, the depth of view, and the direction of view for the AQUABEAM Scope	Pass
Depth of View	To verify the resolving power/resolution, the depth of view, and the direction of view for the AQUABEAM Scope	Pass
Direction of View	To verify the resolving power/resolution, the depth of view, and the direction of view for the AQUABEAM Scope	Pass
Field of View	To verify the field of view and the illumination of light range for the AQUABEAM Scope	Pass

Test Description	Objective	Results
Scope Re-Use testing	To verify the performance of the AQUABEAM Scope re-use. Each re-use cycle will include at least one incident of sterilization and one incident of cleaning	Pass
Scope Adapters Testing	To verify the field of view and the illumination of light range for the AQUABEAM Scope	Pass

PERFORMANCE TESTING - ANIMAL AND/OR CADAVER

Animal testing was performed to demonstrate that the AQUABEAM system ablates targeted tissue in a controlled manner without damage to adjacent tissues.

8 non-castrated male beagles were treated using the AQUABEAM System. Dogs were sacrificed immediately (n=2) or up to 8 weeks (n=6) after treatment. The duration of the procedure ranged from 40 to 84 seconds (average 60.5 seconds). There was no active bleeding on any of the dogs during or after the procedure. Animals sacrificed immediately showed intact capsular architecture with a widely patent lumen between peripheral sphincter and bladder neck indicating the ablated (resected) zone. Beyond this zone, the glandular cells and interstitial stroma maintained normal cellular architecture. Survived animals showed a widely patent prostatic urethral lumen. The urethral channels were lined by several layers of epithelium supported by a 0.4-0.5 thick layer of regenerative fibromuscular and elastic stroma underneath.

SUMMARY OF CLINICAL INFORMATION

Overview

PROCEPT BioRobotics designed and executed WATER, a prospective, multicenter, international double-blinded randomized clinical trial comparing the use of the AQUABEAM System to standard transurethral resection of the prostate (TURP) to provide evidence to support safety and efficacy. In this study, the actual treatment performed with the AQUABEAM System is referred to as "Aquablation."

Study objectives

To evaluate the safety and efficacy of Aquablation for the treatment of lower urinary tract symptoms (LUTS) in men with moderate-to-severe benign prostatic hyperplasia (BPH).

Endpoints

The primary efficacy endpoint was the change in International Prostate Symptom Score (IPSS) at 6 months compared to baseline for the Aquablation treatment arm compared to the TURP arm. A 2-sided 95% confidence interval for the difference in means was used to test for non-inferiority. Non-inferiority would be declared if the entire 2-sided 95% CI is greater than the non-inferiority margin (NIM) of -4.7 (where NIM is expressed as a negative number).

The primary safety endpoint was the occurrence of Clavien-Dindo persistent grade 1 or grade 2 or higher perioperative complications at 3 months. A 2-sided 95% confidence interval for the difference in proportions (proportion of patients with complications in Aquablation vs TURP treatment arms) was used to test for non-inferiority. Non-inferiority would be declared if the

entire 2-sided 95% CI is less than 10%. The safety endpoint was adjudicated by an independent clinical events committee (CEC). The CEC classified (assigned relatedness) to the adverse events based on severity and association to the procedure or other attribution.

For both the primary efficacy and safety endpoints, a gate-keeping strategy was used such that if the non-inferiority test was positive, a superiority test would be performed. A 2-sided (1-α)% confidence interval was used to test for superiority. Superiority would be declared if the entire 2-sided 95% CI is greater than 0%.

Data on IPSS change score and occurrence of Clavien-Dindo persistent grade 1 or grade 2 or higher events were collected at 1, 3, 6, and 12 month timepoints.

Secondary endpoints included:

- Hospital length of stay (LOS)
- Operative time (minutes)
- Resection time (minutes)
- Reoperation/reintervention within 6 months.
- Worsening of sexual function through 6 months on either the IIEF-5 or the MSHQ-EjD questionnaires
- Major adverse urologic event (MAUE) occurrence through 6 months

Additional endpoints included:

- IPSS QOL
- Qmax
- Post void residual (PVR)

Study methodology

WATER is a prospective, multicenter, international, double-blind randomized clinical study. The target patient population was men with LUTS due to BPH with a prostate size of 30-80 g and a baseline IPSS score of at least 12 points. Exclusion criteria included the following: urinary retention, prostate cancer, polyneuropathy, urethral stricture, active infection, post-void residual (PVR) >300. Eligible subjects were randomized 2:1 to Aquablation with AQUABEAM System or standard TURP. Randomization was stratified by study center and baseline IPSS ≥ or <20 points. Beginning at discharge after the study procedure, the subject was seen solely by a second healthcare team (physician and study coordinator) who remained blinded to treatment assignment. Subjects underwent telephone contact at week 1 and returned to clinic at months 1, 3, 6, and 12. 3-year follow-up is planned. At baseline and at each follow-up visit, subjects completed a series of questionnaires as well as uroflow measurements. Blinding assessments, done in follow-up only, showed no evidence of systematic unblinding.

Patient population

181 subjects were enrolled, randomized and treated, 116 with Aquablation and 65 with TURP. Baseline IPSS was 22.6 and baseline Qmax was 9 cc/sec, indicative of moderate-to-severe BPH. Study eligibility deviations were minor and did not affect the scientific validity of study results. Mean prostate size was approximately 53 g. 6-month follow-up was available in 98.3% (114/116) of Aquablation subjects and 95.4% (62/65) of TURP subjects.

Procedure
Procedure times were similar across groups (33 [Aquablation] vs. 36 [TURP] minutes, Table 2). Handpiece in/out time was lower in Aquablation (23 vs. 34 minutes). Resection time was lower in Aquablation (4 vs. 27 minutes). Hospital length of stay was similar at 1.4 days per group.

Table 2. Operative characteristics.

	Aquablation*	TURP*	p-value
Procedure time, minutes	32.8 (16.5)	35.5 (15.3)	0.2752
Handpiece in/out time, minutes	23.3 (8.7)	32.4 (14.6)	<0.0001
Resection time, minutes	3.9 (1.4)	27.4 (12.5)	<0.0001
Hospital length of stay, days	1.4 (0.7)	1.4 (0.8)	0.3327

*All values are: Mean (SD)

Safety Results
The primary safety endpoint (Clavien-Dindo grade 1 persistent or grade 2 or higher event in the first 3 months) occurred in 29 Aquablation subjects (25.0%) and 26 TURP subjects (40.0%). The rate difference (Aquablation – TURP) was -15.0%, with a 95% CI of -29.2 to -1.0%. The upper confidence limit (UCL) was less than the 10% non-inferiority delta, so the endpoint met the objective. The UCL was less than zero, therefore demonstrating statistical superiority of Aquablation versus TURP.

The difference in primary endpoint safety rate was driven primarily by retrograde ejaculation. Of men who were sexually active at both baseline and the study visit, persistent retrograde ejaculation in the first 6 months occurred in 8 Aquablation subjects (11.3%) and 16 TURP subjects (36.4%).

The proportion of men with worsening of sexual function (6-month decrease in MSHQ score of at least 2 points or decrease in IIEF-5 score of at least 6 points) was lower in the Aquablation group (32.9%) vs. the TURP group (52.8%).

In the Aquablation group at 6 months, 30 subjects (25.9%) had a Clavien-Dindo grade 1 persistent or grade 2 or higher event; in the TURP group, 28 subjects (43.1%) had an event. The point estimate for the difference was -17%. The 95% CI for the difference is rates is -31.5 to -3.0%. Using the same methodology as the 3-month endpoint for comparison purposes, the UCL was less than the 10% non-inferiority delta, so the endpoint met the objective and is considered a success. The UCL was less than zero, therefore, demonstrating Aquablation is statistically superior to TURP at 6 months.

Events occurring by month 3, categorized by Clavien-Dindo grade, are shown in Table 3.

Table 3. Distribution of events at month 3 categorized by Clavien-Dindo grades by group rated as possibly, probably or definitely related to the procedure/device.

	Aquablation		TURP	
	Events	**Subjects N (%)**	**Events**	**Subjects N (%)**
Clavien-Dindo Grade 1	**63**		**41**	
Bladder spasm	*3*		*1*	
Bleeding	*12*		*7*	
Dysuria	*12*		*5*	
Pain	*5*		*3*	
Retrograde ejaculation	*8*	**39 (33.6%)**	*16*	**27 (41.5%)**
Urethral damage	*1*		*1*	
Urinary retention	*11*		*4*	
Urinary tract infection	*2*		*0*	
Urinary urgency/frequency/difficulty/leakage	*4*		*1*	
Other	*5*		*3*	
Clavien-Dindo Grade 2	**20**		**15**	
Bladder spasm	*4*		*2*	
Bleeding	*1*		*0*	
Dysuria	*0*	**19 (16.4%)**	*1*	**11 (16.9%)**
Pain	*1*		*2*	
Urinary tract infection	*9*		*5*	
Urinary urgency/frequency/difficulty/leakage	*2*		*3*	
Other	*3*		*2*	
Clavien-Dindo Grade 3a	**4**		**2**	
Bleeding	*1*	**4 (3.4%)**	*1*	**2 (3.1%)**
Urethral stricture or adhesions	*3*		*1*	
Clavien-Dindo Grade 3b	**3**		**3**	
Bleeding	*2*	**3 (2.6%)**	*2*	**3 (4.6%)**
Urethral stricture or adhesions	*0*		*1*	
Urinary retention	*1*		*0*	
Clavien-Dindo Grade 4	**1**	**1 (0.9%)**	**0**	**0 (0.0%)**
Arrhythmia	*1*		*0*	

Efficacy Results

The primary efficacy endpoint was the change in IPSS score from baseline to month 6. Mean IPSS scores decreased from 22.9 at baseline to 5.9 at 6 months in the Aquablation group and from 22.2 at baseline to 6.8 in the TURP group. The IPSS change score at month 6 (Table 5, based on subjects with 6 month data) was 1.8 points larger after Aquablation (95% CI -0.4 to 4.0). The lower confidence limit of the difference was above the pre-specified non-inferiority margin of 4.7, substantiating statistical and clinical non-inferiority of effectiveness. Adjustment for baseline IPSS score did not change this conclusion. The missing data rate was low; detailed analysis of missing data using several methods showed no impact on this conclusion. Statistical superiority was not achieved.

All Aquablation subjects with baseline and 6-month scores had improvements of 6 month IPSS scores compared to baseline.

Table 4. IPSS population means by study visit and treatment.

	Aquablation				TURP			
	N	Mean	SD	Range	N	Mean	SD	Range
Baseline	116	22.9	(6.0)	[12-35]	65	22.2	(6.1)	[12-33]
1 Week	111	19.0	(8.6)	[3-35]	65	18.6	(8.1)	[2-32]
1 Month	116	10.4	(7.5)	[1-33]	65	11.0	(6.9)	[1-32]
3 Months	112	6.7	(5.4)	[0-23]	62	7.4	(6.0)	[1-30]
6 Months	114	5.9	(5.0)	[0-27]	62	6.8	(5.5)	[0-22]

Table 5. IPSS change scores by visit and treatment, based on subjects with follow-up at each time.

	Aquablation				TURP			
	N	Mean	SD	Range	N	Mean	SD	Range
Baseline	116	0.0	0.0	[0-0]	65	0.0	0.0	[0-0]
1 Week	111	-3.8	8.2	[-29-15]	65	-3.6	8.1	[-30-13]
1 Month	116	-12.5	8.6	[-31-8]	65	-11.1	7.7	[-30-10]
3 Months	112	-16.0	7.0	[-31-4]	62	-14.6	7.9	[-30-6]
6 Months	114	-16.9	6.6	[-31- -1]	62	-15.1	7.9	[-30-7]

Mean IPSS QOL (quality of life) score decreased from 4.8 in each group to 1.3 in the Aquablation group at 6 months and 1.5 in the TURP group. The 6-month difference in improvement (0.2 points) was not clinically or statistically significant.

Large, rapid and similar improvements in uroflow parameters were seen in both groups. Qmax increased from 9.4 and 9.1 cc/sec at baseline to 20.3 and 18.0 at 6 months in the Aquablation and TURP groups, respectively. Post void residual improved from 97 and 112 at baseline to 42 and 48 at 6-month follow-up in the Aquablation and TURP groups, respectively.

Table 6. Changes in mean (SD) symptom scores and uroflow measurements.

	Aquablation		TURP	
	Baseline	**Month 6**	**Baseline**	**Month 6**
IPSS	22.9 (6.0)	5.9 (5.0)*	22.2 (6.1)	6.8 (5.5)*
IPSS QOL	4.8 (1.1)	1.3 (1.4)*	4.8 (1.0)	1.5 (1.5)*
Qmax, cc/sec	9.4 (3.0)	20.3 (10.9)*	9.1 (2.7)	18.0 (7.5)*
Post void residual, cc	97 (79)	42 (50)*	112 (93)	48 (57)*

*Statistically significant ($p<.05$) change from baseline

Secondary Endpoints

Secondary endpoints (Table 7) were interpreted using a Holm step-down method. Statistically significant secondary endpoints include superiority for resection time and non-inferiority for reoperation/reintervention, hospital length of stay and major adverse urologic events (MAUE).

Table 7. Holm listing of secondary endpoint p-values. Endpoints meeting the Holm criteria are shown in bold font.

	Nominal P*	Endpoint	Type**	P-value for non-inferiority
1	**0.0083**	**Resection time**	**S**	**<0.0001**
2	**0.01**	**Reoperation/reintervention**	**NI (10%)**	**<0.0001**
3	**0.0125**	**Hospital LOS**	**NI (10%)**	**0.0003**
4	**0.0167**	**MAUE**	**NI (10%)**	**0.0015**
5	0.025	Worsening of sexual function***	S	0.0600
6	0.05	Operative time	S	0.2752

*Calculated as 0.05/[6,5,4,3,2,1]

**NI = non-inferiority (margin); S = superiority

***Includes both ejaculatory and erectile function

Additional Endpoints

Additional efficacy endpoints included the following:

- Incontinence, as measured by Incontinence Severity Index, improved from baseline to month 6 in both groups. Changes of scores were similar across groups.
- Amongst men who were sexually active at both baseline and study visits, the quality and quantity of ejaculate (as measured by MSHQ-EjD) increased slightly but not significantly from baseline levels in the Aquablation group but decreased by approximately 2 points in the TURP group. A repeated measures analysis of variance showed a mean difference of 3.2 points in change scores. MSHQ-EjD bother scores remained at baseline levels for Aquablation and were somewhat decreased for the TURP group.
- IIEF-5, which measures the quality of erections, showed no changes from baseline in either group.
- Dysuria scores increased slightly at one week in both groups but decreased from baseline at month 3 in the Aquablation group but not the TURP group.
- Pelvic pain levels in both groups were low and similar throughout follow-up.
- Reoperation for BPH within 30 days occurred in 0 Aquablation subjects and 1 TURP subject.
- The postoperative blood transfusion rate was low; transfusion was required in 1 Aquablation subject and 0 TURP subjects.

Pediatric Extrapolation

In this De Novo request, existing clinical data were not leveraged to support the use of the device in a pediatric patient population.

LABELING

The AQUABEAM System complies with the labeling requirements under 21 CFR 801.109 for prescription devices in the physician labeling. In addition, the labeling includes the adverse event profile and information providing evidence of prostate resection achieved. The labeling also identifies the validated shelf life for the single use components, reprocessing instructions for patient contacting reusable components and high level disinfection instructions for reusable non-patient contacting components.

TRAINING

New surgeon training will be provided for the AQUABEAM System. The goals of the training include:

- Thorough understanding of key aspects of the AQUABEAM System
- Use of the system for resection contour planning
- Best methods for imaging
- Methods to override or stop resection in case of problems

The new surgeon training consists of three modalities:

1. System and procedure review module
2. Hands-on training lab consisting of:
    a. Didactic review of system applications and treatment planning
    b. Hands on treatment planning simulator
    c. Cadaveric or similar model lab with simulated cases
3. Case support from a qualified proctor (trained surgeon or company trained proctor)
    a. Proctoring until surgeon is proficient with the AQUABEAM System
    b. PROCEPT staff support will also be provided as needed for case preparation

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of a fluid jet system for prostate tissue removal and the measures necessary to mitigate these risks.

Identified Risks to Health	**Mitigation Measures**
Injury from device operation causing one or more of the following: • Bleeding • Bruising • Penile or pelvic pain • Dysuria • Incontinence • Bladder or prostate capsule perforation • Sexual dysfunction, including ejaculatory and erectile dysfunction • TransUrethral Resection (TUR) syndrome • Urethral damage causing false passage or stricture • Rectal incontinence / perforation • Embolism	Clinical performance testing Animal testing Labeling Training
Adverse tissue reaction	Biocompatibility evaluation
Infection	Sterilization validation Reprocessing validation Shelf life testing Labeling
Failure to remove target tissue or removal of non-target tissue	Clinical performance testing Animal testing

	Software verification, validation, and hazard analysis Non-clinical performance testing Labeling Training
Electrical shock or electromagnetic interference	Electrical safety testing Electromagnetic compatibility testing Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the fluid jet system for prostate tissue removal is subject to the following special controls:

1. Clinical performance testing must evaluate the following:
    a. All adverse events associated with the device; and
    b. Improvement in Lower Urinary Tract Symptoms (LUTS).

2. Physician training must be provided that includes:
    a. Information on key aspects and use of the device; and
    b. Information on how to override or stop resection.

3. Animal testing must demonstrate that the device resects targeted tissue in a controlled manner without injury to adjacent non-target tissues.

4. Non-clinical performance data must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be tested:
    a. Measurement of targeting accuracy and reproducibility of high velocity fluid jet
    b. High pressure fluid jet verification testing at target and non-target tissues

5. Software verification, validation, and hazard analysis must be performed.

6. The patient-contacting elements of the device must be demonstrated to be biocompatible.

7. Performance data must demonstrate the electrical safety and electromagnetic compatibility (EMC) of the device.

8. Performance data must demonstrate the sterility of the patient-contacting components of the device.

9. Performance data must support the shelf life of the device by demonstrating continued sterility, package integrity, and device functionality over the identified shelf life.

10. Performance data must validate the instructions for reprocessing and reliability of reusable components.

11. Labeling must include the following:

a. A section that summarizes the clinical testing results, including the adverse event profile and improvement in Lower Urinary Tract Symptoms (LUTS);
b. A shelf life for single use components;
c. A use life for reusable components; and
d. Reprocessing instructions for reusable components.

BENEFIT-RISK DETERMINATION

The benefits and risks of the AQUABEAM System are based on nonclinical laboratory and animal studies as well as data collected in a clinical study described above.

In the WATER clinical study, men with moderate-to-severe LUTS due to BPH experienced improvements in symptoms directly related to bladder outlet obstruction. Notably, all WATER subjects who underwent Aquablation and had a 6-month visit had improved IPSS scores compared to baseline. Associated with these benefits were improvement in overall urinary health status (as evidenced by marked, rapid and sustained reduction in IPSS QOL scores) and objective improvements from baseline in uroflow measurements (Qmax, average urinary flow, and post void residual). These benefits are expected, given the long history of positive results from both clinical use and clinical studies of various methods to resect excess prostate tissue as a treatment for LUTS due to BPH. The study results demonstrate that the benefits of AQUABEAM are non-inferior compared to those of TURP.

The risks of the device, based on non-clinical laboratory and/or animal studies as well as data collected in the WATER clinical study described above, include: bleeding, urinary retention, stricture or adhesions, dysuria, erectile or ejaculatory dysfunction, and incontinence. The device does not introduce safety concerns not present with other typical interventions for this condition (such as TURP). The likelihood of a harmful event was found to be clinically non-inferior to that of a TURP (the gold standard of efficacy and safety for this intended use). Overall, the risk profile assessed by Clavien-Dindo rating system was similar between Aquablation and TURP except for a decreased risk of retrograde ejaculation in the Aquablation group (11.3% vs. 36.4%).

This technology demonstrates non-inferiority to the gold standard TURP with similar efficacy and safety. The safety profile is better than for TURP and the resection time is significantly less. One would expect the benefit-risk ratio to be the same or better than the time tested TURP and as such can reasonably be approved for marketing.

PATIENT PERSPECTIVES

Patient reported outcomes considered for the AQUABEAM System during the review included:

- International Prostate Symptoms Score (IPSS)
- Male Sexual Health Questionnaire (MSHQ)
- International Index of Erectile Function (IIEF-5)

The IPSS consists of 8 questions (7 regarding symptoms and 1 regarding quality of life) and is used as a screening, diagnostic and symptom tracking tool for BPH. Improvement is defined as a decrease of at least 3 points. Subjects treated with the AQUABEAM System showed a reduction in IPSS from baseline to 6 months.

Among men who were sexually active at both baseline and study visits, the quality and quantity of ejaculate (as measured by MSHQ-EjD) increased slightly but not significantly from baseline levels in the Aquablation group but decreased by approximately 2 points in the TURP group. A repeated measures analysis of variance showed a mean difference of 3.2 points in change scores. MSHQ-EjD bother scores remained at baseline levels for Aquablation and were somewhat decreased for the TURP group.

IIEF-5, which measures the quality of erections, showed no changes from baseline in either group.

BENEFIT/RISK CONCLUSION

In conclusion, for the resection and removal of prostate tissue in males suffering from lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia, the probable benefits outweigh the probable risks for the AQUABEAM System. The device provides benefits and the risks can be mitigated by the use of general controls and the identified special controls.

CONCLUSION

The De Novo request for the AQUABEAM System is granted and the device is classified as follows:

Product Code: PZP
Device Type: Fluid jet system for prostate tissue removal
Regulation Number: 21 CFR 876.4350
Class: II