# SUMMARY OF SAFETY AND EFFECTIVENESS DATA

## I. GENERAL INFORMATION

| | |
|---|---|
| Device generic name: | Transurethral Microwave Therapy Device |
| Device trade name: | Prolieve™ Thermodilatation System (Prolieve™) |
| Applicant's name and address: | Celsion Corporation<br>10220-L Old Columbia Road<br>Columbia, MD 21046-2364 |
| Premarket Approval (PMA) application number: | P030006 |
| Date of panel recommendation: | None |
| Date of notice of approval to the applicant: | February 19, 2004 |

## II. INDICATIONS FOR USE

Prolieve™ is a transurethral microwave therapy device that provides a non-surgical, minimally invasive procedure for the treatment of symptomatic Benign Prostatic Hyperplasia (BPH) in men with a prostate size of 20 to 80 grams, a prostatic urethra length between 1.2 cm and 5.5 cm and in whom drug therapy (e.g., Finasteride (Proscar®)) is typically indicated.

## III. CONTRAINDICATIONS

The contraindications for Prolieve™ are:

- Patients whose pain response has been significantly decreased by any means (previous surgery, regional or local anesthetic, or other relevant condition which is determined by the physician upon evaluation) because the patients' ability to detect pain is a treatment safety mechanism.
- Severe urethral stricture preventing catheterization.
- Current urinary or prostatic infection.
- Presence of a penile or urinary sphincter implant.
- Prostate size <20g or >80g.
- Peripheral arterial disease with intermittent claudication or Leriches Syndrome (i.e., claudication of the buttocks or perineum).

- Protruding median lobe resulting in a "ball-valve" type of obstruction at the bladder neck.
- Evidence of prostatic cancer or bladder cancer.
- Presence of metallic implants, e.g. pelvic, femur, penile prosthesis, etc.
- Presence of implanted cardiac pacemakers, or defibrillators.
- Previous transurethral prostatectomy.
- Patients interested in the preservation of future fertility.
- Patients with a previous history of pelvic radiation.
- Patients with coagulation disorders.
- Patients with renal impairment.
- Patients with neurological disorders that might affect bladder function.
- Patients with bladder stones and large post voiding residual (greater than 250 mL).

## IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Essential Prescribing Information labeling for Prolieve™.

## V. DEVICE DESCRIPTION

Prolieve™ is a transurethral microwave thermotherapy device equipped with automated controls designed to deliver microwave energy to the prostate and balloon-administered compression for the treatment of symptomatic BPH. This device utilizes a transurethral catheter with microwave antenna to heat the prostate, with simultaneous 46 Fr. prostatic urethral catheter balloon-administered compression. Water at 34.5°C is circulated through the transurethral catheter system and compression balloon. The microwave heating process is regulated through temperature feedback from three sensors mounted on the surface of a rectal temperature probe. The rectal temperature probe is placed against the rectal mucosa adjacent to the prostatic capsule. A treatment consists of applying microwave energy at 915 MHz ± 5 MHz (50 Watts maximum) to the prostate for 45 minutes reaching an intraprostatic temperature between 41°C and 46°C, at a rectal control temperature up to 41°C and a maximum rectal temperature of 42°C.

The device consists of a permanent instrument and a single-use Microwave Procedure Kit. The permanent instrument generates the microwave power, provides temperature-controlled water circulation, monitors treatment parameters with built in safety alerts, and records treatment data. A monitor screen with graphic user interference (GUI) provides a visual display. The permanent instrument is configured as a single integrated cart unit, which provides computer control, microwave power and temperature measuring capabilities, constant temperature thermoelectric plates, circulatory fluid pump, and rectal temperature probe. The thermoelectric plates are coupled to the heat exchanger cartridge, which is part of the Procedure Kit. In this way, the device can maintain the circulating

water at a temperature of 34.5°C ± 0.5°C at the point of entry into the transurethral catheter system. The single-use Procedure Kit contains a single sterile 18 Fr diameter 36 cm long microwave transurethral catheter, a heat exchanger cartridge system, and a 500 mL bag of sterile water. The transurethral catheter includes a 5cc retention balloon as well as a 3.7 cm long compression balloon for dilatation that reaches 46 Fr diameter when inflated. The microwave antenna consists of a coaxial cable; the active portion is positioned towards the distal end of the compression balloon.

## VI. ALTERNATIVE PRACTICES AND PROCEDURES

For symptomatic bladder obstruction secondary to BPH, the alternative procedures include those shown below.

- "Watchful waiting," some patients may improve or stabilize the symptoms.
- Drug therapy with a single drug or combined therapy with an alpha blocker and Finasteride (Proscar®). The combination relaxes the bladder neck and prostatic urethra and Finasteride can shrink the volume of BPH growth.
- Microwave thermotherapy (TUMT) using intraprostatic temperatures >46°C is effective in partially relieving symptoms of BPH. There are several devices approved for this purpose.
- TUNA that uses radiofrequency energy to destroy intraprostatic tissue resulting in opening of the obstruction.
- Urethral stents placed in the prostatic urethra to expand the opening of the channel.
- Laser treatment for resection, electrovaporization or coagulation of the BPH tissue.
- TURP, transurethral removal, piece by piece of BPH growth with an electrical loop.
- Transurethral incision of the prostate (TUIP), this is limited to prostates <30gm, and
- Open surgery via different approaches (suprapubic, retropubic or perineal) removes only the inner part of the gland.

## VII. MARKETING HISTORY

Prolieve™ has not been marketed in the United States or any other country.

## VIII. POTENTIAL ADVERSE EFFECTS

Microwave heating devices have the potential for producing the conditions listed below as a result of the delivery of therapeutic heat, or of the exposure to electromagnetic radiation. Those in the second column were observed during the clinical investigation of Prolieve™.

| Microwave Heating Devices | Observed with Prolieve™ |
|---|---|
| Bleeding (mild to excessive) | Bleeding (mild to excessive) |
| Urinary clot retention | Urinary clot retention |
| Complete urinary retention | Complete urinary retention |
| Incomplete urinary retention | Incomplete urinary retention |
| Urethral injury (irritation) | Urethral injury (irritation) |
| Chronic pain at site | Chronic pain at site |
| Bladder spasms | Bladder spasms |
| Urinary incontinence | Urinary incontinence |
| Prostatitis | Prostatitis |
| Urinary tract infection | Urinary tract infection |
| Retrograde ejaculation | Retrograde ejaculation |
| Impotence | Erectile Dysfunction |
| Anal Irritation | Anal Irritation |
| Urethral stricture | Bowel Irritation |
| Pelvic abscess | Pressure Sensation |
| Allergic reaction including anaphylaxis | Urinary Urgency |
| Bladder neck contracture | |
| Urethral tear | |
| Rectal wall injury | |
| Infertility | |
| Fistula | |

Please refer to Table 5 on Page 14 for the number and rate of adverse events observed during the clinical study.

## IX. SUMMARY OF PRECLINICAL STUDIES

**Laboratory Studies**

***In Vitro* – Phantom Studies**

Several phantom studies were performed by both Celsion Corporation and Montefiore Medical Center located in the Bronx, New York to evaluate the characteristics of the heat generated by the wave emissions from the device. The phantom material consisted of a tissue equivalent *in vitro* gel phantom, which has electromagnetic and thermal properties that are similar to those of human tissue. Each of these experiments was conducted using a temperature scanner platform with sensors spaced at known distances from the catheter's tip and a thermal sensing crystal sheet which generated visual color changes in response to temperature increases. The temperature scanner characterized the specific

absorption rates (SAR) of the energy absorbed at various distances over time. Both of the *in vitro* tests confirmed the preferential heating at the desired location and demonstrated a symmetrical pattern. The *in vitro* tests performed by Celsion and Montefiore Medical Center confirmed that the heating pattern of the microwave energy was repeatable and produced similar results. The maximum therapeutic heating volume was recorded as 13.6 $cm^3$ which represents a maximum prostate tissue mass of 13.6 grams.

**Animal Studies**

***In Vivo* – Animal Studies**

Canine studies were conducted at Montefiore Medial Center located in Bronx, New York to evaluate the ability of Prolieve™ to generate temperatures above 45°C in the prostate with rectal temperatures below 42°C. Eight (8) large male dogs were used to confirm that the heating pattern is consistent with those demonstrated in the in vitro phantom studies. Intraprostatic probes placed at various locations within the canine prostate recorded the temperature of the prostate, and a rectal probe was used to record rectal temperature. Pathological examinations identified a ring of expected necrosis around the urethra.

**Additional Studies**

**Biocompatibility/Sterility Testing**

Testing was performed on the single use components of Prolieve™, i.e., transurethral catheter and circulating water tubing in their final finished form, according to applicable parts of ISO 10993 Standards. The single-use catheter is a tissue implant device for limited use duration, i.e., ≤24 hours and the tubing is an external communicating device for limited use duration, i.e., ≤24 hours. The tests were conducted by North American Science Associates (NAMSA), Northwood, Ohio, under contract to Celsion. The tests conducted were: USP Systemic Toxicity Study in the Mouse, USP Intracutaneous Toxicity Study in the Rabbit, USP Muscle Implantation Study in the Rabbit, Hemolysis Study-In vitro Procedure (extraction method), Rabbit Pyrogen Study, and Cytotoxicity Study Using the ISO Elution Method. The results of these tests were negative, showing the transurethral catheter is reasonably safe for its intended use.

**Electromagnetic Compatibility (EMC) Testing**

Testing was conducted to assess the potential for the device to cause electromagnetic interference (EMI) in other devices, or to be susceptible to such interference. This testing demonstrated that Prolieve™ meets the EMC standards of IEC601-1-2:2001 and that use of other devices should be at distances greater than 2 meters from the Prolieve™ System. Testing was also conducted to characterize the strength of the electromagnetic field being emitted from Prolieve™ in the vicinity of the treatment location during a procedure. This testing revealed that non-target tissue 5.5 cm or more away from the transurethral catheter was below 3.0 $mW/cm^2$. This level is considered safe based on the recommendations of ANSI/IEEE Std C95.1-1999. Therefore, these data indicate it is safe for medical personnel to operate the device and/or be in contact with the patient during treatment.

**Shelf Life Testing**

A shelf life of one year has been established for the Prolieve™ Catheter with accepted accelerated shelf life testing. Real time shelf life validation is in progress. Package integrity testing was conducted in accordance with ASTM D4169-99, *Performance Testing of Shipping Containers and Systems*. Package burst pressure tests were conducted in accordance with ASTM F1140-88 *Standard Test Method for Failure*

*Resistance of Unrestrained and Non-rigid Packages for Medical Applications.* Package dye penetration tests were conducted in accordance with ASTM F1929-98, *Standard Test Method for Detecting Seal Leaks in Porous Medical Packaging by Dye Penetration.* Performance testing of the transurethral catheter was conducted in accordance with ASTM Standard F623-99 Standard Performance Specification for Foley Catheters.

## X. SUMMARY OF CLINICAL STUDIES

### Pilot Study

**Study Design**

A single center, open label, nonrandomized pilot study was conducted with a primary objective of evaluating the safety of Prolieve™ for the treatment of symptomatic BPH. The initial pilot study of 10 patients was initiated with a treatment time of 60 minutes. Based on the initial results, the study was expanded to include 10 additional patients to determine if a power ramp up could be done safely in a 45-minute treatment. The treatment consisted of applying microwave energy at 915 MHz ± 5 MHz (50Watts maximum) to the prostate for 45 minutes (60 minutes in first 10 patients) at a rectal control temperature up to 41°C and a maximum rectal temperature of 42°C, the automatic treatment abort temperature. Safety and effectiveness were assessed during treatment, and post-treatment intervals of 1, 2, 3, 6, and 12 months. Additional follow-up evaluations were performed on a yearly basis thereafter.

**Demographic Data**

Eighty percent of the patients were Caucasian. One patient (5%) was African-American and three patients (15%) were from other minority groups. The mean patient age was 64.9 years with a range of 47 to 75 years old.

**Patient Assessment**

Safety was evaluated from records of the occurrence of local and systemic symptoms during treatment, the presence of pain or discomfort during the follow-up evaluations, and the occurrence of anticipated and unanticipated adverse effects. Intraprostatic temperature mapping was performed on four patients; temperatures were between 41°C and 46°C. One of the four patients had pain medication pre-treatment. Sixty-five percent (13/20) of the patients did not experience any discomfort during the treatment. One patient was catheterized with the objective of maintaining patient comfort overnight and his catheter was removed the next day. Long-term follow-up on the patients has also demonstrated the safety of the device in that no adverse events were reported during follow-up.

Effectiveness was evaluated by AUA Symptom Index scores. Three months after treatment, the AUA total scores were expected to decrease and show an average of 30% improvement when compared to those at baseline. Upon completion of the pilot study 13/20 patients demonstrated a 45% mean improvement at 3 months followed by 10/20 patients exhibiting a 32% mean improvement at 6 months and 47 % improvement in 10/20 patients at 12 months. At 36 months 9/20 patients had a mean improvement of AUA total score of 32%.

## Pivotal Study

### Study Design

This multi-center, randomized, open-label trial compared a single outpatient treatment of symptomatic BPH with Prolieve™ lasting 45 minutes to that of a daily regimen of 5mg Proscar® (Finasteride). The patients were randomized in a 3:1 ratio of Prolieve™ to Proscar®. At the completion of the 6-month evaluation, patients randomized to Proscar® were permitted to crossover to receive treatment with Prolieve™. A total of 20 of the original 41 patients treated with Proscar® crossed over.

The treatment consisted of applying microwave energy at 915 MHz ± 5 MHz (50Watts maximum) to the prostate for 45 minutes at a rectal control temperature up to 41°C and a maximum rectal temperature of 42°C; the automatic treatment abort temperature of the device. Effectiveness and safety were assessed during treatment and at post-treatment follow-up visits at 2 weeks, 1, 2, 3, 6, and 12 months.

### Patient Assessment

*Effectiveness:* The primary objective of the study was to assess whether treatment with Prolieve™ would demonstrate clinical equivalency to treatment with Proscar®. Clinical equivalency was defined as having no less than 80% of the effectiveness of Proscar®. The primary endpoint of the study was the change in AUA Symptom Index score from baseline to 6 months. The response to treatment in the Prolieve™ treatment was evaluated out to 12 months post-treatment for durability as well. The secondary effectiveness outcome measures included peak flow rate (PFR), post void residual (PVR) as well as evaluation of the following:

- The International Index of Erectile Function (IIEF-5): This section consists of questions asking the patient about their erectile function.
- Quality of Life (QOL): Six questions focused on the patient's feelings about his urinary condition, perception of urinary difficulties, sexual functions, activities of daily living, general well-being and social activities.
- Impact of Lower Urinary Tract Symptoms (LUTS) on Quality of Life: Six questions related to the patient's urinary problems and if these problems interfered with the patient's life.
- BPH Impact Index (BII): Four questions related to the patient's concern over his urinary problems and the amount of physical discomfort experienced.
- BPH Specific Interference with Activities (BSI): Seven questions related to the degree to which the patient's urinary problems interfered with some common activities.
- Sexual Function: Six questions pertaining to the patient's sexual function.
- Pain or discomfort: Four questions related to the presence, location, frequency and severity of pain or discomfort in the urethra.

*Safety:* The objective was to substantiate the safety profile of Prolieve™. Safety was assessed by the frequency of local and systemic side effects during treatment, and the occurrence of anticipated and unanticipated adverse effects during follow-up.

**Accountability**

A total of 190 patients were randomized in the study, 142 to Prolieve™ and 48 to Proscar®. Before the initiation of treatment, 24 patients chose to withdraw from the study prior to any attempt at treatment (17 Prolieve™ / 7 Proscar®). Therefore, while still maintaining the 3:1 ratio, a total of 125 patients in the Prolieve™ arm and 41 patients in the Proscar® arm were included in the statistical analysis and comprise the intent-to treat population (Table 1). At the time the database was closed for analysis 92/125 (74%) of the patients in the treatment arm completed their 12-month follow-up. There were 20 patients treated with Prolieve™ following their participation in the pivotal trial in the Proscar® arm. The information for these 20 patients is included in the safety summary with the 125 patients originally randomized to Prolieve™. Five of the patients in the Prolieve™ intent-to-treat population went for treatment but treatment was canceled during the preparatory steps and these five patients are not included in the safety presentation for the post-treatment period.

**Table 1: Intent-to-Treat Patients by Treatment Arm and Study Center**

| Study Site | Number of Patients Treated or Attempted to Treat | | Total Patients |
|---|---|---|---|
| | Prolieve™ | Proscar® | |
| San Antonio Research<br>San Antonio, Texas | 31 | 14 | 45 |
| Regional Urology<br>Shreveport, Louisiana | 30 | 1 | 31 |
| Montefiore Medical Center<br>Bronx, New York | 12 | 1 | 13 |
| Grand Strand Urology<br>Myrtle Beach, South Carolina | 10 | 2 | 12 |
| Kansas City Urology Care<br>Kansas City, Missouri | 10 | 5 | 15 |
| Pacific Urology Institute<br>Santa Monica, California | 10 | 6 | 16 |
| Dr. Raymond Fay<br>San Francisco, California | 7 | 5 | 12 |
| Nevada Urology Associates<br>Reno, Nevada | 5 | 2 | 7 |
| Atlantic Urology Research<br>Daytona Beach, Florida | 3 | 2 | 5 |
| Physicians in Urology<br>Livingston, New Jersey | 2 | 1 | 3 |
| Georgia Urology Research<br>Atlanta, Georgia | 2 | 0 | 2 |
| University of Maryland<br>Baltimore, Maryland | 2 | 1 | 3 |
| Urology Associates of North Texas<br>Arlington, Texas | 1 | 0 | 1 |
| Michigan Institute of Urology<br>St. Claire's Shore, Michigan | 0 | 1 | 1 |
| Total Patients | 125 | 41 | 166 |

**Demographic Data**

Eighty-three percent of the patients in both treatment arms were Caucasian (104/125, 34/41). The mean age of the patients in the Prolieve™ arm was 63.7 (43-87) years compared to 64.3 (50-83) years for patients in the Proscar® arm. The difference in the mean age between the treatment arms was not statistically significant.

**Data Analysis and Results on Intent-to-Treat Population**

*Effectiveness:* The primary effectiveness analysis was a repeated measure analysis using the least squares model for each follow-up evaluation comparing the two treatment arms. All patients with missing data at any follow-up evaluation or who did not attend a visit were included in the analysis as failures.

**Repeated Measures Mean Improvement Comparison on Intent to Treat Population**

*Primary Effectiveness Variable: AUA Total Score*

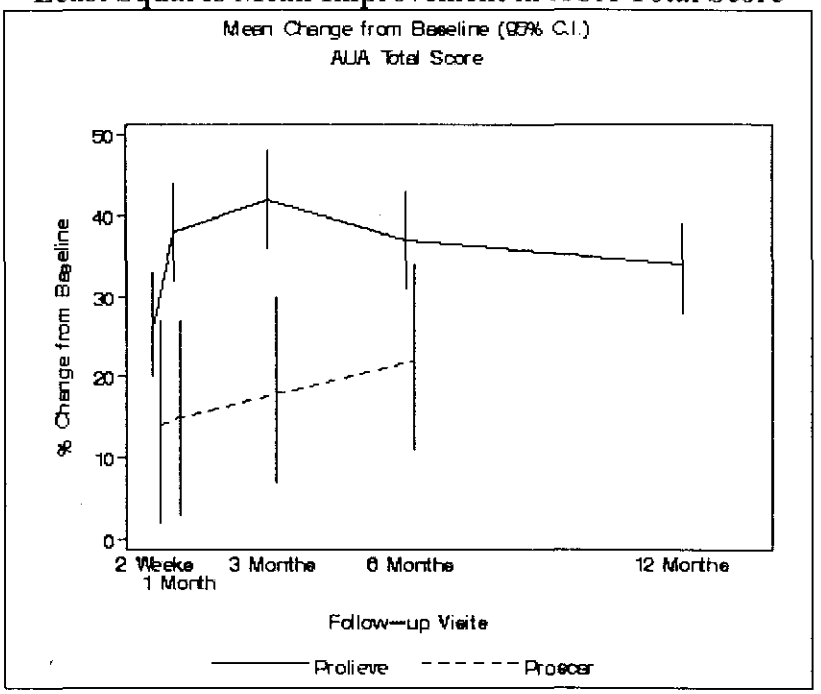
The mean improvement in AUA total score for the patients treated with Prolieve™ was greater than the mean improvement observed for patients treated with Proscar® at each follow-up evaluation (2 week, 1 month, 3 months, and 6 months) except the 12-month visit at which Proscar® patient data was not collected and are presented below in Table 2. Graph A below presents this information in graphic format. The vertical lines represent the confidence intervals.

**Table 2: Repeated Measures Analysis**
**Least Squares Mean Improvement in AUA Total Score**

| Visit | Treatment Arm | Absolute Mean Improvement (95% CI) | Percent Improvement (95% CI) |
|---|---|---|---|
| 2-week | Prolieve™ | **5.7** (4.3, 7.1) | **26%** (20, 33) |
| | Proscar® | **2.8** (0.4, 5..3) | **14%** (2, 27) |
| 1-month | Prolieve™ | **8.4** (7.1, 9.7) | **38%** (32, 44) |
| | Proscar® | **3.0** (0.7, 5.2) | **15%** (3, 27) |
| 3-month | Prolieve™ | **9.2** (8.0, 10.5) | **42%** (36, 48) |
| | Proscar® | **3.6** (1.4, 5.8) | **18%** (7, 30) |
| 6-month | Prolieve™ | **8.1** (6.9, 9.4) | **37%** (31, 43) |
| | Proscar® | **4.4** (2.2, 6.7) | **22%** (11, 34) |
| 12+ month | Prolieve™ | **7.4** (6.2, 8.6) | **34%** (28, 39) |

**note: the data above is based on the Prolieve™ intent-to-treat patients, N=125, and Proscar® treated patients, N=41.*

**Graph A: Repeated Measures Analysis**
**Least Squares Mean Improvement in AUA Total Score**




**Effectiveness Results on Evaluable Patients-Prolieve™ Patients Only**

*AUA Responder Rates for Treated Patients:* All patients having a 30% or greater improvement in AUA total score from baseline during the follow-up evaluation were considered responders. Only patients treated with Prolieve™ who were present at the visit were included in the analysis, i.e., evaluable patients. The percent of treated patients present at the 3-month visit with an improvement in AUA total score of 30% or greater was 69% (79/114). This response was sustained out to the 12+-month visit where 74% (68/92) of the treated patients had a 30% or greater improvement in AUA total score (Table 3) where up to 23% (28/120) of the patients were not available for a 12-month follow-up but 18/28 were later found to have received alternative treatment.

*Mean Improvement for Treated Patients:* Only patients treated with Prolieve™ who were present at the visit were included in the analysis. The mean improvement of 10.1 (47%) (95% CI, 8.5, 11.6) for 92/120 patients observed at the 12+month visit indicates the improvement was sustained.

**Table 3: Response for Total AUA Symptom Score in Percent Improvement**

| Visit | Group | Percent Response | | | |
|---|---|---|---|---|---|
| | | Worsened | No Change 0 to 29% | Improved 30 to 100% | Missing |
| 2 week | Prolieve™ | **27** (23%) | **29** (24%) | **59** (49%) | **5** (4%) |
| | Proscar® | **10** (24%) | **20** (49%) | **10** (24%) | **1** (2%) |
| 1 month | Prolieve™ | **14** (12%) | **26** (22%) | **74** (62%) | **6** (5%) |
| | Proscar® | **13** (32%) | **11** (27%) | **13** (32%) | **4** (10%) |
| 3 month | Prolieve™ | **8** (7%) | **27** (23%) | **79** (66%) | **6** (5%) |
| | Proscar® | **11** (27%) | **8** (20%) | **16** (39%) | **6** (15%) |
| 6 month | Prolieve™ | **6** (5%) | **30** (25%) | **69** (58%) | **15** (13%) |
| | Proscar® | **8** (20%) | **14** (34%) | **13** (32%) | **6** (15%) |
| 12 month | Prolieve™ | **8** (7%) | **16** (13%) | **68** (57%) | **28** (23%) |

**note: the data above is based on the Prolieve™ treated patients, N=120, and Proscar® treated patients, N=41.*

*Secondary Effectiveness Parameters:* The secondary effectiveness parameters evaluated were peak flow rate, post-residual volume, quality of life, erectile function (IIEF-5), impact of lower urinary tract symptoms (LUTS) on quality of life; BPH Impact Index (BII); BPH specific interference with activities (BSI); sexual function; pain and discomfort. In addition a covariate analysis based on prostate weight was performed to assess the impact of treatment success with respect to prostate size. The results for these secondary endpoints and analysis are described below. The secondary effectiveness analysis is performed on the intent-to-treat population, N=125 for the Prolieve™ patients and N=41 on the Proscar® patients.

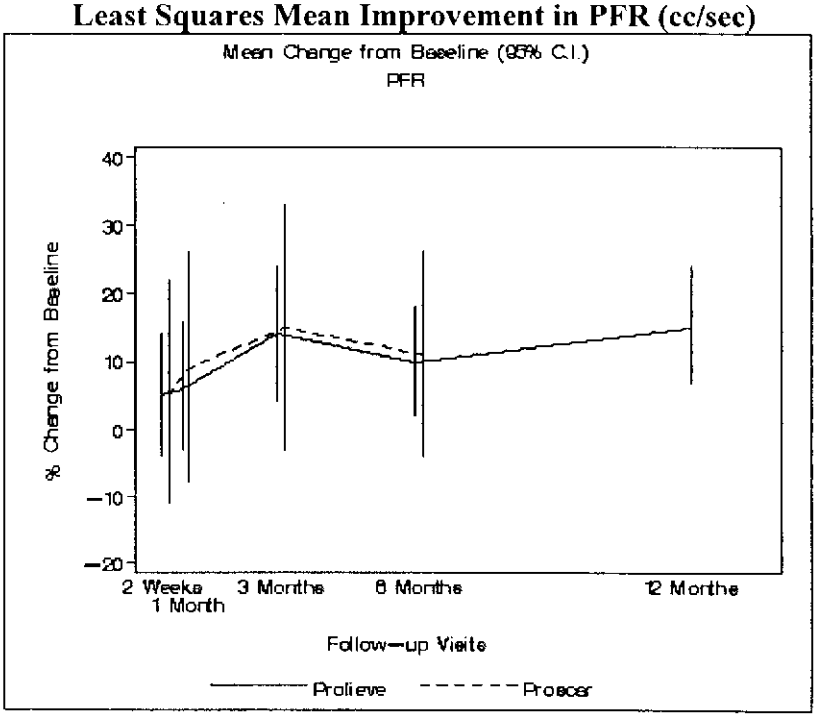
- *PFR (cc/sec):* At the 12+month visit patients treated with Prolieve™ had a 15% improvement in PFR when compared to baseline (95% CI, 7, 24 cc/s) (Table 4 and Graph B).

**Table 4: Repeated Measures Analysis**
**Least Squares Mean Improvement in PFR (cc/sec)**

| Visit | Treatment Arm | Absolute Mean Improvement (95% CI) | Percent Improvement (95% CI) |
|---|---|---|---|
| 2 week | Prolieve™ | **0.5** (-0.4, 13) | **5%** (-4, 14) |
| | Proscar® | **0.5** (-1.0, 2.0) | **5%** (-11, 22) |
| 1 month | Prolieve™ | **0.6** (-0.3, 1.5) | **6%** (-3, 16) |
| | Proscar® | **0.8** (-0.7, 2.4) | **9%** (-8, 26) |
| 3 month | Prolieve™ | **1.4** (0.4, 23) | **14%** (4, 24) |
| | Proscar® | **1.4** (-0.3, 3.0) | **15%** (-3, 33) |
| 6 month | Prolieve™ | **1.0** (0.2, 1.7) | **10%** (2, 18) |
| | Proscar® | **1.0** (-0.3, 2.4) | **11%** (-4, 26) |
| 12+ month | Prolieve™ | **1.5** (0.7, 2.3) | **15%** (7, 24) |

**note: the data above is based on the Prolieve™ intent-to-treat patients, N=125, and Proscar® treated patients, N=41.*

**Graph B: Repeated Measures Analysis**
**Least Squares Mean Improvement in PFR (cc/sec)**



- *QOL:* The mean improvement for the patients treated with Prolieve™ was 4.5 (19%) compared to 1.1 (5%) for the patients treated with Proscar® at the 6-month visit (95% CI, 5, 25). This improvement was sustained to the 12+-month visit where the mean improvement was 4.2 or 18% (95% CI, 14, 22).

- *LUTS:* The mean improvement for the patients treated with Prolieve™ was 2.3 (17%) compared to 0.8 (6%) for the patients treated with Proscar® at the 6-month visit (95% CI, 3, 18). The improvement observed in the patients treated with Prolieve™ was sustained to the 12+-month visit where the mean improvement was 2.0 or 14% (95% CI, 11, 18).

- *BSI:* The mean improvement for the patients treated with Prolieve™ was 3.4 (19%) compared to 0.8 (5%) for the patients treated with Proscar® at the 6-month visit (95% CI, 2, 27). The improvement observed in the patients treated with Prolieve™ was sustained to the 12+-month visit where the mean improvement was 3.8 or 20% (95% CI, 15, 26).

- *BII:* The mean improvement for the patients treated with Prolieve™ was 2.2 (23%) compared to 1.0 (12%) for the patients treated with Proscar® at the 6-month visit (95% CI, 0, 24). The improvement observed in the patients treated with Prolieve™ was sustained to the 12+-month visit where the mean improvement was 2.1 or 23% (95% CI, 17, 28).

- *IIEF-5:* The comparison between the two treatment arms with respect to erectile function appear to be similar at each of the follow-up visits.

- *PVR:* The PVR mean change from baseline for the two treatment arms appear to be similar at each of the follow-up visits.

- *Sexual Function:* A comparison of responses by patients in the two treatment arms was made for the questions asking if the patient experienced pain with erections, intercourse and/or ejaculations. Less than 1% of patients treated with Prolieve™ experienced some form of erectile dysfunction following treatment.

- *Pain and Discomfort:* No differences were observed between the two treatment arms at any of the follow-up evaluations with respect to pain and discomfort.

- *Prostate weight and response rates:* A comparison in response rates based on AUA total score and prostate weight was made for the patients treated with Prolieve™. Those patients with prostate weights of ≤40grams were included in one group while patients with prostate weights>40 grams were placed in the other group. At the 6-month visit the patients in the ≤40gram group had a 71% (51/72) AUA responder rate (percent improvement of 30% or greater compared to baseline) compared to 34% (18/53) for the patients in the >40gram group (95% CI, 20.4, 53.4). These results demonstrated that patients with prostates >40grams did not demonstrate as significant a response as patients with prostate weights of ≤40grams.

**Adverse Events**

The adverse events that were directly attributed to the procedure were urethral irritation, bladder spasms and complete urinary retention resolving by the 2-week visit.

A summary of the adverse events at treatment and during the follow-up evaluation of 1-year is presented in Table 5. The patients included in the Reported at Treatment column are the 125 randomized to Prolieve™ plus the 20 patients who crossed over from the Proscar® treatment arm. There were five patients in whom the treatment was cancelled and they are not included in the 140 patients followed in the post-treatment period.

Adverse events experienced by the Proscar® patients were not recorded other than those events associated and similar to the Prolieve™ patients and are therefore not reported.

**Table 5: Number and Rate of Adverse Events Reported During the Pivotal Investigation**

| Symptom | Reported at Treatment (N=145) | Reported During Post- Treatment (N=140)* | | | | |
|---|---|---|---|---|---|---|
| | | 2- Week (N=131) | 1-M (N=131) | 3-M (N=129) | 6- M (N=121) | 12+M (N=103) |
| Anal irritation | 1 (0.7%) | | | | | |
| Bladder spasm | 17 (12%) | 3 (2.3%) | | 1 (0.8%) | 1 (0.8%) | |
| Bleeding (mild to excessive) | 5 (3.4%) | | | | | |
| Bowel irritation | 1 (0.7%) | | | | | |
| Chronic pain at site | | 2 (1.5%) | 1 (0.8%) | 1 (0.8%) | 1 (0.8%) | |
| Complete urinary retention | 22 (15.2%) | 6 (4.6%) | | | | |
| Incomplete urinary retention | | 7 (5.3%) | 9 (6.9%) | 5 (3.9%) | 3 (2.5%) | 4 (3.9%) |
| Erectile Dysfunction | | 1 (0.8%) | 2 (1.5%) | 1 (0.8%) | 1 (0.8%) | 1 (0.8%) |
| Pressure sensation | 1 (0.7%) | | | | | |
| Prostatitis | | 1 (0.8%) | | 1 (0.8%) | 1 (0.8%) | 1 (1.0%) |
| Retrograde ejaculation | | | | | 1 (0.8%) | |
| Urethral injury (irritation) | 2 (1.4%) | 2 (1.5%) | | | | |
| Urinary clot retention | | | 1 (0.8%) | | | |
| Urinary incontinence | | 2 (1.5%) | 1 (0.8%) | 1 (0.8%) | 1 (0.8%) | 1 (1.0%) |
| Urinary tract infection | | 1 (0.8%) | | | 1 (0.8%) | 1 (1.0%) |
| Urinary urgency | 3 (2.1%) | | | | | |
| Total | 52 (35.9%) | 25 19.1%) | 14(10.7%) | 10(7.8%) | 10(8.3%) | 8(7.8%) |

*Does not include the 5 patients in whom treatment was cancelled.

**Catheterizations associated with treatment**: Sixteen percent (22/140) of the patients were catheterized due to urinary retention post treatment. Sixty four percent (14/22) of these catheterizations were for three days or less. All but one patient was catheterized for less than one week. There were 3 patients who were catheterized for reasons other than urinary retention. One patient experienced bladder spasms requiring catheterization and a second patient had the catheter replaced during treatment due to a leak. The third patient

had a false passage, Prolieve™ treatment was not initiated and the patient was catheterized for 3 days.

## XI. CONCLUSIONS DRAWN FROM THE STUDIES

The laboratory, animal, and clinical study data provide a reasonable assurance of the safety and effectiveness of Prolieve™ for the relief of symptomatic BPH when used as indicated.

The clinical data from patients treated with Prolieve™ demonstrated that the treatment provides patient benefit with low morbidity. The effectiveness results, one year after treatment, demonstrate the durability of treatment response.

Adverse events were generally transitory, resolving within a few days after treatment.

## XII. PANEL RECOMMENDATIONS

Pursuant to section 515(c)(2) of the Food, Drug, and Cosmetic Act (the act) as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Gastroenterology and Urology Devices Panel, an FDA advisory panel, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

## XIII. CDRH DECISION

Based on the data contained in the PMA, CDRH has determined that the Prolieve™ is reasonably safe and effective for the indication to relieve symptoms associated with symptomatic BPH in men with a prostatic urethra length between 1.2 cm and 5.5 cm and a total prostate size between 20 and 80 g. Furthermore, the applicant agreed to conduct a postapproval study to collect data on the long-term (5-year) effect of the device.

The applicant's manufacturing facilities were inspected and determined to be in compliance with the Quality System Regulation (21CFR 820). CDRH issued an approval order to the applicant on February 19, 2004.

## XIV. APPROVAL SPECIFICATIONS

Directions for Use: See the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.