

Vardenafil in Patients With Erectile Dysfunction: Achieving Treatment Optimization

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ABSTRACT: This post hoc analysis of data from a multicenter, randomized, double-blind study determined how many attempts were needed to record at least 1 successful penetration and maintenance of erection long enough for successful intercourse in a broad population of men with erectile dysfunction taking vardenafil at 5, 10, or 20 mg or placebo. The cumulative probability of achieving successful penetration and of maintaining an erection increased with the number of attempts for all 3 vardenafil groups. For the first attempt, the probability of achieving successful penetration was higher in all 3 vardenafil groups compared with placebo; 67% in the 5-mg vardenafil group, 77% in the 10-mg vardenafil group, and 74% in the 20-mg vardenafil group compared with 46% for placebo. By the third attempt, the probability of at least 1 success was 82% for 5, 88% for 10, and 85% for 20 mg vardenafil compared with 68% for pla-

cebo. The probability of maintaining an erection long enough to complete intercourse at the first attempt was 51% for 5, 69% for 10, and 61% for 20 mg vardenafil compared with 28% for the placebo group. By the third attempt, the probability of maintaining an erection was 66% for 5, 81% for 10, and 77% for 20 mg vardenafil in contrast to 53% for placebo. The results of this analysis indicate that patients without initial treatment success should continue treatment or increase the dose because the cumulative probability of success increases with additional attempts with vardenafil, with a plateau at about the fourth dose.

Key words: Impotence, drug therapy, clinical trial, phosphodiesterase inhibitor, cumulative probability.

J Androl 2005;26:604–609

Erectile dysfunction (ED) is a common disorder that can result from a variety of factors, such as pre-existing disease, including hypertension, diabetes, cardiovascular disease, smoking, psychological influences, hormone levels, and spinal cord injury (Lue, 2000). ED affects an estimated 20–30 million men in the United States (National Institutes of Health, 1993) and over 150 million men worldwide (Aytaç et al, 1999). It has been estimated that by 2025, the worldwide prevalence will be approximately 322 million (Aytaç et al, 1999).

Therapeutic options for ED include local treatments, such as transurethral alprostadil, vacuum constriction devices, and surgical treatment, but these are invasive and can be painful, and some are associated with high rates of discontinuation (Lue, 2000). Orally administered treatments include phosphodiesterase type 5 (PDE5) inhibitors, such as sildenafil citrate and vardenafil, alpha adre-

nergic antagonists such as phentolamine and yohimbine, or centrally acting agents such as apomorphine. Oral PDE5 inhibitors are considered the treatment of choice for most men with ED because of their efficacy and safety and the convenience of oral administration.

Vardenafil is a selective PDE5 inhibitor, which has been demonstrated in vitro to be 10 times more potent than sildenafil at inhibiting PDE5 (Sáenz de Tejada et al, 2001). The recommended starting dose of vardenafil for most patients is 10 mg and can be increased to 20 mg or decreased to 5 mg depending on efficacy and tolerability. The efficacy of vardenafil has been documented in several large trials in a broad population of men with ED and in men with difficult-to-treat ED, including men with type 1 or 2 diabetes mellitus or a history of radical prostatectomy (Porst et al, 2001, 2003; Hellstrom et al, 2002; Brock et al, 2003; Goldstein et al, 2003).

A pivotal study conducted in the United States and Canada demonstrated that vardenafil improved erectile function when compared with placebo in a broad population of men with ED of various causes and severity (Hellstrom et al, 2002). Up to 85% of men reported improved erections with vardenafil, and treatment improved mean rates of successful penetration and successful maintenance of erection over all attempts over 26 weeks

This research was supported by Bayer Corporation, Pharmaceutical Division, West Haven, Conn.

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Received for publication December 4, 2005; accepted for publication June 1, 2005.

DOI: 10.2164/jandrol.05026

(Hellstrom et al, 2002). The objective of this post hoc analysis reported here was to determine how many attempts were required to record at least 1 successful penetration and maintenance of erection long enough for successful intercourse by patients treated with vardenafil compared with placebo.

Materials and Methods

Study Design

This multicenter, randomized, double-blind, placebo-controlled, fixed-dose study compared vardenafil at 5, 10, and 20 mg and placebo and has been described previously (Hellstrom et al, 2002). It was performed in 54 centers in the United States and Canada and consisted of 3 phases: a 4-week baseline period during which no treatment or device for ED was allowed; a 26-week treatment phase during which patients received vardenafil or placebo; and a 1-week follow-up phase for continued monitoring of adverse events.

Inclusion Criteria

Men aged 18 years or more with ED, as defined by the National Institutes of Health Consensus statement (National Institutes of Health, 1993), who had been in a stable heterosexual relationship for greater than 6 months were eligible for the study. Patients who had experienced a 50% or greater failure rate in maintaining an erection on at least 4 attempts at sexual intercourse on 4 separate days during the untreated baseline period were eligible for the study.

Exclusion Criteria

Men with a history of ED after spinal cord injury, radical prostatectomy, retinitis pigmentosa, angina pectoris, or poorly controlled diabetes mellitus ($\text{HbA}_{1\text{C}} > 12\%$) were excluded from the study. Other exclusion criteria included (but were not limited to) primary hypoactive sexual desire, nonresponse to sildenafil, a history of hepatitis B or hepatitis C, and the concomitant use of nitrates.

Treatment

Patients were instructed to take 1 dose of the study drug approximately 1 hour before intended sexual intercourse, and without regard to food intake. No more than 1 treatment dose was allowed per calendar day.

Efficacy Variables

Explorative post hoc analyses were performed on data from the intent-to-treat (ITT) population (all patients who had received at least 1 dose of study medication) with at least 1 valid diary question answered for 2 questions on the Sexual Encounter Profile (SEP). The questions were, "Were you able to insert your penis into your partner's vagina?" (SEP-2), and "Did your erection last long enough for you to have successful intercourse?" (SEP-3). Answers to the SEP-2 and SEP-3 questions were recorded in patient diaries after every attempt at intercourse during the double-blind phase. The criteria evaluated were the cumu-

lative probability of achieving a first success using the number of valid diary attempts for the penetration (SEP-2) and maintenance (SEP-3) diary question.

All valid diaries were sorted by calendar day and time within calendar day. A valid diary entry required date of study drug consumption, SEP-2 and SEP-3 answers reflecting a medicated attempt at intercourse, and no evidence of the sexual activity starting later than 12 hours after dosing. A patient attempt with no enlargement of the penis and a missing answer for SEP-2 or SEP-3 was treated as a "no" answer in the analyses.

Safety

The safety analysis included patients who had received at least 1 dose of study medication and had postbaseline safety and tolerability data. Adverse events were monitored in all patients, and the investigator assessed each adverse event for its seriousness, intensity (mild, moderate, or severe), and relationship to the study medication. A full physical examination was performed at screening, and abbreviated examinations were performed at weeks 12 and 26 following commencement of therapy. Routine laboratory tests and vital signs were performed at screening, at baseline, and at regular intervals during treatment.

Statistical Methods

The cumulative probability of success for the first time by attempt x is defined as the probability of success for the first time at attempt 1 plus the probability of success for the first time at attempt 2 plus the probability of success for the first time at attempt x , as shown by the following example. Of 10 patients, if 5 have success for the first time at attempt 1, 2 have success for the first time at attempt 2, 1 has no further attempts, and 1 has success for the first time at attempt 3, then the cumulative rate of success for the first time by attempt 3 is $5/10 + 2/10 + 1/9 = 0.81$. The cumulative probability at attempt x can be interpreted as the estimated probability of having at least 1 successful attempt among the first x attempts.

Results

Patient Characteristics

In total, 805 men were randomized to treatment, and over the course of the 26-week treatment phase, 297 men (37%) discontinued: 54% of patients randomized to placebo discontinued, whereas 38%, 27%, and 30% in the vardenafil 5-mg, 10-mg, and 20-mg groups discontinued, respectively. More patients (20%) in the placebo group withdrew because of insufficient therapeutic effect, compared with 13%, 5%, and 5% in the 3 vardenafil groups, respectively. Adverse events caused discontinuation for 2% of patients in the placebo group and 4%, 3%, and 8% of patients in the 5-mg, 10-mg, and 20-mg vardenafil groups, respectively. The safety population included 762 men, and 749 men were valid for the ITT population. Patient characteristics at baseline for the total safety population were similar across treatment groups (Table 1).

Table 1. Patient characteristics (safety population)

Characteristic*	Placebo (n = 182)	Vardenafil		
		5 mg (n = 193)	10 mg (n = 199)	20 mg (n = 188)
Age at enrollment, mean y	57	57	57	58
Race, % caucasian	77	77	80	82
BMI, mean kg/m ²	28.8	29.4	28.4	28.7
Time since first noticed ED, mean y	5.1	5.9	6.0	6.6
Time since ED first diagnosed, mean y	2.9	3.6	3.6	4.2
Baseline IIEF EF score	13.7	12.6	13.4	12.8
Prior sildenafil use (%)	68	77	74	66

* BMI indicates body mass index; ED, erectile dysfunction; EF, erectile function domain; and IIEF, international index of erectile function.

The mean age was in the mid- to late 50s. Patients were diagnosed with ED an average of 3.6 years before screening.

Efficacy

The probability of achieving successful penetration at the first attempt was greater in all 3 vardenafil groups compared with placebo; 67% in the 5-mg vardenafil group, 77% in the 10-mg vardenafil group, and 74% in the 20-mg vardenafil group compared with 46% for placebo (Figure 1). The cumulative probability of achieving successful penetration increased with the number of attempts for all 3 vardenafil groups. By the third attempt, the probability of at least 1 success was 82% for 5, 88% for 10, and 85% for 20 mg vardenafil compared with 68% for placebo. For all 3 vardenafil doses, the cumulative probability reached a plateau by the fourth attempt.

The probability of maintaining an erection sufficient for successful intercourse with 1 dose was 51% for 5, 69% for 10, and 61% for 20 mg vardenafil compared with 28% for placebo (Figure 2). The cumulative probability of maintaining an erection increased with the number of attempts for all 3 vardenafil groups. By the third attempt,

the probability of maintaining an erection long enough to complete intercourse was 66% for 5, 81% for 10, and 77% for 20 mg vardenafil in contrast to 53% for placebo. For 10 and 20 mg vardenafil, the cumulative probability plateaued by the fourth attempt. For 5 mg vardenafil, the cumulative probability increased gradually with the number of attempts, reaching a plateau at around 9 attempts.

The total number of successes among a given number of attempts differed substantially between the placebo group and vardenafil groups for both achieving successful penetration and maintaining an erection. For example, among the first 3 attempts in all 3 vardenafil groups, more patients had 2 or 3 successes compared with placebo (Figures 3a and b).

Safety and Tolerability

Treatment-emergent adverse events were mostly mild to moderate in nature, and vardenafil was generally well tolerated (Hellstrom et al, 2002). Table 2 lists adverse events with an incidence of at least 5% in any treatment group. Headache was the most common adverse event in the vardenafil groups, ranging from 10% to 22% compared with 4% among patients in the placebo group.

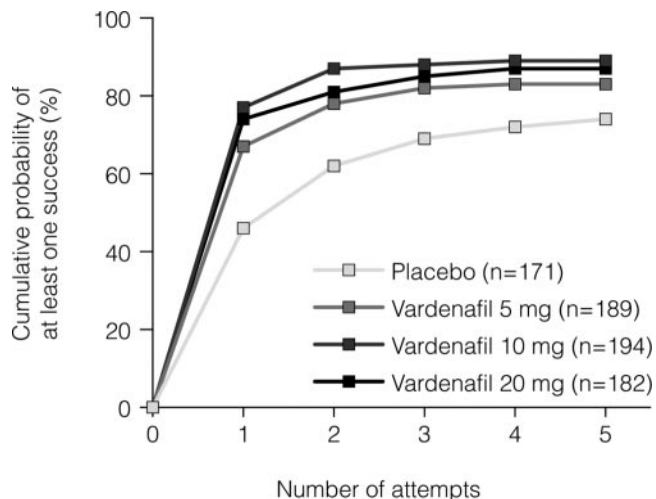


Figure 1. Cumulative probability of achieving at least 1 successful penetration (ITT).

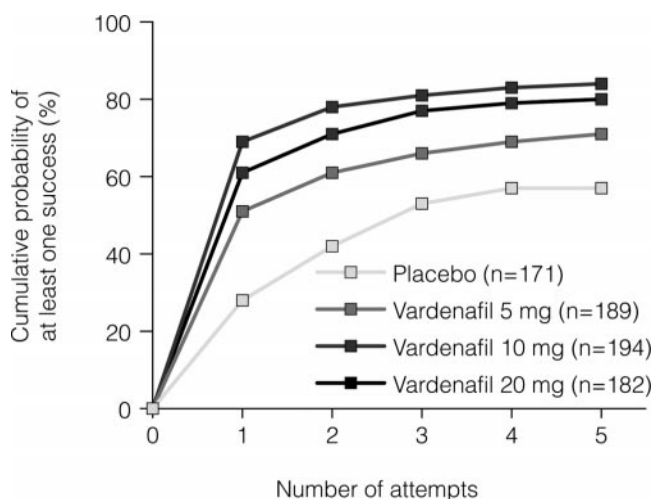


Figure 2. Cumulative probability of achieving at least 1 success at maintaining an erection long enough to complete intercourse (ITT).

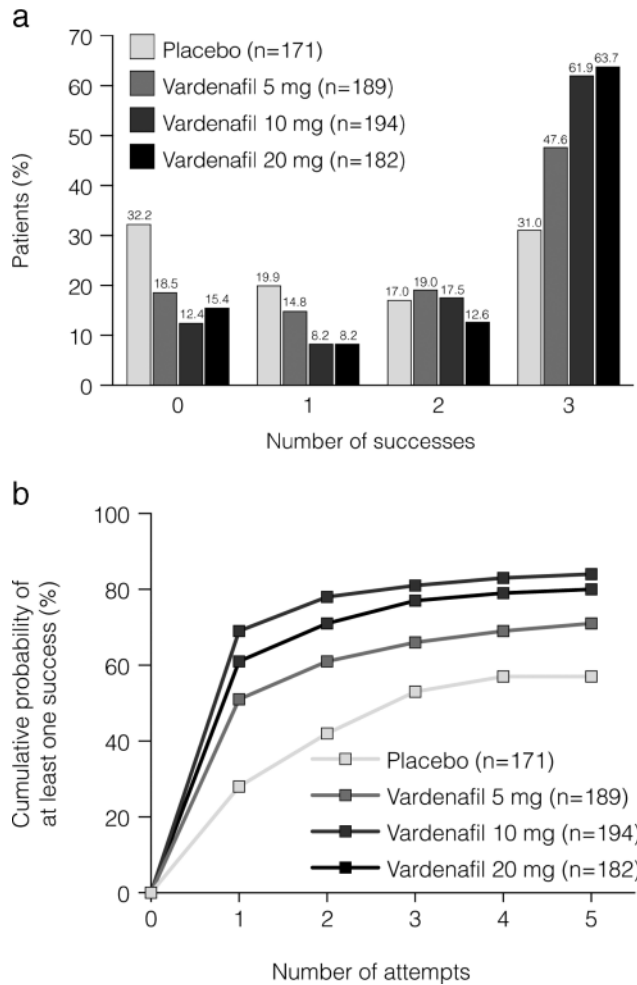


Figure 3. (a) Proportion of patients who achieved successful penetration on 0, 1, 2, or 3 occasions within the first 3 intercourse attempts. (b) Proportion of patients who maintained an erection long enough to complete intercourse on 0, 1, 2, or 3 occasions within the first 3 attempts.

The rate of serious adverse events was similar across treatment groups, with a 5% incidence in the placebo and 5-mg, 3% in the 10-mg, and 4% in the 20-mg vardenafil groups. Laboratory abnormalities were similar across groups, and changes in vital signs were minor and mostly similar across groups, with no evident relationship to dose (Hellstrom et al, 2002). Discontinuations as a result of adverse events were infrequent, ranging from 2% to 7% across study groups.

Discussion

This post hoc analysis of data from the North American pivotal study demonstrates that the cumulative probability of achieving successful penetration increased with the number of attempts for 5, 10, and 20 mg vardenafil, reaching a plateau by about the fourth attempt. The prob-

Table 2. Number of treatment-emergent adverse events with an incidence of more than 5% in any treatment group (safety population)

	No. of Adverse Events (%)			
	Placebo (n = 182)	Vardenafil		
		5 mg (n = 193)	10 mg (n = 199)	20 mg (n = 188)
Headache	8 (4)	19 (10)	44 (22)	40 (21)
Rhinitis	9 (5)	17 (9)	27 (14)	32 (17)
Flushing	0 (0)	9 (5)	20 (10)	24 (13)
Dyspepsia	1 (<1)	2 (1)	8 (4)	12 (6)
Accidental injury	5 (3)	11 (6)	7 (4)	8 (4)

ability of achieving successful penetration at the first attempt was greater for all 3 doses of vardenafil compared with placebo. By the third attempt, the probability of achieving successful penetration had increased to greater than 80% for all doses of vardenafil (compared with 68% with placebo). Similarly, treatment with 5, 10, and 20 mg vardenafil increased the probability of maintaining an erection long enough to complete intercourse. Therapy with vardenafil improved the probability of maintaining an erection at the first attempt compared with placebo, and by the third attempt, the probability of maintaining an erection was as high as 81% in the 10-mg vardenafil group (compared with 53% in the placebo group). The cumulative probability of achieving a first-time successful penetration or maintaining an erection takes into account all the previous attempts and therefore increases with successive attempts. On average, patients enrolled in this study had moderate ED at baseline, according to mean erectile function domain scores. Even patients receiving placebo would be expected to have some success after several attempts at intercourse. Although success rates with placebo were lower than with vardenafil for earlier attempts, the cumulative probability for placebo also increased with subsequent attempts. It should be noted, however, that the overall mean per-patient success rates for weeks 0–26 were significantly lower with placebo compared with vardenafil for penetration (52% with placebo vs 76% with 10 mg vardenafil, $P < .0001$) and maintenance of erection (33% with placebo vs 65% with 10 mg vardenafil, $P < .0001$; Hellstrom et al, 2002). A limitation of this current analysis was that it relied on patient diary data, and only valid entries were used. Therefore, the first valid diary entry might not have been the patient’s first true attempt.

Reliability is an important characteristic of successful ED treatment. In the Men’s Attitude Toward Life Events and Sexuality study, an international survey involving 3291 men with ED, 47% cited “works reliably every time” as an attribute they were seeking in ED therapy, and 22% of men who had previously abandoned use of

sildenafil gave “only worked occasionally” as a reason for stopping therapy (Meuleman et al, unpublished). Men can be disappointed if a therapy does not work after a few attempts and might not try the treatment again. However, many nonpharmacological factors influence the success of ED therapy (Althof, 2002). These include patient variables (performance anxiety, depression, unrealistic expectations, or unconventional sexual arousal patterns), partner variables (health status or disinterest in or inability to resume lovemaking), the quality of couple’s overall relationship, and the interval of sexual abstinence. Physicians should discuss these possible factors influencing the success of ED treatment when prescribing.

The cumulative probability of success with sildenafil was assessed in a post hoc analysis of patient diary data from 6 double-blind, flexible-dose, placebo-controlled studies involving 1276 men with ED (McCullough et al, 2002). Although the cumulative probability of successful intercourse increased with successive attempts with sildenafil, a plateau in cumulative probability was not apparent until approximately 8 attempts had been made. By the fourth attempt, cumulative probability of successful intercourse with sildenafil was around 70% and did not reach 80% until about the ninth attempt. In contrast, in the current analysis, the cumulative probability of successful penetration and maintenance of erection with 10 mg vardenafil reached a plateau of greater than 80% at about the fourth attempt.

The results of these analyses of cumulative probability of success should be considered when educating patients who begin oral ED therapies because patients might give up on treatment prematurely if immediate success is not achieved. The need to take the drug on several occasions to provide adequate opportunity for success and the opportunity to titrate the dose if the starting dose proves unsuccessful should be explained to the patient (McCullough et al, 2002).

Previous studies have demonstrated the utility of flexible dosing of vardenafil in some patients (Carson et al, 2004; Hatzichristou et al, 2004; Potempa et al, 2004). In a double-blind, 12-week study of 463 men with ED, the initial dose of vardenafil (10 mg) could be increased or decreased after 4 weeks depending on efficacy and tolerability of vardenafil. Even though most had a positive response to 10 mg at week 4, an incremental benefit was observed in some patients receiving the higher doses in the final 8 weeks (Carson et al, 2004). A high degree of success with flexible dosing of vardenafil was reported in a study by Potempa et al (2004), who observed improved erections in 92% of patients and successful penetration in 89% of patients. The study highlighted the ease with which vardenafil could be titrated to optimize individual efficacy and tolerability.

In this analysis, vardenafil was generally well tolerated

and the most common adverse events reported are well known and consistent with the pharmacological profile of PDE5 inhibitors and adverse-event reports for clinical trials with other PDE5 inhibitors (Padma-Nathan and Giuliano, 2001; Padma-Nathan et al, 2001). Most of the adverse events were mild to moderate in severity and usually resolved with continued use of vardenafil (Hellstrom et al, 2002).

This retrospective analysis of data from the North American pivotal study demonstrates that the cumulative probability of achieving successful penetration and maintaining an erection long enough to complete intercourse increased with the number of attempts for 5, 10, and 20 mg vardenafil, plateauing after approximately 4 attempts. Patients without initial treatment success on their starting dose should be encouraged to continue treatment for at least 4 doses because the cumulative probability of success increases with additional doses of vardenafil. If the patient does not adequately respond, the physicians could have the option of titrating to a higher treatment dose.

Acknowledgments

Members of the Vardenafil Study Group were Randall P. Abele, MD (Edmonton Prostate Centre, Edmonton, Alberta, Canada); Gerald L. Andriole, MD (Washington University School of Medicine, St Louis, Mo); Stephen M. Auerbach, MD (California Professional Research, Newport Beach, Calif); Jack Barkin, MD (Toronto, Ontario, Canada); Winston Barzell, MD (Urology Treatment Center, Sarasota, Fla); Donald Bergner, MD (Tampa Bay Medical Research Inc, Clearwater, Fla); Richard Casey, MD (Male Health Centres, Oakville, Ontario, Canada); Stacy Childs, MD (Wyoming Research Foundation, Cheyenne, Wyo); Selwyn Cohen, MD (Clinical Research Consultants Inc, Trumbull, Conn); David O. Cook, MD (Piedmont Medical Research Associates Inc, Winston-Salem, NC); Jeffrey Deeths, MD (Nebraska Clinical Research Center, Omaha, Neb); Craig F. Donatucci, MD (Duke University Medical Center, Durham, NC); Mostafa M. Elhilali, MD (Royal Victoria Hospital, Montreal, Quebec, Canada); Pamela I. Ellsworth, MD (Dartmouth Hitchcock Medical Center, Division of Urology, Lebanon, NH); Howard B. Epstein, MD (University of Florida–Jacksonville, Health Science Center, Jacksonville, Fla); Robert A. Feldman, MD (Urology Specialists, PC, CT Clinical Research Center, Waterbury, Conn); Louis Fields, MD (Thornhill, Ontario, Canada); Roger Fincher, MD (Spokane, Wash); William Fitch III, MD (Urology Consultants, PA, San Antonio, Tex); Jenelle E. Foote, MD (Midtown Urology, Atlanta, Ga); Jeffrey Frankel, MD (Seattle, Wash); Harold A. Fuselier, MD (Ochsner Foundation Hospital, Ochsner Clinic, Department of Urology, New Orleans, La); Larry I. Gilderman, DO (University Clinical Research Associates Inc, Pembroke Pines, Fla); Marc Gittelman, MD (South Florida Medical Research, Aventura, Fla); Evan Goldfischer, MD (Hudson Valley Urology Center, Poughkeepsie, NY); James E. Gottesman, MD (Seattle Urological Associates, Seattle, Wash); Fred Govier, MD (Virginia Mason Medical Center, Department of Urology, Seattle, Wash); Michael Greenspan, MD (Hamilton & District Urology Association, Hamilton, Ontario, Canada); Wayne J. Hellstrom, MD (Tulane University Medical Center, New Orleans, La); Charles B. Herring, MD (New Hanover Medical Research Associates, Wilmington, NC); Gary S. Karlin, MD (Lawrenceville Urology, Lawrenceville, NJ); Joel M. Kaufman, MD (Urology Research Options, Aurora, Colo); Robert J. Krane, MD (Massachusetts General Hospital, Department of Urology, Boston, Mass); John N. Krie-

ger, MD (A Puget Sound Health Care System, Section of Urology, Seattle, Wash); Alan Lau, MD (University of Illinois at Chicago, Chicago, Ill); William A. Leitner, MD (Urology Centers of Alabama, PC, Birmingham, Ala); Joel Lilly, MD (Seattle Urological Associates, Seattle, Wash); Jack Lubensky, MD (Radiant Research Inc, Center for Clinical Research, Austin, Tex); Nizamuddin Maruf, MD (MidAtlantic Clinical Research Center, Rockville, Md); Keith Matthews, MD (Uromed, Montreal, Quebec, Canada); Kevin T. McVary, MD (Northwestern Center for Clinical Research, Chicago, Ill); Andrew McCullough, MD (New York University Medical Center, Urology Research, New York, NY); Arnold Melman, MD (Montefiore Medical Center, Department of Urology, Bronx, NY); William B. Monnig, MD (The Urology Group, Cincinnati, Ohio); Craig Niederberger, MD (University of Illinois at Chicago, Chicago, Ill); Harin Padma-Nathan, MD (The Male Clinic, Beverly Hills, Calif); Allan B. Patrick, MD (Fredericton, New Brunswick, Canada); Jon Lee Peterson, MD (Health Advance n Touch Research, Houston, Tex); Peter J. Pommerville, MD (Victoria, British Columbia, Canada); V. Gary Price, MD (North Texas Clinical Research, Fort Worth, Tex); George Raad, MD (Metrolina Medical Research Associates, Charlotte, NC); Paul R. Sieber, MD (Urological Associates of Lancaster, Lancaster, Pa); Alan W. Skolnick, MD (Health Advance Touch Research, Houston, Tex); Christopher P. Steidle, MD (Northeast Indiana Research, Fort Wayne, Ind); Cecile Storrie, MD (MDS Harris, Inc, Dallas, Tex); David Talley, MD (Urology San Antonio Research, PA, San Antonio, Tex); Joseph J. Tepas, MD (University of Florida–Jacksonville Health Science Center, Jacksonville, Fla); Timothy S. Truitt, MD (Health Advance Institute, Melbourne, Fla); Luc Valiquette, MD (Hopital St. Luc, Montreal, Quebec, Canada); Alexander Vukasin, MD (Urology Group of Princeton, PA, Princeton, NJ); Mitchell Wiatrak, MD (Midwest Research Specialists, Milwaukee, Wis); John Williams, MD (University of Florida–Jacksonville Health Science Center, Jacksonville, Fla); Rafael Wurzel, MD (Grove Hill Medical Center, New Britain, Conn); Joseph Zadra, MD (Barrie, Ontario, Canada).

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