A Phase 3, Placebo Controlled Study of the Safety and Efficacy of Avanafil for the Treatment of Erectile Dysfunction After Nerve Sparing Radical Prostatectomy

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Purpose: We evaluated the safety and efficacy of 100 and 200 mg avanafil for the treatment of adult males with erectile dysfunction after bilateral nerve sparing radical prostatectomy.

Materials and Methods: This was a double-blind, placebo controlled, parallel group, phase 3 study in males age 18 to 70 years with a history of erectile dysfunction of 6 months or more after bilateral nerve sparing radical prostatectomy. Patients were randomized to 100 or 200 mg avanafil or placebo (taken 30 minutes before sexual activity) for 12 weeks. Primary end points included successful vaginal insertion (Sexual Encounter Profile [SEP] question 2), successful intercourse (SEP3) and change in score on the erectile function domain of the International Index of Erectile Function (IIEF-EF) questionnaire.

Results: A total of 298 patients were randomized and 84.6% completed the study. At baseline 16.1% were age 65 years or older and 71.5% had severe erectile dysfunction (mean overall IIEF-EF domain score 9.2). After 12 weeks there were significantly greater increases in SEP2 and SEP3 and change in mean IIEF-EF domain score with 100 and 200 mg avanafil vs placebo ($p < 0.01$). Following dosing with avanafil 36.4% (28 of 77) of sexual attempts (SEP3) at 15 minutes or less were successful vs 4.5% (2 of 44) for placebo ($p < 0.01$). Avanafil was generally well tolerated. No serious adverse events were reported and fewer than 2% of patients discontinued the study due to an adverse event.

Conclusions: Avanafil in 100 and 200 mg doses was effective and well tolerated in improving erectile function after prostatectomy. Results suggest a rapid onset of action and sustained duration of effect, with all 3 primary end points being achieved at both dose levels.

Abbreviations and Acronyms

AE = adverse event

ED = erectile dysfunction

EF = erectile function

IIEF = International Index of Erectile Function

ITT = intent to treat

PDE5i = phosphodiesterase type 5 inhibitor

TEAE = treatment emergent adverse event

Key Words: erectile dysfunction; prostatectomy; phosphodiesterase 5 inhibitors; clinical trial, phase III

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Study received institutional review board approval.

Clinical Trial Registration NCT00895011 (www.clinicaltrials.gov).

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Prostate cancer treatment is frequently associated with the development of ED.[1,2] Data from the Prostate Cancer Outcomes Study, a population based longitudinal cohort of 1,291 men, showed that 56% of men who underwent bilateral nerve sparing radical prostatectomy reported impotence at 18 months or more after surgery.[3] Further data from a single center study (293) indicated that if left untreated, the rate of EF after recovery was only 36% (mean followup 27 months).[4] Even lower rates of recovery have been reported for men older than 65 or older than 70 years.[3–5]

Currently first line treatment for most men with various causes of ED consists of oral PDE5i therapy including sildenafil, vardenafil, tadalafil and avanafil.[6–9] Overall, data show that treatment with a PDE5i improves sexual function in the majority of men with mild to moderate ED after nerve sparing radical prostatectomy. However, response rates are considerably lower in men with severe ED[10,11] and men older than 65 years.[5,10,12]

Avanafil is a highly selective[13,14] and potent (IC_{50} = 4.3 to 5.2 nM)[15] PDE5i that has recently been approved for the treatment of men with ED.[9] Data from phase 1, 2 and 3 clinical trials show that avanafil is rapidly absorbed (time to maximum plasma concentration 30 to 45 minutes) after oral administration, has a relatively short (3 to 5-hour) half-life[15] and an onset of action of 15 minutes or less in some patients.[16–19] In phase 3 clinical trials avanafil improved EF in males with mild to severe ED with[18] and without[17] diabetes. In this study we evaluated the safety and efficacy of 100 and 200 mg avanafil in the treatment of adult males with ED after bilateral nerve sparing radical prostatectomy.

MATERIALS AND METHODS

Study Design

This randomized, double-blind, placebo controlled, parallel group study enrolled patients at 53 sites in the United States to assess the safety and efficacy of avanafil in the treatment of mild to severe ED in men following bilateral nerve sparing radical prostatectomy. All patients read and signed an institutional review board approved informed consent form and were assured that they could withdraw from the study at any time without jeopardizing medical care related to or required as a result of study participation. This study was conducted in accordance with the International Standard of Good Clinical Practice procedures (as defined by the International Conference on Harmonisation)[20] and in accordance with the principles of the Declaration of Helsinki.[21]

During a 4-week nontreatment run-in, patients maintained a diary of all attempts at sexual intercourse. Patients with a 50% or greater failure rate in maintaining an erection for a sufficient duration to allow successful intercourse, a score of 5 to 25 (inclusive) on the EF domain of the IIEF questionnaire,[22,23] and who made at least 4 attempts at sexual intercourse during the run-in period were randomized (1:1:1) to 100 or 200 mg avanafil or placebo, and treated for 12 weeks (fig. 1).

The study drug was taken approximately 30 minutes before initiation of sexual activity and results were recorded in a diary. Up to 2 doses could be taken within a 24-hour period if taken at least 12 hours apart. There were no restrictions on food or alcohol intake.

Key Inclusion and Exclusion Criteria

Adult males age 18 to 70 years with a history of ED of 6 months or more after bilateral nerve sparing retropubic radical prostatectomy for localized carcinoma of the prostate (6 months or more before screening) and with staging of prostate carcinoma pT2 or less and Gleason score 7 (4 + 3) or less were included in the study. Patients were excluded for prior use of radiotherapy, chemotherapy, androgen deprivation therapy, cryotherapy, nonnerve sparing surgery and/or bladder or penile surgery, or if these were likely to be required during the study. Use of penile rehabilitation treatment (ie oral medications, intracavernous injections and/or intraurethral therapies) was not permitted before beginning the 4-week, nontreatment run-in period of the study or throughout the study. Patients with a history of diabetes or a history of dose limiting AEs during prior treatment with a PDE5i were excluded. Patients were also excluded if they experienced ED as a consequence of advanced neurological disease, spinal cord injury or diabetes, or had a history of severe ED requiring routine medical therapy before prostate surgery.

Study End Points

Primary study end points were the change in percentage of sexual attempts in which patients are able to insert the

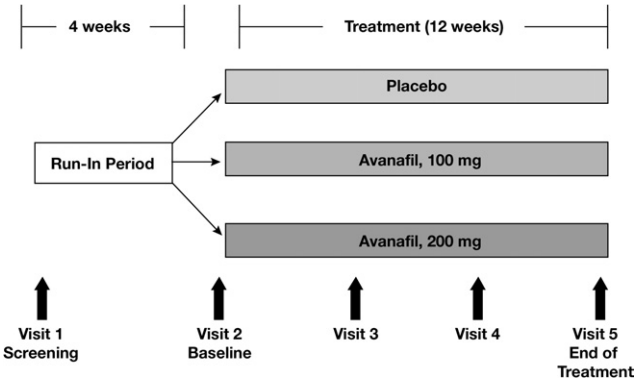

Figure 1. Study design