Rapid Efficacy of the Highly Selective α_{1A}-Adrenoceptor Antagonist Silodosin in Men With Signs and Symptoms of Benign Prostatic Hyperplasia: Pooled Results of 2 Phase 3 Studies

Leonard S. Marks,*,† Marc C. Gittelman,‡ Lawrence A. Hill,‡ Weining Volinn‡ and Gary Hoel‡

From the University of California at Los Angeles and Urological Sciences Research Foundation, Los Angeles, California (LSM), South Florida Medical Research, Aventura, Florida (MCG), and Watson Laboratories, Salt Lake City, Utah (LAH, WV, GH)

Abbreviations and Acronyms

AE = adverse event

BPH = benign prostatic hyperplasia

I-PSS = International Prostate Symptom Score

LOCF = last observation carried forward

Q_{max} = peak urinary flow rate

QoL = quality of life

Submitted for publication November 11, 2008.

Supported by Watson Pharma, Inc.

Study received institutional review board approval.

Clinical Trial Registration NCT00224107, NCT00224120 (www.clinicaltrials.gov).

* Correspondence: Department of Urology, Geffen School of Medicine at UCLA, 3831 Hughes Ave., Culver City, California 90232 (telephone: 310-559-9800; FAX: 310-559-7821; e-mail: lsmarks@ucla.edu).

† Financial interest and/or other relationship with Allergan, American Medical Systems, Astellas, Bayer, Beckman Coulter, Diagnostic Ultrasound, GTX, GlaxoSmithKline, Gen-Probe, Indevus, Light Sciences Oncology, Lilly/ICOS, Merck, Novartis, Onconome, Pfizer, Sanofi, Solvay, Watson, National Institutes of Health, CapCURE, Pardee Foundation and Seder Foundation.

‡ Financial interest and/or other relationship with Watson Pharmaceuticals.

For another article on a related topic see page 2780.

Purpose: We evaluated the efficacy and safety of silodosin for treatment of benign prostatic hyperplasia symptoms in 2 randomized, placebo controlled, phase 3 studies.

Materials and Methods: Men 50 years or older with an International Prostate Symptom Score of 13 or greater and peak urinary flow rate of 4 to 15 ml per second received placebo or 8 mg silodosin daily with breakfast for 12 weeks. The primary end point was International Prostate Symptom Score change from baseline to last observation. Change in peak urinary flow rate was a secondary end point. Differences in treatment efficacy were assessed by ANCOVA.

Results: Of 923 patients (mean age 65 years) 466 received silodosin and 457 placebo. After 0.5 week (range 3 to 4 days) of treatment patients receiving silodosin vs placebo achieved significant improvement in total International Prostate Symptom Score (difference −1.9, $p < 0.0001$) and irritative (−0.5, $p = 0.0002$) and obstructive (−1.4, $p < 0.0001$) subscores. The mean ± SD change from baseline in total International Prostate Symptom Score was −4.2 ± 5.3 for silodosin vs −2.3 ± 4.4 for placebo. Differences (silodosin vs placebo) in International Prostate Symptom Score and subscores increased by week 12 ($p < 0.0001$). Mean change from baseline in peak urinary flow rate (ml per second) 2 to 6 hours after initial dose was greater ($p < 0.0001$) with silodosin (2.8 ± 3.4) than placebo (1.5 ± 3.8). Differences remained significant ($p < 0.001$) through week 12. The most common treatment emergent adverse event was (mostly mild) retrograde ejaculation (silodosin 28.1% of patients, placebo 0.9%). Few patients receiving silodosin (2.8%) discontinued because of retrograde ejaculation. Proportions of patients with treatment emergent orthostatic hypotension were similar for silodosin (2.6%) and placebo (1.5%).

Conclusions: Treatment with silodosin produced rapid improvement in urinary symptoms that was sustained for 12 weeks. Silodosin was well tolerated with a low incidence of orthostatic hypotension.

Key Words: prostatic hyperplasia, KMD 3213, signs and symptoms

BENIGN prostatic hyperplasia is a chronic condition associated with lower urinary tract symptoms. The prevalence of symptomatic BPH in the United States ranges from approximately 24% in men 40 to 49 years old to approximately 44% in men 70 years old or older.[1] With an aging population the number of men affected by

0022-5347/13/1891-0122/0
THE JOURNAL OF UROLOGY®

http://dx.doi.org/10.1016/j.juro.2012.11.020
Vol. 189, S122-S128, January 2013
Printed in U.S.A.

Please cite this article as J Urol 2013;189: S122-S128. DOI: http://dx.doi.org/10.1016/j.juro.2012.11.020

BPH is likely to increase.[2] Although prostate enlargement is a frequent sign of BPH, the severity of BPH related urinary symptoms generally correlates poorly with prostate size or the extent of bladder outlet obstruction.[2,3] Symptom severity appears to be dependent, at least in part, on smooth muscle tone in the prostate and bladder neck.[3,4] In vitro studies using human prostate tissue have demonstrated that smooth muscle tone is mediated by α_{1A}-adrenoceptors, which are abundant in the prostate and the bladder neck.[5] Consequently α_1-adrenoceptor antagonists (α-blockers) have become the first line treatment for the relief of BPH symptoms. First generation α-blockers such as doxazosin have the potential to cause orthostatic hypotension in normotensive subjects, because they block not only α_{1A}-adrenoceptors but also α_{1B}-adrenoceptors, which help maintain vascular smooth muscle tone.[6,7] Concerns about the cardiovascular safety of such agents prompted the development of α-blockers with increased α_{1A} to α_{1B}-adrenoceptor subtype selectivity.[4,8] Nonclinical and clinical pharmacology data suggest that more selective α-blockers are less likely than nonselective α-blockers to cause cardiovascular adverse effects.[4,9] Preclinical studies of the recently developed α-blocker silodosin indicate that silodosin has greater α_{1A} to α_{1B}-adrenoceptor subtype selectivity[10,11] and greater selectivity for prostatic and urethral tissues vs vascular tissue[7,12,13] than does any other currently available α-blocker. Furthermore, unlike other α-blockers that require a waiting period between meals and dosing, silodosin is a once daily medication taken with a meal. In this article we present pooled results from 2 phase 3 clinical studies evaluating the efficacy and safety of silodosin in a large population of men with signs and symptoms of BPH.

MATERIALS AND METHODS

Patients and Study Design

Two 12-week, identically designed, parallel group, multicenter, randomized, double-blind, placebo controlled phase 3 studies (SI04009, SI04010; Clinical Trials Registration Numbers NCT00224107, NCT00224120) were conducted in the United States to evaluate the efficacy and safety of silodosin in men with signs and symptoms of BPH. Screening of patients began for both studies in May 2005, and the last patients completed the studies in August 2006 (SI04009) and May 2006 (SI04010). Both studies were approved by central or local institutional review boards before patient enrollment began, and were conducted in accordance with good clinical practice as described in the guidelines of the International Conference on Harmonization (Technical Requirements for Registration of Pharmaceuticals for Human Use), the United States Code of Federal Regulations governing the protection of human subjects and the Declaration of Helsinki.

Eligible men were at least 50 years old with an I-PSS of 13 or higher, a peak urinary flow rate of 4 to 15 ml per second and a post-void residual volume less than 250 ml. Complete exclusion criteria are provided in the Appendix. Concomitant medications precluding study participation and prohibited during the trial were α-adrenoceptor antagonists and 5α-reductase inhibitors. Diuretics, antispasmodics and anticholinergics were allowed only if doses were stable during the study.

After a screening period of up to 4 weeks patients received single-blind treatment with placebo for 4 weeks, which was followed immediately by the 12-week double-blind treatment period. Two weeks after the start and at the end of the placebo run-in period, I-PSS and Q_{max} were determined to assess individual responses to placebo. Patients with at least a 30% decrease in I-PSS or an increase in Q_{max} of 3 ml per second or greater during the run-in period were excluded from randomization. Eligible patients were randomly assigned (1:1) to double-blind treatment with placebo or 8 mg silodosin once daily with breakfast. Treatment assignments were made according to a randomization schedule using PROC PLAN in SAS®, version 8.2. Randomization was performed with a permuted block design and was not stratified by treatment center or region. Blinding was maintained throughout the study by the use of identical medication packaging with placebo matching silodosin in size and external appearance. Emergency information labels that indicated the patient's assigned treatment were available to the investigator should knowledge of treatment assignment be needed to ensure the patient's well-being. If unblinding of the investigator, site personnel or the patient was required in a particular case that patient was to be discontinued from the study.

Assessments

Total I-PSS, irritative and obstructive I-PSS subscores, and QoL related to urinary symptoms were measured at weeks 0 (baseline), 0.5, 1, 2, 4 and 12. QoL was assessed with use of the separately scored I-PSS question 8, "If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?" (Responses were measured on a scale from 0 to 6, from delighted to terrible.) Q_{max} was assessed at baseline, 2 to 6 hours after the first dose, and at weeks 1, 2, 4 and 12. For all patients in both studies investigators determined and reported urinary flow measurements. Subsequently all urinary flow measurements were assessed again by a blinded central reader (MCG) and any conflicts were resolved in discussion with the investigator. AE reports were collected at every visit except at post-randomization week 0.5. Additional safety assessments included 12-lead electrocardiograms, clinical laboratory tests and vital sign measurements including postural hypotension tests and physical examinations.

Statistical Analysis

Pooled data from the 2 studies were used for all analyses. Justification for sample sizes is provided in the Appendix. All randomized study participants who provided baseline data for the primary efficacy variable were included in the efficacy analyses. The primary efficacy end point was the mean change from baseline to week 12 in total I-PSS. The secondary efficacy end point was mean change in Q_{max} from baseline to week 12. Last observations were carried forward to impute values missing for week 12. Safety