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THRESHOLD PHARMACEUTICALS, INC.—EXPLORING NEW TERRITORY IN THE TREATMENT OF BENIGN PROSTATIC HYPERPLASIA

Current strategies for treating the burgeoning prevalence of benign prostatic hyperplasia (BPH) carry substantial drawbacks. One author elucidates the dilemma in treating BPH in this way: "The therapeutic goal of treating benign prostatic hyperplasia through early detection and effective therapy is to relieve the symptoms, improve patients' quality of life, decrease post-void residual urine volume, and prevent the associated morbidity when the condition remains untreated (*1*)."

"On so many levels it changes the whole approach in the treatment of BPH. There may also be applications beyond BPH, possibly in the field of cancer prevention. This is potentially the most exciting development of my career!"

—Michael K. Brawer, MD

With clinical studies supporting the potential for more effective ways to treat BPH, **Threshold Pharmaceuticals Inc.** (Redwood City, CA), has targeted a novel and highly promising approach to this universal need. This biotechnology company's initial clinical focus is on the discovery and development of small molecule therapeutics based on Metabolic Targeting, a powerful scientific approach that offers broad potential to treat cancer and BPH.

During the past year, Threshold's investigational product, **TH-070** (**Lonidamine**), an orally administered small molecule reported to inhibit glycolysis by inactivating hexokinase—the enzyme that catalyzes the first step in glycolysis—has successfully completed a Phase II clinical trial. Threshold's ongoing registration program includes multiple multicenter, randomized, double-blinded, placebo-controlled studies, including at least one dose-comparison study. Two clinical trials are expected to commence in June 2005, at least one of which will be a Phase III trial.

Therapies currently available for the treatment of BPH work to alleviate BPH symptomology, however, TH-070 establishes a new paradigm by addressing the underlying mechanism that fosters BPH. Alpha1-adrenoreceptor antagonists (α-blockers) provide symptomatic relief, however, have side effects ranging from orthostatic hypotension to sexual dysfunction. 5-alpha reductase inhibitors (ARI's) can cause impotence, ejaculatory disorders, reduced libido and gynecomastia. Additionally, the time required to obtain symptom relief using drugs in this category can range from 3 to 6 months. Various surgical modalities used to treat BPH are invasive with the attendant risks. Promising results of ongoing clinical trials using TH-070 support the potential that this novel strategy eradicates the *source* of BPH.

Clinical Evidence Supports the Role of TH-070 for the Treatment of BPH

A recently completed Phase II clinical trial (*2*) evaluated the efficacy of a 28 day course of oral TH-070 (150 mg p.o. QD) in subjects with symptomatic BPH. Patients

were assessed at baseline, at 14 and 28 days, and 1, 2, 3 and 6 months intervals for prostate volume by transrectal ultrasound (TRUS), maximum flow rate (Qmax) on uroflowmetry, post-voiding urine volume (PVR), international prostatic symptoms score (IPSS), prostate-specific antigen (PSA), serum chemistry and adverse events.

The authors report that: "Subjects experienced an average decrease of 11.2% ($p < 0.001$) in prostate volume on day 28. Qmax improved by a mean of 3.2mL/sec from 9.4mL/sec at baseline to 12.6mL/sec at day 28 ($p = 0.002$). PVR decreased by 62% from a mean of 82.1cc at baseline to 31.6cc at day 28 ($p < 0.001$). I-PPS scores improved by 7.3 points from 19.5 prior to treatment to 12.2 at day 28 ($p < 0.001$). PSA decreased on average by 17.8% from a mean of 3.6 at baseline to 2.8ng/ml at day 28 ($p < 0.001$). LND [Lonidamine] was generally well-tolerated, with no moderate or severe adverse events."

From their findings, the authors conclude that: "In this study LND treatment led to a rapid and significant reduction in prostate volume and corresponding symptomatic improvements in patients with BPH, which are sustained for as much as six months post-treatment. Based on its proposed novel mechanism of action, LND may represent a promising new treatment for BPH."

Michael K. Brawer, MD, is Director of the Northwest Prostate Institute (Seattle, WA) and CEO and Co-Founder of MedReviews, Inc. Dr. Brawer was formerly a professor of urology and adjunct professor of pathology at the University of Washington, and has worked extensively in the field of urology and specifically in the development of TH-070. Says Dr. Brawer: "In addition to the undesirable side-effects of current therapies is the issue that they are a chronic medication administered for life. The exciting aspect of TH-070 is that it appears to address the underlying mechanism of the disease. Further, it's approved in Italy for use in oncology, has been tested extensively in humans for over 20 years, and found to have only mild, transient side effects."

Dr. Brawer conveys the potential for TH-070 in this way: "On so many levels, it changes the whole approach in the treatment of BPH. There may also be applications beyond BPH, possibly in the field of cancer prevention." He adds that: "This is potentially the most exciting development of my career!"

For a new generation less willing to accept the human and economic burden of untreated or inadequately treated prostate disease—Threshold's multi-disciplinary team is addressing this substantial unmet need and bringing to the healthcare community the awareness of the importance of early detection and treatment of BPH.

Please note that TH-070 is an investigational product. Its safety and efficacy have not yet been established, nor has it been approved by the FDA.

For more information concerning TH-070, call Threshold Pharmaceuticals, Inc. at 1-800-770-4988, or visit the company's Web site at www.thresholdpharm.com.

References:

1. Fitzpatrick, JM, Desgrandchamps F. *BJU Int.* 2005 Mar;95(4):575-9.
2. Data on file at Threshold Pharmaceuticals, Inc.