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Platinum Priority – Benign Prostatic Hyperplasia

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Monotherapy with Tadalafil or Tamsulosin Similarly Improved Lower Urinary Tract Symptoms Suggestive of Benign Prostatic Hyperplasia in an International, Randomised, Parallel, Placebo-Controlled Clinical Trial

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Abstract

Background: Tadalafil improved lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH; LUTS/BPH) in clinical studies but has not been evaluated together with an active control in an international clinical study.
Objective: Assess tadalafil or tamsulosin versus placebo for LUTS/BPH.
Design, setting, and participants: A randomised, double-blind, international, placebo-controlled, parallel-group study assessed men ≥45 yr of age with LUTS/BPH, International Prostate Symptom Score (IPSS) ≥13, and maximum urinary flow rate (Q_{max}) ≥4 to ≤15 ml/s. Following screening and washout, if needed, subjects completed a 4-wk placebo run-in before randomisation to placebo ($n = 172$), tadalafil 5 mg ($n = 171$), or tamsulosin 0.4 mg ($n = 168$) once daily for 12 wk.
Measurements: Outcomes were assessed using analysis of covariance (ANCOVA) or ranked analysis of variance (ANOVA) (continuous variables) and Cochran-Mantel-Haenszel test or Fisher exact test (categorical variables).
Results and limitations: IPSS significantly improved versus placebo through 12 wk with tadalafil (−2.1; $p = 0.001$; primary efficacy outcome) and tamsulosin (−1.5; $p = 0.023$) and as early as 1 wk (tadalafil and tamsulosin both −1.5; $p < 0.01$). BPH Impact Index significantly improved versus placebo at first assessment (week 4) with tadalafil (−0.8; $p < 0.001$) and tamsulosin (−0.9; $p < 0.001$) and through 12 wk (tadalafil −0.8, $p = 0.003$; tamsulosin −0.6, $p = 0.026$). The IPSS Quality-of-Life Index and the Treatment Satisfaction Scale–BPH improved significantly versus placebo with tadalafil (both $p < 0.05$) but not with tamsulosin (both $p > 0.1$). The International Index of Erectile Function–Erectile Function domain improved versus placebo with tadalafil (4.0; $p < 0.001$) but not tamsulosin (−0.4; $p = 0.699$). Q_{max} increased significantly versus placebo with both tadalafil (2.4 ml/s; $p = 0.009$) and tamsulosin (2.2 ml/s; $p = 0.014$). Adverse event profiles were consistent with previous reports. This study was limited in not being powered to directly compare tadalafil versus tamsulosin.
Conclusions: Monotherapy with tadalafil or tamsulosin resulted in significant and numerically similar improvements versus placebo in LUTS/BPH and Q_{max}. However, only tadalafil improved erectile dysfunction.
Trial registration: Clinicaltrials.gov ID NCT00970632

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1. Introduction

Benign prostatic hyperplasia (BPH) is a histologic diagnosis characterised by smooth muscle and epithelial cell proliferation in the prostate transition zone leading to nonmalignant prostate enlargement. It is widely recognised that BPH is not the exclusive cause of lower urinary tract symptoms (LUTS) [1,2]. However, clinical drug trials often enrol men based in part on a clinical diagnosis of nonneurogenic LUTS suggestive of BPH (LUTS/BPH).

The prevalence of bothersome LUTS/BPH increases with age, and epidemiologic and pathophysiologic links between LUTS/BPH and erectile dysfunction (ED) have been demonstrated [3,4]. Medical therapy for LUTS/BPH currently consists of α-blockers, 5α-reductase inhibitors, or combination therapy [1,2]. Although efficacious, these therapies have the potential for side-effects relating to sexual dysfunction [5]. Tadalafil is a phosphodiesterase type 5 (PDE5) inhibitor (PDE5-I) widely approved for the treatment of ED. Several placebo-controlled studies in men with LUTS/BPH have demonstrated improvements in International Prostate Symptom Scores (IPSS) with tadalafil [6–10]. Tadalafil was recently approved in the United States for treatment of signs and symptoms of BPH (LUTS/BPH) and for the treatment of coexisting LUTS/BPH and ED. Although the mechanisms for improvements in LUTS with PDE5 inhibition have yet to be fully clarified, proposed contributors include inhibition of PDE5 isoenzymes present in the bladder, prostate, urethra, and supporting vasculature and consequent increases in intracellular nitric oxide–cyclic guanosine monophosphate concentration, relaxation of the smooth muscle cells in these structures, improved blood perfusion, and reduced afferent signalling from the urogenital tract [11–15].

The primary objective of this study was to compare the effect of tadalafil 5 mg once daily with placebo on LUTS/BPH. Given that the α-blocker tamsulosin is often a first-line treatment for LUTS/BPH, tamsulosin was included as an active control, with a secondary objective of comparing tamsulosin 0.4 mg once daily with placebo. Although not designed for statistical testing of noninferiority or superiority between tadalafil and tamsulosin, the study was adequately powered for the comparison of each active treatment with placebo. This study provides for the first time data for both tadalafil and tamsulosin from a single large, randomised, placebo-controlled, international study.

2. Patients and methods

A double-blind, placebo- and active-controlled, parallel-design trial was conducted at 44 urology sites in Australia, Austria, Belgium, France, Germany, Greece, Italy, Mexico, The Netherlands, and Poland. Following screening (and a 4-wk wash-out for BPH, overactive bladder, or ED drugs, as needed), participants began a 4-wk single-blind placebo lead-in period, followed by randomisation (1:1:1 ratio) to once-daily tadalafil 5 mg, tamsulosin 0.4 mg, or placebo for 12 wk (Fig. 1). Dosing was to occur

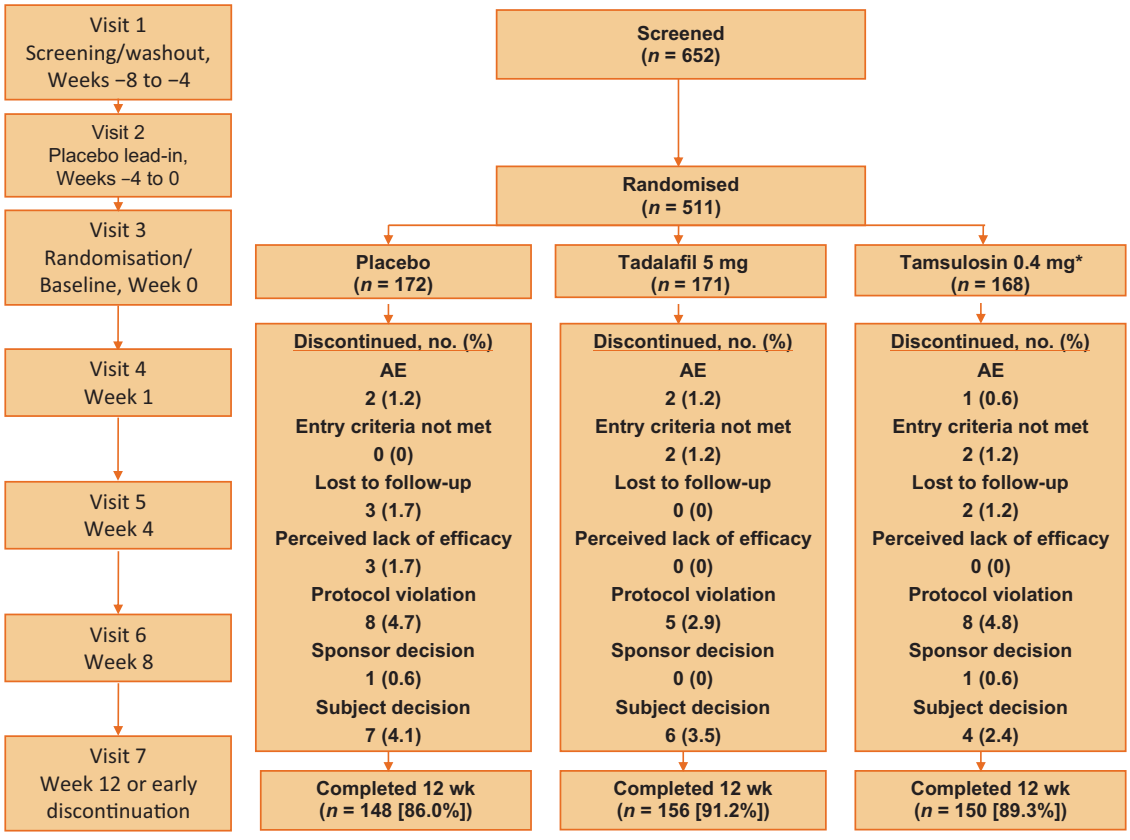

Fig. 1 – Disposition of subjects. Subject Consolidated Standards of Reporting Trials (CONSORT) diagram.
AE = adverse event.
*** One subject randomised to tamsulosin did not take at least one dose of study drug and was excluded from the efficacy analyses.**