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Original Article

Combined therapy with dutasteride and tadalafil vs dutasteride or tadalafil monotherapy in benign prostatic hyperplasia: a randomised phase III trial

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Objectives

To evaluate the efficacy and safety of a fixed-dose combination (FDC) of dutasteride and tadalafil vs monotherapy in patients with benign prostatic hyperplasia (BPH).

Patients and Methods

This phase III trial enrolled 667 patients. After screening and washout, eligible patients were stratified by the baseline International Prostate Symptom Score (IPSS) and randomised (1:1:1) to receive FDC dutasteride 0.5 mg/tadalafil 5 mg (FDC 0.5/5 mg), dutasteride 0.5 mg, or tadalafil 5 mg for 48 weeks. The primary endpoint was the change in total IPSS from baseline to Week 48. Efficacy and safety were assessed at 4, 12, 24, 36, and 48 weeks.

Results

In total, 619 patients were analysed for efficacy. The least squares (LS) mean (standard error [SE]) change in total IPSS at 48 weeks from baseline was −9.49 (0.37) for the FDC 0.5/5 mg group vs −4.40 (0.37) for dutasteride 0.5 mg group (LS mean difference [LSMD] −5.09, 95% confidence interval [CI] −6.13 to −4.50; $P < 0.001$), and −9.53 (0.36) for the FDC 0.5/5 mg group vs −4.24 (0.37) for tadalafil 5 mg group (LSMD −5.29, 95% CI −6.30 to −4.27; $P < 0.001$). The FDC 0.5/5 mg group demonstrated the most pronounced improvement in quality of life. Although the maximum urinary flow rate and post-void residual volume improved in all groups, differences were not statistically significant. In the comparison between the FDC 0.5/5 mg and dutasteride 0.5 mg groups, the LSMD (95% CI) of change from baseline to Week 48 in the international index of erectile function - erectile function (IIEF - EF) total score was 4.03 (2.35 to −5.71) ($P < 0.05$). Among the 655 patients analysed for safety, treatment-emergent adverse events occurred in 32.88% (FDC 0.5/5 mg) vs 21.20% (dutasteride 0.5 mg) and 26.48% (tadalafil 5 mg), with few serious adverse events observed.

Conclusions

The FDC 0.5/5 mg demonstrated superior efficacy, and an acceptable safety profile compared with dutasteride and tadalafil monotherapies in patients with BPH.

Keywords

dutasteride, tadalafil, benign prostatic hyperplasia, fixed-dose combination, LUTS

Introduction

Benign prostatic hyperplasia (BPH) is a common urological condition in men aged >40 years, affecting approximately 40–70% of those aged >60 years [1]. It causes lower urinary tract obstruction due to prostatic stroma and epithelial cell proliferation, leading to LUTS that significantly impact the quality of life (QoL) [2]. Untreated LUTS can lead to complications, such as urinary retention, renal insufficiency, and bladder stones, potentially necessitating surgical intervention [3].

Current pharmacological treatments for BPH include α-blockers, 5α-reductase inhibitors (5ARIs), anticholinergics, antidiuretics, and phosphodiesterase type 5 inhibitors (PDE5i). The α-blockers and PDE5i primarily relax the bladder and prostate smooth muscles, while 5ARIs reduce prostate volume (PV) and improve urinary symptoms by inhibiting dihydrotestosterone (DHT) [4]. Long-term use of 5ARIs can prevent disease progression, reduce the risk of acute urinary retention, and reduce the need for surgery. However, symptom improvement requires at least 3 months of continuous use, with common side effects including decreased libido and erectile dysfunction [5]. The α-blockers provide faster LUTS relief but can cause side effects such as retrograde ejaculation [6]. Combined therapy with 5-ARIs and α-blockers has been extensively studied, with dutasteride and α-blocker combined therapy (CombAT study; ClinicalTrials.gov identifier: NCT00090103) indicating that the combination of dutasteride and tamsulosin was more effective than monotherapy in reducing the IPSS and the risk of acute urinary retention and BPH-related surgery [7].

The PDE5i, initially developed for erectile dysfunction, have been shown to effectively improve LUTS in patients with BPH. Their mechanism includes relaxing the prostate and bladder trigone muscles, increasing blood flow, improving neural transmission, and facilitating improvement in urinary symptoms [8]. Unlike α-blockers, PDE5i do not cause retrograde ejaculation and may alleviate sexual dysfunction associated with 5ARIs. The combination of PDE5i and 5ARIs is an ideal treatment strategy because it rapidly improves LUTS and complements the side effects of 5ARIs. The combination of dutasteride and tadalafil can effectively improve LUTS while reducing PV.

However, large-scale clinical studies on 5ARIs and PDE5i combined therapy are lacking. It has been reported that adding dutasteride to tadalafil improves urinary symptoms [9]. However, no comparative studies of dutasteride, tadalafil, and their single combinations have been conducted.

This clinical trial aimed to evaluate the efficacy and safety of a fixed-dose combination of dutasteride 0.5/tadalafil 5 mg (FDC 0.5/5 mg) in patients with BPH over 48 weeks, assessing its impact on the total IPSS compared to monotherapy.

Patients and Methods

Study Design

This multicentre, randomised, double-blind, double-dummy, parallel-design trial included participants who voluntarily enrolled and met the inclusion criteria. After a minimum 4-week washout period, eligible participants were randomised (1:1:1) to receive either (i) FDC 0.5/5 mg plus two placebos, (ii) dutasteride 0.5 mg plus two placebos, or (iii) tadalafil 5 mg plus two placebos once daily at a consistent time regardless of meals for 48 weeks. Efficacy and safety assessments were conducted at 4, 12, 24, 36, and 48 weeks from baseline.

Participants

The study included male patients aged 45–80 years who met the following criteria: (i) total IPSS ≥13, (ii) PV ≥30 mL (measured by TRUS), and (iii) maximum urinary flow rate (Q_{max}) of 4–15 mL/s, and a minimum voided volume ≥125 mL. The exclusion criteria were as follows: (i) serum PSA level ≥4.0 ng/mL, (ii) history of urogenital malignancies; (iii) history of prostate surgery or other invasive prostate treatments; (iv) use of α-blockers, PDE5i, antidiuretic hormones, anticholinergic drugs, cholinergic drugs, antispasmodics, nitrates, or herbal remedies affecting the prostate within 4 weeks before screening; or 5-ARIs within 24 weeks; (v) history of acute urinary retention within the last 12 weeks; (vi) non-BPH conditions causing voiding disturbances or changes in urinary flow rate; and (vii) post-void residual (PVR) volume >200 mL. Smoking was defined as a lifetime history of smoking ≥100 cigarettes. Drinking was defined as lifetime alcohol intake of ≥12 units with any consumption within the past 12 months. BPH family history was defined as self-reported, physician-diagnosed BPH in a first-degree male relative.

Sample Size Calculation

In the absence of studies on FDC 0.5/5 mg, calculations were based on combined therapy studies of dutasteride and tamsulosin [10,11] and monotherapy studies of dutasteride and tadalafil [12,13]. Assuming a total IPSS difference of −2.39 with a standard deviation (SD) of 6.87, a sample size of 174 participants per group provided 90% power to confirm the FDC's superiority over each monotherapy (one-sided alpha level of 0.025).

Intervention and Randomisation

Participants were randomised using an Interactive Web-Based Response System, stratified by baseline total IPSS (<20 vs ≥20). Randomisation codes were generated using the Statistical Analysis System (SAS®) version 9.4 (SAS Institute Inc., Cary, NC, USA) 'proc plan' procedure, assigning participants in a 1:1:1 ratio to the FDC 0.5/5 mg, dutasteride 0.5 mg, or tadalafil 5 mg groups.

Blinding

This double-blind, double-dummy study minimised subjective bias. Post-enrolment randomisation ensured that investigators and participants were blinded to the allocated medication using placebos that were indistinguishable in form and appearance from the active drugs. Randomisation codes concealed treatment allocation until the conclusion of the trial.

Efficacy Assessment

The primary outcome was the change in total IPSS from baseline to 48 weeks. Secondary outcomes included changes in total IPSS at 4, 12, 24, and 36 weeks; changes in IPSS subdomains (obstructive and irritative symptoms); changes in QoL scores; changes in Q_{max} and PVR at 24 and 48 weeks; changes in PV at 48 weeks; and changes in the serum PSA level at 24 and 48 weeks. Exploratory outcomes were the change in the IIEF - EF from baseline to 4, 12, 24, 36, and 48 weeks. The success rates of Sexual Encounter Profile (SEP) Question 2 and Question 3 were measured from baseline to 4, 12, 24, 36, and 48 weeks.

Safety Assessment

Safety assessments included monitoring adverse events (AEs) and treatment-emergent AEs (TEAEs) using vital signs, laboratory tests, electrocardiograms, and physical examinations. Vital signs included blood pressure and heart rate, while laboratory tests included haematology, biochemistry, and urine analysis. AEs were recorded from baseline until the trial's conclusion, documenting symptoms, onset date, duration, intensity, and causality in case report forms. AEs were classified according to the system organ class using the latest Medical Dictionary for Regulatory Activities (MedDRA) version.

Statistical Analysis

The statistical methods used for this clinical trial were detailed in a separate Statistical Analysis Plan (SAP, version 1). All statistical analyses were pre-specified in a separate SAP and conducted using SAS version 9.4. Efficacy analyses were performed in the full analysis set and safety analyses in the safety set. Between-group comparisons for continuous variables used ANOVA or Kruskal–Wallis tests, and categorical variables used chi-square or Fisher's exact tests, as appropriate. Pre-specified subgroup analyses for the primary endpoint were performed and summarised using forest plots.

Ethics Statement

This study adhered to the applicable regulations, good clinical practice, and ethical principles outlined in the Declaration of Helsinki. The Institutional Review Board approved this study, and all patients provided written informed consent.

Results

Patient Demographics and Disposition

A total of 794 patients were screened across 21 clinical trial sites, of which 127 were excluded. Of these, 123 failed to meet the inclusion and exclusion criteria, and four withdrew consent. Ultimately, 667 patients were enrolled and randomised. The FDC 0.5/5 mg group included 224 patients, of whom 220 received treatment and 190 completed the trial. The dutasteride 0.5 mg group included 221 patients, with 217 receiving treatment and 184 completing the study. The tadalafil 5 mg group included 222 patients, with 218 receiving treatment and 179 completing the trial (Fig. 1).

The mean (SD) age was 62.26 (7.37) years, with a mean (SD) height of 169.18 (5.67) cm, weight of 72.41 (9.35) kg, and body mass index of 25.27 (2.75) kg/m^2. Smokers accounted for 52.92% of the population; and 75.56% reported alcohol consumption. The mean (SD) BPH duration was 29.47 (45.83) months. The demographic and baseline characteristics did not significantly differ among the groups (Table 1).

Primary Efficacy Outcome

The least squares (LS) mean (standard error [SE]) changes in the total IPSS at 48 weeks after baseline were −9.49 (0.37) for the FDC 0.5/5 mg group and −4.40 (0.37) for dutasteride 0.5 mg group. The LS mean difference (LSMD) between the groups was −5.09 (95% CI −6.13 to −4.05), which was statistically significant ($P < 0.001$). The LS mean (SE) changes

Fig. 1 Study disposition. Patient Consolidated Standards of Reporting Trials (CONSORT) diagram.

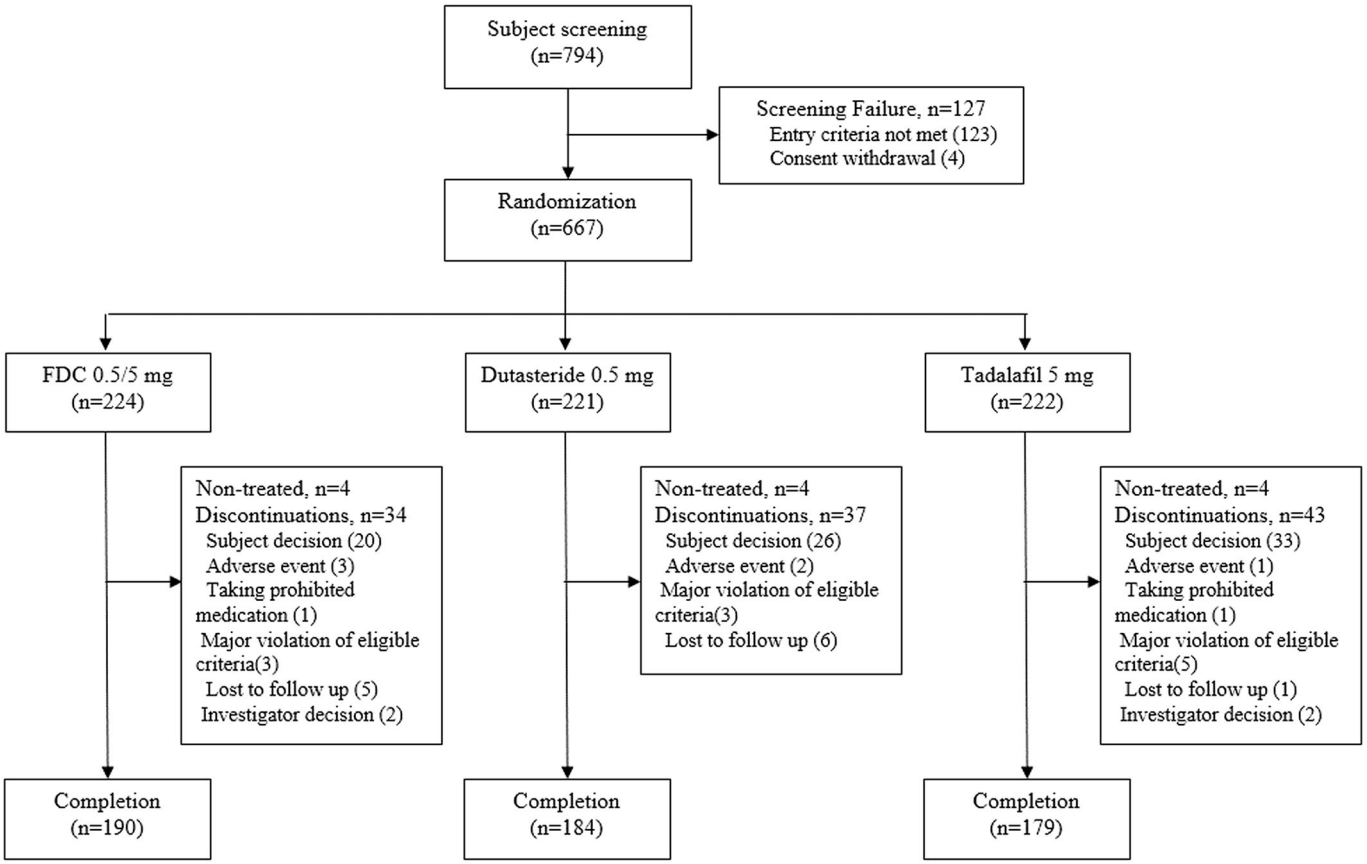


Table 1 Baseline characteristics and the study participants (full analysis set).

Characteristic	FDC 0.5/5 mg, *n* = 210	Dutasteride 0.5 mg, *n* = 207	Tadalafil 5 mg, *n* = 202	Total, *N* = 619
Age, years, mean (SD)	61.97 (7.45)	62.22 (7.64)	62.62 (6.92)	62.26 (7.34)
Smoking, *n* (%)	113 (53.81)	107 (51.69)	110 (54.46)	330 (53.31)
Drinking, *n* (%)	160 (76.19)	164 (79.23)	154 (76.24)	478 (77.22)
Q_{max}, mL/s, mean (SD)	10.42 (2.62)	10.82 (2.43)	10.72 (2.51)	10.65 (2.52)
Voided volume, mL, mean (SD)	212.95 (88.71)	198.33 (75.21)	220.13 (102.35)	210.41 (89.65)
PVR, mL, mean (SD)	28.72 (36.97)	29.75 (37.01)	33.81 (39.52)	30.74 (37.84)
PSA level, ng/mL, mean (SD)	1.94 (2.92)	1.74 (2.29)	1.88 (1.90)	1.86 (2.41)
PV, mL, mean (SD)	40.41 (11.82)	39.13 (11.35)	40.64 (10.54)	40.05 (11.26)
IPSS total, points, mean (SD)	19.70 (5.35)	19.32 (5.06)	19.79 (5.09)	19.61 (5.17)
IPSS obstructive subdomain, points, mean (SD)	11.99 (3.81)	11.82 (3.66)	12.27 (3.48)	12.02 (3.65)
IPSS irritative subdomain, points, mean (SD)	7.71 (2.78)	7.50 (2.59)	7.52 (2.74)	7.58 (2.70)
QoL, point, mean (SD)	4.08 (0.78)	3.97 (0.82)	4.14 (0.82)	4.06 (0.81)

in the total IPSS at 48 weeks after baseline were −9.53 (0.36) for the FDC 0.5/5 mg group and −4.24 (0.37) for tadalafil 5 mg group. The LSMD between the groups was −5.29 (95% CI −6.30 to −4.27), which was statistically significant ($P < 0.001$; Table 2).

Secondary Efficacy Outcomes

The LS mean (SE) change from baseline to Week 48 in the IPSS obstructive subscore was −5.99 (0.25) in the FDC 0.5/5 mg group, −2.90 (0.25) in dutasteride 0.5 mg group, and

Table 2 Change from baseline in total IPSS (full analysis set).

	FDC 0.5/5 mg, *n* = 181	Dutasteride 0.5 mg, *n* = 174	Tadalafil 5 mg, *n* = 170
Baseline			
n	181	174	170
Mean (SD)	19.86 (5.41)	19.41 (5.00)	19.91 (5.14)
Median	19.00	18.50	19.00
Min, Max	13.00, 35.00	13.00, 32.00	13.00, 33.00
Week 48			
n	153	153	143
Mean (SD)	10.14 (5.71)	15.05 (5.97)	15.37 (5.68)
Median	9.00	15.00	15.00
Min, Max	1.00, 28.00	3.00, 35.00	1.00, 32.00
Change from baseline at Week 48			
n	153	153	143
Mean (SD)	−9.59 (5.17)	−4.27 (4.75)	−4.25 (4.37)
Median	−10.00	−4.00	−3.00
Min, Max	−26.00, 10.00	−21.00, 9.00	−23.00, 12.00
MMRM results*			
LS mean (SE)	−9.53 (0.38)	−4.34 (0.38)	
LSMD (95% CI)		−5.19 (−6.25 to −4.13)	
P		<0.001	
MMRM results†			
LS mean (SE)	−9.58 (0.37)		−4.27 (0.38)
LSMD (95% CI)			−5.31 (−6.34 to −4.27)
P			<0.001

*Max, maximum; Min, minimum; MMRM, mixed effect models for repeated measures (included baseline total IPSS, treatment, visit, and visit by treatment interaction). *Testing for difference between FDC 0.5/5 mg and dutasteride 0.5 mg: MMRM model. †Testing for difference between FDC 0.5/5 mg and tadalafil 5 mg: MMRM model.*

−2.75 (0.24) in tadalafil 5 mg group. In the comparison between the FDC 0.5/5 mg and dutasteride 0.5 mg groups, the LSMD (95% CI) was −3.04 (−3.73 to −2.36) ($P < 0.001$). In the comparison between the FDC 0.5/5 mg group and tadalafil 5 mg group, the LSMD (95% CI) was −3.24 (−3.90 to −2.57) ($P < 0.001$). The LS mean (SE) change in the IPSS irritative subscore was −3.52 (0.18) in the FDC 0.5/5 mg group,−1.51 (0.17) in dutasteride 0.5 mg group, and −1.49 (0.18) in tadalafil 5 mg group. In the comparison between the FDC 0.5/5 mg and dutasteride 0.5 mg groups, the LSMD (95% CI) was −2.00 (−2.49 to −1.52) ($P < 0.001$). In the comparison between the FDC 0.5/5 mg and tadalafil 5 mg groups, the LSMD (95% CI) was −2.05 (−2.54 to −1.56) ($P < 0.001$). Regarding the QoL score, the LS mean (SE) change from baseline to Week 48 was −1.98 (0.09) in the FDC 0.5/5 mg group, −1.23 (0.09) in dutasteride 0.5 mg group, and −1.61 (0.09) in tadalafil 5 mg group ($P < 0.001$; Fig. 2).

Changes in Q_{max} and PVR at 24 and 48 weeks after baseline showed no statistically significant differences. However, the FDC 0.5/5 mg group exhibited a tendency for a larger increase in Q_{max} and greater reduction in PVR compared to those associated with monotherapies. The changes in PV from baseline to Week 48 were −7.52 mL for the FDC 0.5/5 mg group, −7.64 mL for dutasteride 0.5 mg group, and −1.47 mL for tadalafil 5 mg group, with a difference observed between the FDC 0.5/5 mg and tadalafil 5 mg groups ($P < 0.001$; Fig. 2). Forest plots for the primary endpoint showed that the benefit of the FDC over each monotherapy was generally consistent across pre-specified subgroups of age, PV, baseline PSA level, and baseline symptom severity (Fig. 3). Notably, patients with higher baseline symptom burden (baseline total IPSS ≥20) had a larger treatment effect of the FDC compared with those with baseline IPSS <20 (Fig. 3).

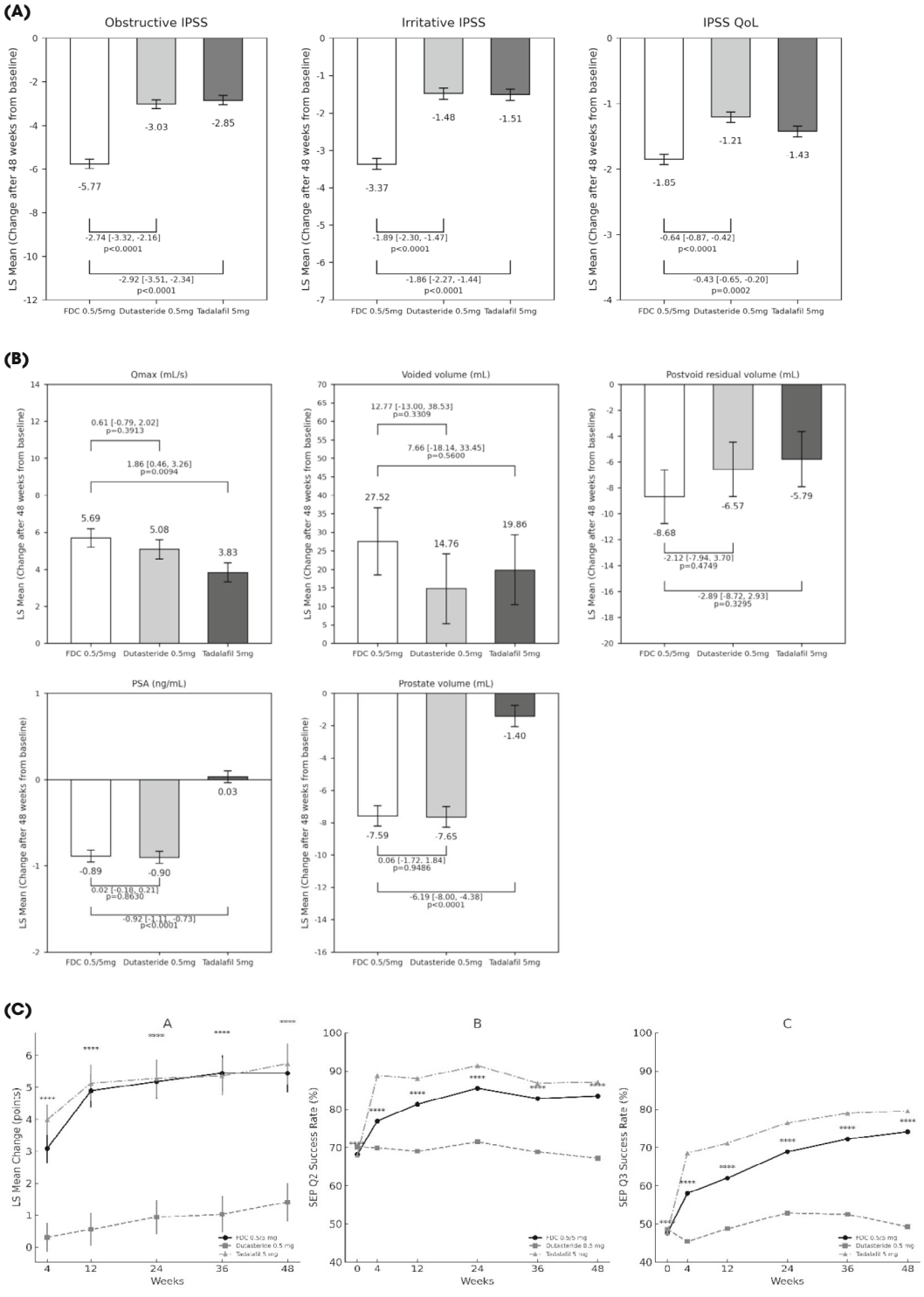
Exploratory Outcomes

The LS mean (SE) change from baseline to Week 48 in the IIEF - EF total score was 5.44 (0.69) in the FDC 0.5/5 mg group, 1.41 (0.69) in the dutasteride 0.5 mg group, and 5.74 (0.64) in the tadalafil 5 mg group. In the comparison between the FDC 0.5/5 mg and dutasteride 0.5 mg groups, the LSMD (95% CI) was 4.03 (2.35–5.71), which was statistically significant ($P < 0.001$). In contrast, the comparison between the FDC 0.5/5 mg and tadalafil 5 mg groups showed no statistically significant difference. In the analysis of SEP Question 2 and Question 3 success rates, the FDC 0.5/5 mg group demonstrated statistically superior outcomes compared with the dutasteride 0.5 mg group, whereas no significant difference was observed compared with the tadalafil 5 mg group (Fig. 2).

Safety

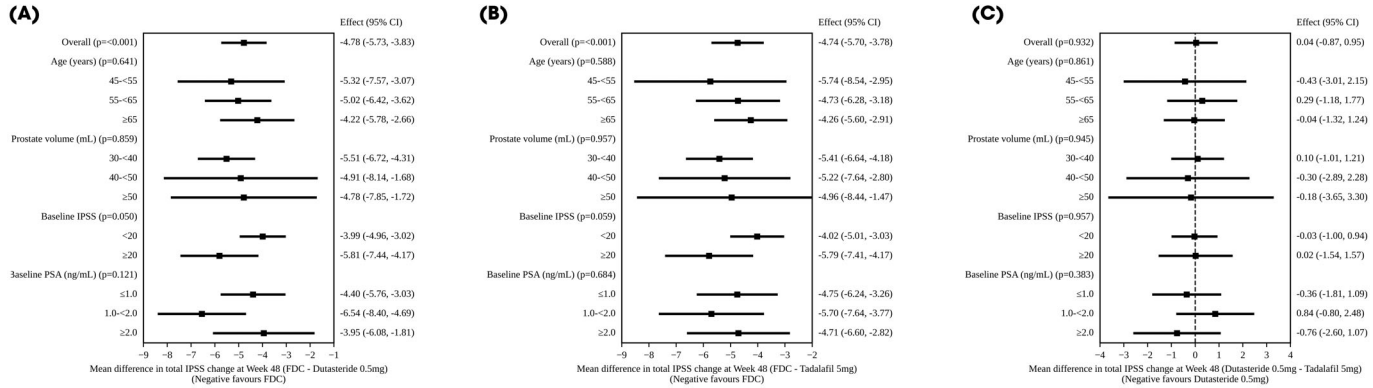
In total, 655 patients were included in the safety analysis. Of these, 176 patients (26.87%) experienced 329 TEAEs. In all, 72 patients (32.88%) in the FDC 0.5/5 mg group experienced

Fig. 2 (**A**) Change from baseline in obstructive IPSS, irritative IPSS and QoL at Week 48. (**B**) Change from baseline in Q_{max}, voiding volume, PVR, PSA level, and PV at Week 48. (**C**) Changes from baseline in IIEF - EF total score, SEP Question 2 success rates, SEP Question 3 success rates at Week 48.



131 TEAEs. In all, 46 patients (21.20%) treated with dutasteride 0.5 mg experienced 97 TEAEs. In all, 58 (26.48%) patients in the tadalafil 5 mg group experienced 101 TEAEs. AEs related to the reproductive system were observed in two patients receiving dutasteride 0.5 mg. In addition, 67 patients (10.23%) experienced 102 adverse drug reactions (ADRs). In

Fig. 3 Forest plots of subgroup analyses of change in total IPSS at Week 48. (**A**) FDC 0.5/5 mg vs dutasteride 0.5 mg (**B**) FDC 0.5/5 mg vs tadalafil 5 mg (**C**) dutasteride 0.5 mg vs tadalafil 5 mg. Effects are mean differences (treatment − comparator) with 95% CIs. Overall *P* values are shown next to 'Overall'; subgroup header *P* values are shown for each subgroup.



all, 28 (12.79%) patients in the FDC 0.5/5 mg group experienced 43 ADRs. In all, 14 (6.45%) patients in the dutasteride 0.5 mg group experienced 19 ADRs. In all, 25 (11.42%) patients treated with the tadalafil 5 mg group experienced 40 ADRs. In all, 23 (3.51%) patients experienced 27 serious AEs; however, none of them were causally related to the study drug. Statistically significant differences were not observed among the groups during safety assessments, which included laboratory tests, electrocardiograms, and vital sign monitoring (Table 3). A total of 655 patients were included in the safety analysis set. Among them, 176 patients (26.87%) experienced at least one TEAE. Most TEAEs were mild or moderate in severity, which were Grade 1 or 2 according to the Common Terminology Criteria For Adverse Events (CTCAE) criteria. The incidence of TEAEs was 32.88% in the FDC 0.5/5 mg group, 21.20% in the dutasteride 0.5 mg group, and 26.48% in the tadalafil 5 mg group. CTCAE Grade ≥3 AEs were reported in 11 patients overall, occurring in four patients in the FDC 0.5/5 mg group (2.28%) and four patients in the dutasteride 0.5 mg group (1.84%), and in two patients in the tadalafil 5 mg group (0.91%). No Grade 4 (life-threatening) TEAEs were observed in any treatment arms. One Grade 5 TEAE (death) occurred in the FDC 0.5/5 mg group, which did not represent a drug-related AE.

Discussion

In this study, we found that the combination of dutasteride and tadalafil, which act via distinct mechanisms, resulted in significantly greater improvement in LUTS associated with BPH compared to monotherapy with either agent.

Dutasteride inhibits both the type 1 and type 2 isoenzymes of 5ARI, blocking the conversion of testosterone to DHT. This results in a marked decrease in intraprostatic DHT levels, suppressing prostatic cell proliferation and reducing PV [14]. It has been reported that 5ARI effectively reduces prostate size and improves IPSS in patients with BPH. McConnell et al. [15] confirmed that drug treatment including dutasteride and finasteride delayed the progression of BPH and improved LUTS, and the Roehrborn review [5] emphasised the long-term effect of dutasteride in reducing the incidence of acute urinary retention and BPH-related surgery.

Tadalafil selectively inhibits PDE5 by activating the nitric oxide–cyclic GMP pathway to induce smooth muscle relaxation and vasodilation. With a long half-life of ~17.5 h, tadalafil provides sustained effects with once daily dosing, enhancing convenience and adherence [16]. Oelke et al. [17] conducted a 12-week, randomised controlled trial in which patients received a once daily placebo, tadalafil 5 mg, or tamsulosin 0.4 mg. They reported that monotherapy with either tadalafil or tamsulosin resulted in significant and comparable improvements compared to placebo in LUTS due to BPH. These findings provide evidence that tamsulosin and tadalafil exhibit similar efficacy in BPH treatment.

The present study was designed based on the CombAt study, which evaluated combined therapy with dutasteride and tamsulosin; however, we substituted tamsulosin with tadalafil. The CombAt study is one of the most representative large-scale investigations employing dutasteride, demonstrating that combined therapy with dutasteride and tamsulosin significantly improved LUTS, enhanced the urinary flow rate, and reduced the incidence of clinical progression events compared to monotherapy in BPH treatment.

Wada et al. [9] evaluated the effect of adding dutasteride to tadalafil in patients with LUTS secondary to BPH who were dissatisfied with tadalafil monotherapy. Their study compared outcomes before and 24 weeks after the addition of dutasteride, demonstrating significant improvement in IPSS and QoL scores, resulting in a significant reduction in PV.

Table 3 Summary of safety (safety analysis set).

Variable, number of patients (%) [number of events]	FDC 0.5/5 mg, *n* = 219	Dutasteride 0.5 mg, *n* = 217	Tadalafil 5 mg, *n* = 219	Total, *N* = 655
TEAEs				
Any events	72 (32.88) [131]	46 (21.20) [97]	58 (26.48) [101]	176 (26.87) [329]
Infections and infestations	17 (7.76) [20]	8 (3.69) [10]	10 (4.57) [14]	35 (5.34) [45]
Nervous system disorders	15 (6.85) [9]	9 (4.15) [10]	7 (3.20) [8]	31 (4.73) [36]
Musculoskeletal and connective tissue disorders	15 (6.85) [17]	7 (3.23) [9]	7 (3.20) [7]	29 (4.43) [33]
Gastrointestinal disorders	11 (5.02) [16]	5 (2.30) [9]	10 (4.57) [11]	26 (3.97) [36]
Respiratory, thoracic and mediastinal disorders	3 (1.37) [3]	5 (2.30) [7]	7 (3.20) [11]	15 (2.29) [20]
Cardiac disorders	2 (0.91) [3]	5 (2.30) [5]	8 (3.65) [8]	15 (2.29) [16]
Vascular disorders	7 (3.20) [7]	3 (1.38) [3]	5 (2.28) [5]	15 (2.29) [15]
Eye disorders	6 (2.74) [7]	5 (2.30) [5]	3 (1.37) [3]	14 (2.14) [15]
Metabolism and nutrition disorders	5 (2.28) [5]	2 (0.92) [2]	6 (2.74) [6]	13 (1.98) [13]
General disorders and administration site conditions	4 (1.83) [4]	2 (0.92) [2]	6 (2.74) [7]	12 (1.83) [13]
Skin and subcutaneous tissue disorders	3 (1.37) [3]	3 (1.38) [6]	5 (2.28) [5]	11 (1.68) [14]
Renal and urinary disorders	3 (1.37) [3]	6 (2.76) [6]	2 (0.91) [2]	11 (1.68) [11]
Reproductive system and breast disorders	3 (1.37) [4]	3 (1.38) [3]	3 (1.37) [3]	9 (1.37) [10]
Investigations	2 (0.91) [2]	2 (0.92) [4]	3 (1.37) [4]	7 (1.07) [10]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	3 (1.37) [4]	3 (1.38) [4]	1 (0.46) [1]	7 (1.07) [9]
Hepatobiliary disorders	3 (1.37) [4]	2 (0.92) [2]	2 (0.91) [2]	7 (1.07) [8]
Injury, poisoning, and procedural complications	2 (0.91) [3]	3 (1.38) [3]	1 (0.46) [1]	6 (0.92) [7]
Ear and labyrinth disorders	1 (0.46) [1]	2 (0.92) [2]	3 (1.37) [3]	6 (0.92) [6]
Psychiatric disorders	2 (0.91) [4]	1 (0.46) [1]	0	3 (0.46) [5]
Surgical and medical procedures	1 (0.46) [2]	1 (0.46) [1]	0	2 (0.31) [3]
Blood and lymphatic system disorders	0	1 (0.46) [1]	0	1 (0.15) [1]
Congenital, familial and genetic disorders	0	1 (0.46) [1]	0	1 (0.15) [1]
Immune system disorders	0	1 (0.46) [1]	0	1 (0.15) [1]
ADRs				
Any events	28 (12.79) [43]	14 (6.45) [18]	25 (11.42) [40]	67 (10.23) [102]
Nervous system disorders	11 (5.02) [13]	5 (2.30) [6]	5 (2.28) [6]	21 (3.21) [25]
Gastrointestinal disorders	4 (1.83) [4]	2 (0.92) [3]	5 (2.28) [5]	11 (1.68) [12]
Musculoskeletal and connective tissue disorders	6 (2.74) [7]	1 (0.46) [1]	3 (1.37) [3]	10 (1.53) [11]
Vascular disorders	5 (2.28) [5]	0	3 (1.37) [3]	8 (1.22) [8]
General disorders and administration site conditions	2 (0.91) [2]	0	4 (1.83) [5]	6 (0.92) [7]
Reproductive system and breast disorders	2 (0.91) [3]	2 (0.92) [2]	2 (0.91) [2]	6 (0.92) [7]
Respiratory, thoracic and mediastinal disorders	2 (0.91) [2]	2 (0.92) [2]	2 (0.91) [3]	6 (0.92) [7]
Cardiac disorders	1 (0.46) [1]	1 (0.46) [1]	4 (1.83) [4]	6 (0.92) [6]
Skin and subcutaneous tissue disorders	3 (1.37) [3]	0	2 (0.91) [2]	5 (0.76) [5]
Investigations	1 (0.46) [1]	1 (0.46) [2]	2 (0.91) [2]	4 (0.61) [5]
Eye disorders	0	1 (0.46) [1]	1 (0.46) [1]	2 (0.31) [2]
Metabolism and nutrition disorders	0	0	2 (0.91) [2]	2 (0.31) [2]
Renal and urinary disorders	2 (0.91) [2]	0	0	2 (0.31) [2]
Hepatobiliary disorders	0	0	1 (0.46) [1]	1 (0.15) [1]
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	0	0	1 (0.46) [1]	1 (0.15) [1]
Psychiatric disorders	0	1 (0.46) [1]	0	1 (0.15) [1]
Patients with serious AEs	12 (5.48) [14]	7 (3.23) [9]	4 (1.83) [4]	23 (3.51) [27]
Patients with serious ADRs	1 (0.46) [1]	0	0	1 (0.15) [1]
Patients with TEAEs leading to drug discontinuation	3 (1.37) [3]	2 (0.92) [3]	1 (0.46) [1]	6 (0.92) [7]
Patients with TEAEs leading to death	1 (0.46) [1]	0	0	1 (0.15) [1]

Note: denominator of percentage is the number of Patients in each group. Number of Patients (percentage of Patients) [number of events].

Moreover, the improvement was reported to be comparable to that observed with the combination of dutasteride and an α-blocker. Gotoh et al. [18] reported that in patients diagnosed with BPH and LUTS, switching from dutasteride 0.5 mg monotherapy to combined therapy with an additional tadalafil 5 mg resulted in a statistically significant reduction in total IPSS scores at 4, 12, and 24 weeks compared to baseline. These findings are consistent with those of the present study. Although previous studies have examined the addition of agents to dutasteride or tadalafil monotherapy in patients with BPH, this study is the first to directly compare individual monotherapies with combined therapy.

Casabé et al. [19] evaluated the effects of finasteride 0.5 mg and tadalafil 5 mg over 26 weeks on LUTS. Their study assessed the combination effect of finasteride, which is a 5ARI similar to dutasteride and tadalafil. The results demonstrated that co-administration of tadalafil and finasteride led to an early improvement in LUTS associated with BPH, consistent with our findings. Although their study had a relatively short duration (26 weeks) and included only a finasteride monotherapy control arm, the present study was conducted over 48 weeks and incorporated an additional control arm that received tadalafil monotherapy with an experimental FDC group. This design enabled a more comprehensive evaluation of the efficacy and safety of combined therapy.

Casabé et al. [19] reported that the combination of tadalafil and finasteride improved sexual function compared with finasteride alone. The present study demonstrated that the combination of tadalafil and dutasteride was more effective in improving sexual function than dutasteride monotherapy. These results are consistent with previous evidence indicating that tadalafil is effective not only in the management of BPH but also in the treatment of erectile dysfunction.

Beyond the primary endpoint, the secondary efficacy outcomes, including improvements in IPSS obstructive and irritative domains and QoL scores, were significantly better in the FDC group than in the control groups. Notably, the obstructive symptom domain improved by approximately 3.0–3.2 points more in the FDC group, suggesting that the dual actions of dutasteride and tadalafil worked synergistically to relieve symptoms. However, objective parameters such as Q_{max} and PVR did not differ significantly between the groups. According to Gotoh et al. [18], patients diagnosed with BPH and LUTS who switched from dutasteride 0.5 mg monotherapy to combined therapy with tadalafil 5 mg showed no statistically significant changes in Q_{max} and residual urine volume at 4, 12, and 24 weeks compared to baseline. This indicates that the accuracy of Q_{max} and PV is compromised by variations in patients' voided volume and overall condition, limiting their utility as objective indices for assessing improvement in LUTS due to BPH. These limitations have been highlighted in previous studies [20,21].

Subgroup forest plots supported the robustness of the primary efficacy findings across clinically relevant strata, including age, PV, and baseline PSA level. Notably, the treatment benefit of FDC appeared greater among men with more severe baseline symptoms, with borderline evidence of effect heterogeneity. This pattern is clinically plausible: patients with a higher symptom burden may have greater potential for improvement, and the complementary mechanisms of dutasteride (prostate size reduction) and tadalafil (smooth muscle relaxation) may provide more pronounced symptom relief in this group.

Safety analysis showed that, although the overall incidence of TEAEs was slightly higher in the FDC group than in the dutasteride and tadalafil groups, the majority of these AEs were mild to moderate in severity. Furthermore, the incidence of ADRs and serious AEs did not differ significantly among the three groups. These safety results indicate that combined therapy maintains a clinically acceptable safety profile while providing superior efficacy, which is consistent with previous reports of good tolerability of combination regimens [22]. The incidence and severity distribution of TEAEs were comparable across treatment arms, with most events being CTCAE Grade 1–2. Notably, the rate of CTCAE Grade ≥3 remained low in all groups. These findings support the overall tolerability of the FDC and are consistent with known safety profiles of dutasteride and tadalafil monotherapies.

In summary, this study demonstrates that FDC therapy with dutasteride and tadalafil provides superior improvement in LUTS compared to monotherapy in patients with BPH while being well tolerated. This is expected to enhance medication convenience, improve patient compliance, and reduce the medical costs. However, a limitation of this study is the absence of a placebo group. Long-term evaluations are needed to assess the sustained effects on LUTS and safety.

Conclusions

The FDC 0.5/5 mg demonstrated efficacy, safety, and tolerability among study participants. These results suggest that this new FDC regimen may provide significant benefits in the management of LUTS associated with BPH.

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Disclosure of Interests

The authors have no conflicts of interest to disclose.

Ethics Statement

This study was approved by a central Institutional Review Board (Ulsan University Hospital, Ulsan University College of Medicine, Ulsan, South Korea. IRB No. 2021-0935) and local Institutional Review Boards at each study site (IRB No.: 2021-0935, KHNMC 2021-05-041, DSMC 2021-05-075, KCH-M-2021-05-009, EMCS-2021-05-027, 2105-003-117, B-2106-692-001, SMC 2021-05-118, SCHUH 2021-05-010, 3-2021-0263, 4-2021-0661, 2021-0941, CNUH-2021-191, CBNUH 2021-05-018, KC21MDDT0539, KC21MDDT0564, UUH 2021-05-044, HALLYM 2021-05-019, GURI 2021-05-038, HDT 2021-05-009 and EUMC 2022-03-029).

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Abbreviations: ADR, adverse drug reaction; (TE)AE, (treatment-emergent) adverse event; 5ARI, 5α-reductase inhibitor; CTCAE, Common Terminology Criteria For Adverse Events; DHT, dihydrotestosterone; FDC 0.5/5 mg, fixed-dose combination dutasteride 0.5 mg/tadalafil 5 mg; IIEF - EF, international index of erectile function - erectile function; LS mean, least square mean; LSMD, LS mean difference; PDE5(i), phosphodiesterase type 5 (inhibitors); PV, prostate volume; PVR, post-void residual; Qmax, maximum urinary flow rate; QoL, quality of life; SAP, Statistical Analysis Plan; SAS, Statistical Analysis System; SE, standard error; SEP, Sexual Encounter Profile.