INTERNATIONAL JOURNAL OF UROLOGY
International Journal of Urology (2015) 22, 582–587 doi: 10.1111/iju.12741

Original Article: Clinical Investigation

Treatment satisfaction and clinically meaningful symptom improvement in men with lower urinary tract symptoms and prostatic enlargement secondary to benign prostatic hyperplasia: Secondary results from a 6-month, randomized, double-blind study comparing finasteride plus tadalafil with finasteride plus placebo

Claus G Roehrborn,[1] Adolfo Casabé,[2] Sidney Glina,[3] Sebastian Sorsaburu,[4] Carsten Henneges[5] and Lars Viktrup[4]

[1]University of Texas Southwestern Medical Center, Dallas, Texas, USA; [2]Instituto Médico Especializado, Buenos Aires, Argentina; [3]Instituto H. Ellis and Department of Urology, Ipiranga Hospital, Sao Paolo, Brazil; [4]Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana, USA; and [5]Global Statistical Sciences, Lilly Deutschland GmbH, Bad Homburg, Germany

Abbreviations & Acronyms
5-ARI = 5-alpha reductase inhibitor
AUA = American Urological Association
BPH = benign prostatic hyperplasia
BPH-LUTS = benign prostatic hyperplasia with lower urinary tract symptoms
CI = confidence interval
CombAT = Combination of Avodart® and Tamsulosin
DUT = dutasteride
FIN = finasteride
IPSS = International Prostate Symptom Score
LUTS = lower urinary tract symptoms
OR = odds ratio
PBO = placebo
PBO/FIN = placebo once daily with finasteride 5 mg
PDE5I = phosphodiesterase 5 inhibitor
PSA = prostate-specific antigen
PVR = postvoid residual volume
Q_{max} = urinary peak flow rate
QoL = quality of life
SD = standard deviation
TAD = tadalafil
TAD/FIN = tadalafil 5 mg once daily with finasteride 5 mg
TAM = tamsulosin
TSS-BPH = Treatment Satisfaction Scale-Benign Prostatic Hyperplasia
VA-COOP = Veterans Affairs Cooperative Studies Benign Prostatic Hyperplasia Study Group

Correspondence: Claus G Roehrborn M.D., Department of Urology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., J8-130, Dallas, TX 75390-9110, USA. Email: claus.roehrborn@UTSouthwestern.edu

Received 7 October 2014; accepted 21 January 2015. Online publication 31 March 2015

Objectives: To report the secondary analyses of treatment satisfaction and clinically meaningful improvements in a randomized study comparing coadministration of tadalafil 5 mg with finasteride 5 mg versus finasteride alone in men with prostatic enlargement secondary to benign prostatic hyperplasia.

Methods: An international, randomized, double-blind, parallel study was carried out in men aged ≥45 years who were 5-alpha reductase inhibitor naïve, and had an International Prostate Symptom Score ≥13 and prostate volume ≥30 mL; 350 men received placebo/finasteride and 345 received tadalafil/finasteride over 26 weeks. Treatment satisfaction was assessed per protocol using the Treatment Satisfaction Scale-Benign Prostatic Hyperplasia. Responder cut-offs, analyzed post-hoc were total International Prostate Symptom Score improvement ≥3 points or ≥25% from randomization.

Results: Baseline patient characteristics were generally comparable between responders and non-responders. The proportion of patients with an International Prostate Symptom Score improvement ≥3 points with tadalafil/finasteride and placebo/finasteride, respectively, at week 4 was 57.0% and 47.9% (OR 1.45, 95% confidence interval 1.07–1.97), at week 12 was 68.8% and 60.7% (OR 1.48, 95% confidence interval 1.07–2.05) and at week 26 was 71.4% and 70.2% (OR 1.14, 95% confidence interval 0.81–1.61); for IPSS change ≥25%, the corresponding proportions were 44.8% and 32.9% (OR 1.66, 95% confidence interval 1.21–2.28), 55.5% and 51.9% (OR 1.18, 95% confidence interval 0.87–1.62), and 62.0% and 58.3% (OR 1.23, 95% confidence interval 0.89–1.70). Treatment satisfaction at week 26 was significantly greater with tadalafil/finasteride versus placebo/finasteride for total treatment satisfaction scale score (P=0.031) and satisfaction with efficacy subscore (P = 0.025); scores were not significantly different between treatments for satisfaction with dosing or side-effects (both $P \geq 0.371$).

Conclusions: Tadalafil/finasteride results in significantly more patients achieving early clinical meaningful improvements in symptoms, and in greater treatment satisfaction versus placebo/finasteride.

Key words: benign prostatic hyperplasia, finasteride, lower urinary tract symptoms, tadalafil, treatment satisfaction.

Introduction

LUTS might include storage symptoms (increased frequency/urgency or incontinence) and voiding symptoms (slow/intermittent urine stream or straining), and have a negative impact on QoL measures.[1,2] The prevalence of LUTS in men increases with age, and LUTS are often seen secondary to BPH with prostatic enlargement.

Medical therapy for the treatment of LUTS in men with substantial prostatic enlargement often commences with 5-ARI, which act through inhibiting the conversion of testosterone to dihydrotestosterone, resulting in a decrease in prostate volume and a reduction in the risk of disease progression to end-points such as acute urinary retention or surgery; however, improvements in LUTS with 5-ARI are gradual, and commonly become significant versus PBO only

after at least 6–12 months of dosing.[2–4] Combination therapy with fast-acting agents approved for the treatment of LUTS, such as α_1-adrenoceptor antagonists (alpha-blockers), is therefore common, and is recommended in guidelines for the treatment of LUTS from the Japanese Urological Association, the AUA and the EUA to achieve more rapid relief of symptoms.[2–4] Notably, however, sexual dysfunction increases in prevalence in the aging male population in which LUTS secondary to BPH is most common, and sexual side-effects might be observed with 5-ARI, and particularly with combination therapy with 5-ARI and alpha-blockers.[5,6]

The PDE5I TAD, which has a half-life of 17.5 h, is approved globally for the once daily treatment of LUTS secondary to BPH. Based on data from multiple clinical studies carried out worldwide, TAD 5 mg once daily results in significant improvements in total IPSS, generally from the first study visit at week 1 or 2.[7–11] Given the rapid onset of action of TAD, and the lack of negative sexual side-effects with PDE5I therapy, we recently carried out a study to assess the effects of TAD in combination with the 5-ARI FIN in men with LUTS and prostatic enlargement. Reports on the overall results and on results for both LUTS and sexual function in the population of men with erectile dysfunction at baseline have been presented previously.[12,13] In the current report, we supplemented the previously reported population-level data with post-hoc analyses comparing the proportion of men who experienced a clinically meaningful improvement in LUTS, as measured by the IPSS. In addition, we present prespecified analyses of satisfaction with treatment for LUTS based on the TSS-BPH.

Methods

The original study was an international, randomized, double-blind, PBO-controlled trial of FIN/TAD versus FIN/PBO over 6 months in men with BPH-LUTS and prostatic enlargement. Detailed descriptions of the study design, patient eligibility criteria and results for overall improvements in LUTS, and in erectile dysfunction for affected men, have been published previously.[12,13] In brief, eligible patients were men aged ≥45 years with BPH-LUTS for >6 months, prostate volume ≥30 mL, IPSS total score ≥13 and were naïve to 5-ARI therapy. Men received either TAD/FIN or PBO/FIN for 26 weeks. Efficacy measures were assessed at baseline and at study weeks 4, 12 and 26. The study was carried out in accordance with the Declaration of Helsinki and all applicable regulations. Institutional review boards at each site approved the study, and all participants provided written informed consent before undergoing study procedures.

Analyses for the present study included post-hoc analysis of minimal clinically important differences in IPSS and prespecified analysis of treatment satisfaction based on the TSS-BPH. For the post-hoc analyses of clinically meaningful differences, change in IPSS of ≥3 was derived from Barry *et al.*, who found that a decrease in IPSS of 3 points was detectable to patients, a cut-off also used by the 2010 AUA guidelines; analysis using a cut-off of 25% change in IPSS, which incorporates baseline symptom severity, was based on other previous reports.[4,14–18] OR, 95% CI and *P*-values for clinically meaningful differences were from a repeated measures logistic regression analysis model that included terms for treatment group, region, visit and visit-by-treatment interaction as fixed effects, and subject as the random variable. An unstructured covariance structure was used.

Treatment satisfaction was assessed using the TSS-BPH.[19–21] The TSS-BPH is a validated, subject-rated instrument that measures satisfaction with treatment. This 13-item questionnaire is grouped into an overall score and the three subscores "satisfaction with efficacy," "satisfaction with dosing" and "satisfaction with side-effects"; lower scores show greater satisfaction. Consistent with prior reports, mean TSS-BPH scores were adjusted to a scale of 0–100 using the formula:[20,21]

$$100 \times \frac{\text{Observed mean score} - \text{Minimum possible mean score}}{\text{Maximum possible mean score} - \text{Minimum possible mean score}}.$$

The TSS-BPH overall score and subscores were analyzed using prespecified van Elteren tests stratifying by region (European Union versus other).

All tests for treatment effects were carried out at a two-sided alpha-level of 0.05 unless otherwise stated; two-sided 95% CI were produced for continuous variables. All data were analyzed using the SAS 9.2 software (SAS Institute, Cary, NC, USA). For the figure comparing results in the present study with earlier reports of 5-ARI and alpha-blocker combination therapy, data were derived from data labels in Roehrborn *et al.*, estimated from Lepor *et al.*, and taken from Casabe *et al.*[5,12,22]

Results

A total of 695 patients were randomized and received at least one dose of the study drug (345 patients randomized to TAD/FIN and 350 to PBO/FIN), and 592 patients (85.1%) completed 26 weeks of double-blind therapy. At baseline, the overall mean (SD) age was 63.7 years (7.7); 85.5% of patients were Caucasian, 10.1% were Native American and 3.0% were Black/African-American. BPH-LUTS severity was mild to moderate (IPSS <20) for 68.3% of patients and severe (IPSS ≥20) for 31.7% of patients. Mean (SD) Q_{max} was 10.1 mL/s (2.8), PVR was 64.1 mL (60.1), prostate volume was 49.4 mL (20.4) and PSA was 2.4 ng/mL (2.0).

Responder analyses

Analyses of response based on the proportion of patients achieving clinically meaningful improvements (responders) for the two IPSS cut-offs showed that for both definitions, an increasing proportion of patients were responders at each successive study visit, as shown in Figure 1. For the ≥3 point definition at weeks 4, 12 and 26, the proportion of TAD/FIN responders was 57.0%, 68.8% and 71.4%, respectively, and for PBO/FIN the proportions were 47.9%, 60.7% and 70.2%, respectively. For the responder definition of ≥25% decrease in total IPSS, at weeks 4, 12 and 26 the proportion of TAD/FIN responders was 44.8%, 55.5%, and 62.0%, respectively, and for PBO/FIN the proportions were 32.9%, 51.9% and 58.3%, respectively. As shown in Figure 1a, OR of IPSS decrease ≥3 points were statistically significant in favor of TAD/FIN at week 4 and week 12 (OR 1.45, 95% CI 1.07–1.97 and OR 1.48, 95% CI 1.07–2.05, respectively), but were not

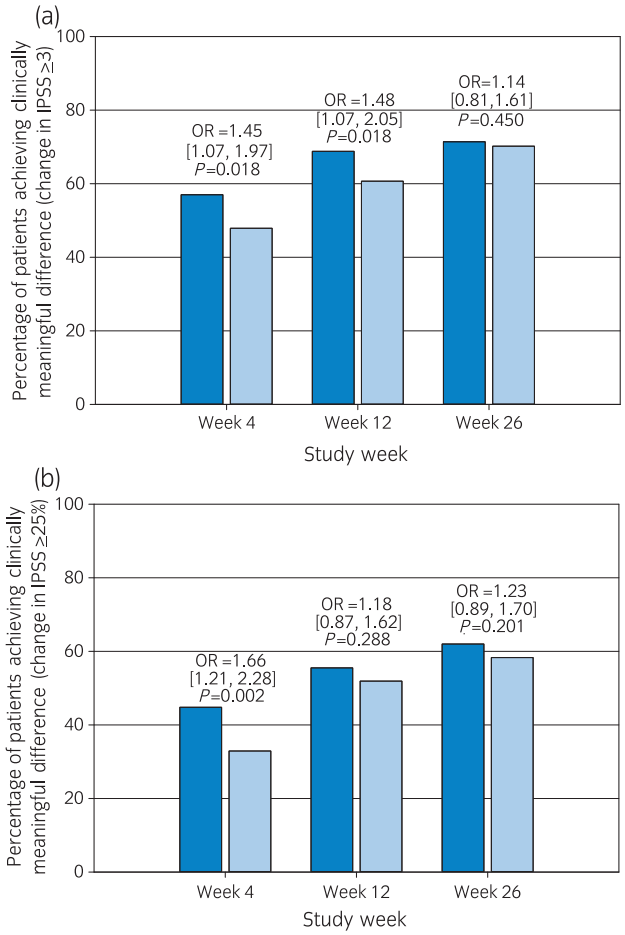

Fig. 1 Percentage of patients with a clinically meaningful difference (a) in total IPSS ≥3 points (b) in total IPSS ≥25%. OR, 95% CI and *P*-values were from a repeated measures logistic regression analysis model that included terms for treatment group, region, visit and visit-by-treatment interaction as fixed effects, and subject as the random effect. (▬), TAD/FIN; (▭), PBO/FIN.

significantly different at week 26 (OR 1.14, 95% CI 0.81–1.61), while for IPSS decrease ≥25% (Fig. 1b), differences were statistically significant at week 4 (OR 1.66, 95% CI 1.21–2.28).

In order to examine whether any patient characteristics were predictive of response, baseline patient characteristics were assessed based on responder status at week 12. Characteristics were generally comparable for responders and non-responders based on either the IPSS 3-point or 25% improvement cut-offs (Table 1).

Treatment satisfaction

Treatment satisfaction was assessed using the TSS-BPH at the final on-treatment study visit (generally 26 weeks); results are shown in Table 2. Patient satisfaction was significantly greater (corresponding to lower scores) in the TAD/FIN group versus the PBO/FIN group based on the TSS-BPH total score (mean 2.0 *vs* 2.1, respectively, $P = 0.031$) and satisfaction with efficacy subscore (mean 33.7 *vs* 36.6, respectively; $P = 0.025$). No significant differences were seen for the satisfaction with dosing or satisfaction with side-effects subscores.

Discussion

In the present study with TAD coadministration for early symptom relief when commencing 5-ARI therapy, a significantly greater proportion of patients receiving TAD versus PBO along with FIN had clinically meaningful responses at study weeks 4 and 12. The proportion of responders continued to increase in both arms through week 26, although differences in the proportion of responders between treatments were no longer significant for either responder definition at study week 26, or at study week 12 for a 25% change in IPSS. Nevertheless, treatment satisfaction at week 26 was significantly greater in men receiving TAD/FIN versus PBO/FIN, which is consistent with the significantly lower mean IPSS with TAD/FIN previously reported for week 26.[12] In contrast to the significantly greater satisfaction observed with efficacy with TAD/FIN versus PBO/FIN, no statistically significant differences in satisfaction with dosing or with side-effects were observed.

No specific patient characteristic was observed to be predictive of response in the present study, though as expected due to a greater possible range for improvement, patients with more severe LUTS (total IPSS ≥20) more often reached a 3-point IPSS improvement. No difference was observed when applying the 25% cut-off.

There have been several previous reports of studies assessing combination therapy of 5-ARI and alpha-blockers; however, comparison with the present results is complicated by different study periods and because data for the same responder cut-offs were not reported in most studies.[5,22–25] Roehrborn *et al.* did report responder rates (both IPSS ≥3 point change and ≥25% change) at 24 months for the randomized, double-blind CombAT study of TAM, DUT or TAM/DUT dosing in 4844 men with BPH-LUTS secondary to prostatic enlargement.[5] At 24 months, responder rates for TAM, DUT and TAM/DUT arms for the IPSS cut-off of ≥3 points were 62%, 65%, and 72%, respectively, and for a ≥25% decrease in IPSS were 55%, 59% and 67%, respectively. In the present study, for PBO/FIN and TAD/FIN at 26 weeks these rates were 70% and 71%, respectively, for the cut-off of ≥3 points, and 58% and 62%, respectively, for the ≥25% cut-off.

Although there are no available data on responder end-points at early time-points (3 months or less) from studies of co-administered therapies for BPH-LUTS, two studies of alpha-blocker/5-ARI combination therapy reported mean IPSS changes at early time-points, and thus provide an opportunity to put our current findings into context. In the study of men receiving terazosin, FIN or terazosin/FIN (VA-COOP), differences in IPSS improvements between combination therapy and FIN monotherapy were observed at week 4 (Fig. 2), and the magnitude of the difference between combination and monotherapy remained relatively constant at later visits through 1 year.[22] However, in VA-COOP, mean prostate volume was approximately 37.5 mL, and when assessed by subgroups of prostate volume, men with larger prostates receiving FIN or combination therapy, but not terazosin alone, experienced greater improvements in IPSS at end-point (52 weeks, earlier time-points not presented) than men with lower prostate volume, a finding also reported for long-term data from the Medical Therapy of

Table 1 Baseline characteristics for all patients by cut-offs for clinically meaningful difference in total IPSS score (≥3-point or ≥25%) at 12 weeks

	IPSS change			
Characteristic	Decrease <3 (*n* = 250)	Decrease ≥3 (*n* = 426)	Decrease <25% (*n* = 320)	Decrease ≥25% (*n* = 356)
Age				
Mean (SD)	63.9 (7.9)	63.7 (7.5)	64.1 (7.8)	63.6 (7.5)
>65 years, *n* (%)	104 (41.6)	180 (42.3)	135 (42.2)	149 (41.9)
Race				
Caucasian, *n* (%)	223 (89.2)	357 (83.8)	284 (88.8)	296 (83.1)
Black or African-American, *n* (%)	9 (3.6)	10 (2.3)	11 (3.4)	8 (2.2)
Asian, *n* (%)	2 (0.8)	4 (0.9)	2 (0.6)	4 (1.1)
Native American or Alaska Native, *n* (%)	16 (6.4)	51 (12.0)	22 (6.9)	45 (12.6)
Region				
USA and Canada, *n* (%)	70 (28.0)	72 (16.9)	85 (26.6)	57 (16.0)
Latin America, *n* (%)	52 (20.8)	124 (29.1)	70 (21.9)	106 (29.8)
Europe, *n* (%)	128 (51.2)	230 (54.0)	165 (51.6)	193 (54.2)
LUTS characteristics				
Moderate (IPSS <20), *n* (%)	187 (74.8)	275 (64.6)	220 (68.8)	242 (68.0)
Severe (IPSS ≥20), *n* (%)	63 (25.2)	151 (35.4)	100 (31.3)	114 (32.0)
Q_{max}				
Q_{max} <10 mL/s, *n* (%)	118 (47.2)	199 (46.7)	153 (47.8)	164 (46.1)
Q_{max} ≥10–15 mL/s, *n* (%)	132 (52.8)	225 (52.8)	166 (51.9)	191 (53.7)
Q_{max} (mL/s), mean (SD)	10.0 (2.7)	10.1 (2.8)	10.0 (2.8)	10.2 (2.8)
Bladder/prostate characteristics				
Urine PVR (mL), mean (SD)	64.8 (59.8)	63.3 (60.5)	65.3 (58.5)	62.5 (61.8)
Prostate volume (mL), mean (SD)	48.5 (17.5)	49.9 (21.3)	48.8 (18.3)	49.9 (21.4)
Serum PSA (ng/mL), mean (SD)	2.2 (1.9)	2.5 (2.0)	2.2 (1.9)	2.5 (2.0)

Table 2 TSS-BPH total and subscores by treatment

TSS score	Measure	TAD/FIN (*n* = 345)	PBO/FIN (*n* = 350)	*P*-value*
Total (1–5)†	Mean (SD)	2.0 (0.63)	2.1 (0.66)	0.031
	Median	1.9	2.0	
Total normalized (0–100)†	Mean	26.7	29.1	
	Median	24.2	26.7	
Satisfaction with efficacy (0–100)†	Mean (SD)	33.7 (20.0)	36.6 (21.1)	0.025
	Median	28.1	31.3	
Satisfaction with dosing (0–100)†	Mean (SD)	10.2 (10.9)	11.1 (11.2)	0.371
	Median	12.5	12.5	
Satisfaction related to side-effects (0–100)†	Mean (SD)	8.6 (21.3)	8.5 (21.2)	0.751
	Median	0	0	

**P*-value from van Elteren test stratified by region. †Range; total normalized score and subscale scores are adjusted to a scale of 0–100. Lower scores show greater satisfaction.

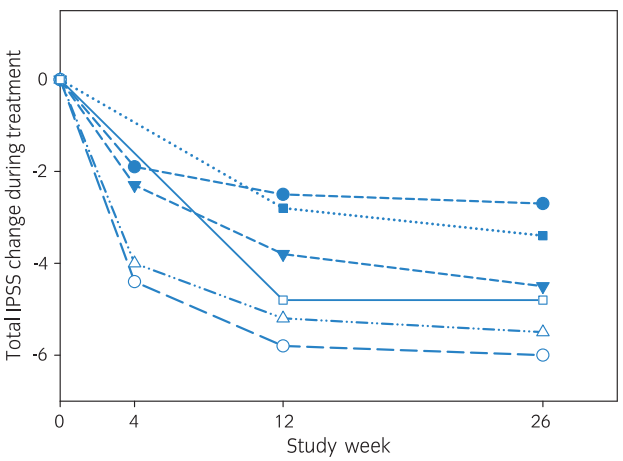

Fig. 2 Least squares mean change in total IPSS for FIN (–●–) and terazosin/FIN (–○–) in VA-COOP; FIN (–▼–) and TAD/FIN (–△–) herein; and DUT (·■·) and TAM/DUT (–□–) in the CombAT study.[5,12,22] Baseline mean (SD) IPSS values in VA-COOP were: FIN 16.2 (5.4), FIN/terazosin 15.9 (5.7); in the CombAT study were DUT 16.4 (6.0), DUT/TAM 16.6 (6.4); and in the present study were FIN 17.4 (5.9), TAD/FIN, 17.1 (5.6).[5,22] Baseline mean prostate volumes (mL) reported in VA-COOP were: FIN 36.2, FIN/terazosin 37.2; in the CombAT study were DUT 54.6, DUT/TAM 54.7; and in the present study were FIN 50.6, TAD/FIN, 48.2.[5,12,22] Data were estimated from Lepor *et al.*, Figure 1,[22] derived from data labels on Roehrborn *et al.*, Figure 2[5]; and taken from Casabe *et al.*, Table 2.[12] Note that data shown for VA-COOP were reported at 4, 13 and 26 weeks.

Prostatic Symptoms study of men with a mean prostate size of approximately 35 mL.[26,27] The CombAT study, aforementioned in regard to responder data, also presented change in IPSS at early time-points (starting at 12 weeks). Notably, men in the CombAT study had significant prostatic enlargement, with a mean prostate volume of 55.0 mL, which was comparable with the mean prostate volume of 49.4 mL observed in the present study. As shown in Figure 2, in both the CombAT and the present study, significant improvements with combination therapy versus 5-ARI monotherapy were observed at the earliest reported time-point, and while remaining statistically significant, the magnitude of the difference decreased numerically in both studies at 26 weeks. As the overall magnitude of improvements continued to increase through 26 weeks in both treatment arms, this presumably reflects an increasing contribution of the 5-ARI to symptom improvements in these populations of men with

substantial prostatic enlargement at baseline. Notably, in the CombAT study, the treatment difference between DUT and TAM/DUT observed at 26 weeks (–1.4) was maintained and remained statistically significant through 2 years of therapy (–1.3, $P < 0.001$).[5] Thus, in a population of men with prostatic enlargement, where the contribution of the 5-ARI to response might be similar to the present study, the difference in IPSS improvements also decreased numerically between the earliest visit and 26 weeks, but was then maintained at that same, statistically significant level, during long-term therapy. To what extent such findings can be extrapolated to patients treated with a combination of FIN and TAD is not known, and future studies should evaluate the persistence of effects with TAD/FIN combination beyond 26 weeks.

Currently, DUT, but not FIN, is approved for use in the treatment of LUTS in men with confirmed enlarged prostate in some Asian countries, such as Japan.[3] Although not currently an approved treatment or assessed directly in the present study, the early impact on symptoms of the combination of TAD and DUT has recently been assessed by Park *et al.* in a randomized, parallel group study that also assessed the combination of TAM and DUT.[28] In the study, Korean men aged at least 50 years with IPSS ≥12 (baseline mean IPSS ~17.8) and with prostate volume ≥30 mL (baseline mean prostate volume ~35.8 mL) were randomized, after a 4-week therapy washout period, to once daily treatment with DUT 0.5 mg plus either TAD 5 mg (TAD/DUT, $n = 86$) or TAM 0.2 mg (TAM/DUT, $n = 82$). After 12 weeks of randomized therapy, mean change in IPSS was –2.3 in the TAD/DUT arm and –2.5 in the TAM/DUT arm ($P = 0.634$). Changes in the IPSS voiding and storage subscores and IPSS QoL index were also comparable, with all changes within 0.1 points when compared between treatment arms. Similarly, Q_{max} increased by 2.5 mL/s with TAD/DUT and 2.6 mL/s with TAM/DUT, and PVR decreased by 1.4 mL with TAD/DUT and 1.6 mL with TAM/DUT. Thus, comparable improvements were seen across a range of BPH-LUTS measures for men receiving DUT plus TAD and those receiving the combination of DUT plus TAM, which is currently a recommended treatment for some men based on the AUA and EUA guidelines.[2,4] Furthermore, data accumulated thus far from studies of DUT and FIN monotherapy in men with BPH-LUTS suggest that both these 5-ARIs lead to comparable LUTS improvements and prostate volume reductions.[2,4] Therefore, although the present study did not directly address the combination of TAD and DUT, and it is not currently an approved treatment combination, the available clinical evidence suggests that results similar to those observed here for TAD/FIN could reasonably be anticipated with TAD/DUT.

Limitations of the present study included a lack of TSS-BPH data at study weeks 4 and 12, but also the overall limited amount of published data on treatment satisfaction with other BPH-LUTS therapies, which prevented comparison of TAD/FIN data at earlier time-points and with other compounds. The present study was designed to assess the ability of TAD to provide early symptom relief in men with LUTS and prostatic enlargement at the commencement of 5-ARI therapy, and was not designed to compare the effects of TAD and FIN combination therapy over several years, as in prior alpha-blocker and 5ARI combination therapy studies, or to assess the natural history of the condition when treated with PBO only.[25,29] Furthermore, the short period of treatment and lack of follow up after FIN treatment cessation precluded the opportunity to measure the incidence of acute urinary retention and surgical intervention, or the persistence of sexual dysfunction after FIN discontinuation.

In conclusion, the proportion of patients who had clinically meaningful improvements in BPH-LUTS when treated with TAD/FIN increased numerically throughout the study, with a significantly greater proportion of TAD/FIN versus PBO/FIN responders observed at week 4 by both the ≥3-point and ≥25% IPSS improvement definitions, and at week 12 for a ≥3-point improvement in IPSS. Treatment satisfaction was significantly greater with TAD/FIN compared with PBO/FIN at 26 weeks, consistent with the previously reported results of significantly greater mean improvement in total IPSS. These data further support the utility of coadministration of TAD for early symptom improvement in men starting treatment with a 5-ARI.

Acknowledgments

This study was funded by Eli Lilly and Company. Thomas Melby of inVentiv Health Clinical (Cary, NC, USA) assisted in the preparation of this manuscript.

Conflict of interest

Claus G Roehrborn has financial interests and/or other relationships with Eli Lilly and Company, and with Allergan, Afferent Pharmaceuticals, Auxiliary Medical Services, Cancer and Leukemia Group B Clinical Trial Group, GlaxoSmithKline, New England Research Institutes, NeoTract, National Institute of Diabetes and Digestive and Kidney Diseases, Protox, Southwest Oncology Group, Urologix, VA Corporate Studies, and Watson Pharmaceuticals.

Adolfo Casabé has been an investigator, consultant, and speaker/lecturer for Eli Lilly and Company, and has been an investigator for Pfizer, GlaxoSmithKline, Bayer and Janssen, and a speaker for Pfizer.

Sidney Glina has been an investigator and speaker, and served on advisory boards for Eli Lilly and Company, and has been an investigator for AstraZeneca and Cubist Pharmaceuticals, a speaker for Bayer HealthCare, Eurofarma, and Pfizer, and on advisory boards for Aché Laboratórios Farmacêuticos S.A. and Besins Healthcare.

Sebastian Sorsaburu, Carsten Henneges, and Lars Viktrup were employees and minor shareholders of Eli Lilly and Company.

References

1 Abrams P, Cardozo L, Fall M *et al*. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Neurourol Urodyn.* 2002; **21**: 167–78.

2 Oelke M, Bachmann A, Descazeaud A *et al*. EAU Guidelines on the Treatment and Follow-up of Non-neurogenic Male Lower Urinary Tract Symptoms Including Benign Prostatic Obstruction. *Eur. Urol.* 2013; **64**: 118–40.
3 Homma Y, Gotoh M, Yokoyama O *et al*. Outline of JUA clinical guidelines for benign prostatic hyperplasia. *Int. J. Urol.* 2011; **18**: 741–56.
4 American Urological Association Guideline: Management of Benign Prostatic Hyperplasia (BPH), 2010.
5 Roehrborn CG, Siami P, Barkin J *et al*. The effects of dutasteride, tamsulosin and combination therapy on lower urinary tract symptoms in men with benign prostatic hyperplasia and prostatic enlargement: 2-year results from the CombAT study. *J. Urol.* 2008; **179**: 616–21.
6 Fwu CW, Eggers PW, Kirkali Z, McVary KT, Burrows PK, Kusek JW. Change in sexual function in men with lower urinary tract symptoms/benign prostatic hyperplasia associated with long-term treatment with doxazosin, finasteride and combined therapy. *J. Urol.* 2014; **191**: 1828–34.
7 Egerdie RB, Auerbach S, Roehrborn CG *et al*. Tadalafil 2.5 or 5 mg administered once daily for 12 weeks in men with both erectile dysfunction and signs and symptoms of benign prostatic hyperplasia: results of a randomized, placebo-controlled, double-blind study. *J. Sex. Med.* 2012; **9**: 271–81.
8 Oelke M, Giuliano F, Mirone V, Xu L, Cox D, Viktrup L. 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. *Eur. Urol.* 2012; **61**: 917–25.
9 Porst H, Kim ED, Casabe AR *et al*. Efficacy and safety of tadalafil once daily in the treatment of men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia: results of an international randomized, double-blind, placebo-controlled trial. *Eur. Urol.* 2011; **60**: 1105–13.
10 Roehrborn CG, McVary KT, Elion-Mboussa A, Viktrup L. Tadalafil administered once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a dose finding study. *J. Urol.* 2008; **180**: 1228–34.
11 Takeda M, Yokoyama O, Lee SW, Murakami M, Morisaki Y, Viktrup L. Tadalafil 5 mg once-daily therapy for men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia: results from a randomized, double-blind, placebo-controlled trial carried out in Japan and Korea. *Int. J. Urol.* 2014; **21**: 670–5.
12 Casabe A, Roehrborn CG, Da Pozzo LF *et al*. Efficacy and safety of the coadministration of tadalafil once daily with finasteride for 6 months in men with lower urinary tract symptoms and prostatic enlargement secondary to benign prostatic hyperplasia. *J. Urol.* 2014; **191**: 727–33.
13 Glina S, Roehrborn CG, Esen A *et al*. Sexual function in men with lower urinary tract symptoms and prostatic enlargement secondary to benign prostatic hyperplasia: results of a 6-month, randomized, double-blind, placebo-controlled study of tadalafil co-administered with finasteride. *J. Sex. Med.* 2015; **12**: 129–38.
14 Barry MJ, Williford WO, Chang Y *et al*. Benign prostatic hyperplasia specific health status measures in clinical research: how much change in the American Urological Association symptom index and the benign prostatic hyperplasia impact index is perceptible to patients? *J. Urol.* 1995; **154**: 1770–4.
15 Lepor H. Phase III multicenter placebo-controlled study of tamsulosin in benign prostatic hyperplasia. Tamsulosin Investigator Group. *Urology* 1998; **51**: 892–900.
16 Narayan P, Tewari A. A second phase III multicenter placebo controlled study of 2 dosages of modified release tamsulosin in patients with symptoms of benign prostatic hyperplasia. United States 93-01 Study Group. *J. Urol.* 1998; **160**: 1701–6.
17 Chapple CR, Montorsi F, Tammela TL, Wirth M, Koldewijn E, Fernandez FE. Silodosin therapy for lower urinary tract symptoms in men with suspected benign prostatic hyperplasia: results of an international, randomized, double-blind, placebo- and active-controlled clinical trial performed in Europe. *Eur. Urol.* 2011; **59**: 342–52.
18 Nickel JC, Brock GB, Herschorn S, Dickson R, Henneges C, Viktrup L. Proportion of tadalafil-treated patients with clinically meaningful improvement in lower urinary tract symptoms associated with benign prostatic hyperplasia - integrated data from 1499 study participants. *BJU Int.* 2014; doi: 10.1111/bju.12926.
19 Black L, Grove A, Morrill B. The psychometric validation of a US English satisfaction measure for patients with benign prostatic hyperplasia and lower urinary tract symptoms. *Health Qual. Life Outcomes* 2009; **7**: 55.
20 Hareendran A, Abraham L. Using a treatment satisfaction measure in an early trial to inform the evaluation of a new treatment for benign prostatic hyperplasia. *Value Health* 2005; **8**(Suppl 1): S35–40.
21 Oelke M, Giuliano F, Baygani SK, Melby T, Sontag A. Treatment satisfaction with tadalafil or tamsulosin vs placebo in men with lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH): results from a randomised, placebo-controlled study. *BJU Int.* 2014; **114**: 568–75.
22 Lepor H, Williford WO, Barry MJ *et al*. The efficacy of terazosin, finasteride, or both in benign prostatic hyperplasia. Veterans Affairs Cooperative Studies Benign Prostatic Hyperplasia Study Group. *N. Engl. J. Med.* 1996; **335**: 533–9.
23 Debruyne FM, Jardin A, Colloi D *et al*. Sustained-release alfuzosin, finasteride and the combination of both in the treatment of benign prostatic hyperplasia. European ALFIN Study Group. *Eur. Urol.* 1998; **34**: 169–75.
24 Kirby RS, Roehrborn C, Boyle P *et al*. Efficacy and tolerability of doxazosin and finasteride, alone or in combination, in treatment of symptomatic benign prostatic hyperplasia: the Prospective European Doxazosin and Combination Therapy (PREDICT) trial. *Urology* 2003; **61**: 119–26.
25 McConnell JD, Roehrborn CG, Bautista OM *et al*. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. *N. Engl. J. Med.* 2003; **349**: 2387–98.
26 Lepor H, Williford WO, Barry MJ, Haakenson C, Jones K. The impact of medical therapy on bother due to symptoms, quality of life and global outcome, and factors predicting response. Veterans Affairs Cooperative Studies Benign Prostatic Hyperplasia Study Group. *J. Urol.* 1998; **160**: 1358–67.
27 Kaplan SA, Lee JY, Meehan AG, Kusek JW. Long-term treatment with finasteride improves clinical progression of benign prostatic hyperplasia in men with an enlarged versus a smaller prostate: data from the MTOPS trial. *J. Urol.* 2011; **185**: 1369–73.
28 Park HJ, Park NC. Combination therapy with dutasteride and tadalafil in men with moderate-to-severe benign prostatic hyperplasia. *Eur. Urol.* 2013; **12** (Suppl): e1092.
29 Roehrborn CG, Siami P, Barkin J *et al*. The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign prostatic hyperplasia: 4-year results from the CombAT study. *Eur. Urol.* 2010; **57**: 123–31.