

A prospective randomised placebo-controlled study of the impact of dutasteride/tamsulosin combination therapy on sexual function domains in sexually active men with lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH)

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Objective

To prospectively assess the impact of the fixed-dose combination (FDC) of the 5 α -reductase inhibitor (5ARI), dutasteride 0.5 mg and the α_1 -adrenoceptor antagonist, tamsulosin 0.4 mg (DUT-TAM FDC) therapy on sexual function domain scores in sexually active men with lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH), using the Men's Sexual Health Questionnaire (MSHQ).

Patients and Methods

This European and Australian double-blind, placebo-controlled, parallel-group study was conducted at 51 centres. Inclusion criteria: age ≥ 50 years, International Prostate Symptom Score ≥ 12 , prostate volume ≥ 30 cc, prostate-specific antigen 1.5–10 ng/mL. Patients were randomised 1:1 to DUT-TAM FDC therapy or placebo for 12 months. The change from baseline to Month 12 on the total MSHQ (primary endpoint) and MSHQ erection, ejaculation and satisfaction domains (secondary outcome) was assessed, using a mixed model repeated measures analysis. Safety was evaluated.

Results

The intention-to-treat population included 489 patients (243 DUT-TAM FDC therapy; 246 placebo). A significant decrease (worsening) was observed with DUT-TAM FDC therapy versus placebo on the total MSHQ score (-8.7 vs -0.7 ; standard error [SE]: 0.81, 0.78; $P < 0.001$), and the ejaculation (-7.5 vs -0.6 ; SE: 0.56, 0.55; $P < 0.001$) and satisfaction (-0.6 vs $+0.3$; SE: 0.3, 0.29, $P = 0.047$) domains, but not the erection domain (-1.0 vs -0.5 ; SE: 0.19, 0.19, $P = 0.091$).

Conclusion

This is the first domain-specific quantitative evaluation of DUT-TAM FDC therapy on sexual function in men with LUTS secondary to BPH. The observed changes in the MSHQ with DUT-TAM FDC therapy were mainly driven by changes in the ejaculation domain. These findings will help give context to erectile and ejaculatory dysfunction AEs reported spontaneously in earlier 5ARI studies.

Keywords

erectile dysfunction, ejaculatory dysfunction, DUT-TAM FDC therapy

Introduction

Benign prostatic hyperplasia (BPH) is associated with lower urinary tract symptoms (LUTS) and is an independent risk factor for erectile dysfunction (ED) [1] and ejaculatory disorders [2]. The fixed-dose combination (FDC) of the 5 α -reductase inhibitor (5ARI), dutasteride 0.5 mg and the α_1 -adrenoceptor antagonist, tamsulosin 0.4 mg (DUT-TAM FDC) is a recommended first-line therapy to treat moderate-to-severe LUTS in men with BPH who are at risk of disease progression [3,4].

Although supported by guideline recommendations [4], patient preference [5,6], and clinical studies findings indicating efficacy [3,7–10], clinicians are reluctant to initiate 5ARI therapy due to the potential for sexual dysfunction [3,9–12]. In nearly all studies conducted in this area to date, the assessment of sexual function has been restricted to the overall incidence of sexually-related adverse events (AEs) reported spontaneously as part of regular clinical trial AE reporting [3,7–10]. There are several disadvantages to this method of reporting sexual AEs. Spontaneous AE reporting is dependent on both the subjective burden of distress and whether the patient chooses to mention it during the study visit (without prompt). In addition, this method of reporting is not quantitative, information about the onset and resolution of these AEs is often very limited, and it is subject to the patients' interpretation and possible misunderstanding of the domains of sexual function (including erection, ejaculation, orgasm/climax, and libido) [13]. Consequently, our understanding of the effects on 5ARIs and other treatments for LUTS secondary to BPH on sexual function and dysfunction is relatively poor.

During the last decade, validated quantitative scoring instruments for the precise measurement of specific domains of male sexual function have been developed [14]. Most of the existing self-administered questionnaires focus primarily on ED with limited information on orgasm, libido, ejaculation, and overall satisfaction [14]. However, the Male Sexual Health Questionnaire (MSHQ), developed for use in a BPH registry, has been validated to assess the specific aspects of male sexual dysfunction [15]. This 25-item questionnaire comprises three core domains: erection, ejaculation, and satisfaction. There are also additional items related to sexual activity, desire, and bother associated with sexual dysfunction [14].

The objective of the present study was to prospectively assess the changes in sexual function domains from baseline to 12 months, using the MSHQ, in sexually active men with LUTS secondary to BPH and risk factors for disease progression who were treated with DUT-TAM FDC therapy compared with placebo.

Patients and Methods

Study Design

This was a European and Australian double-blind, placebo-controlled, parallel-group study conducted at 51 centres (GSK116115/NCT0177269; initiation date: 18 February, 2013; completion date: 5 April, 2016) comparing DUT-TAM FDC therapy (dutasteride 0.5 mg and tamsulosin 0.4 mg; one capsule daily) with placebo. Patients were randomised (1:1) to DUT-TAM FDC therapy or placebo for 12 months following a 4-week placebo run-in period. Lifestyle advice, relevant to maintaining sexual function and improving LUTS, was provided at baseline to patients in both treatment groups.

This study was approved by the appropriate regulatory and ethics committees, and performed in accordance with the Declaration of Helsinki of 2008 and Good Clinical Practice guidelines. Written informed consent was obtained from each patient before study participation. Further details on ethics and good clinical practice can be found in the Supplementary Information provided online.

Patients

Patients were sexually active men (i.e. engaged in sexual activity with a partner during the past 4 weeks and plans to be active during the next 4 weeks) aged ≥ 50 years, with a confirmed clinical diagnosis of BPH, an IPSS of ≥ 12 (at screening), a prostate volume of ≥ 30 cc (assessed using transrectal ultrasonography) and a total serum PSA level of ≥ 1.5 ng/mL (at screening). Prior use of BPH therapy was permitted, with the exception of 5ARIs.

Patients were excluded from this study if they had a total serum PSA level of >10.0 ng/mL (at screening), a history or evidence of prostate cancer, and/or used prohibited medications.

Endpoints

Primary Endpoint

The primary endpoint was the change in sexual function from baseline to Month 12, measured by change in total MSHQ score (16 questions; range 7–80; higher scores indicate better sexual function) [15].

Secondary Endpoint

The change from baseline in total MSHQ score at 1, 3, 6 and 9 months was assessed as a secondary endpoint. Additional secondary endpoints included: the percentage of patients reaching defined thresholds of change from baseline in the total MSHQ score at 12 months (+1, +5, +10, +15, +20, +25, –1, –5, –10, –15, –20, –25 points); the change from

baseline on the MSHQ erection (questions 1–3; range 0–15), ejaculation (questions 5–11; range 1–35) and satisfaction (questions 13–18; range 6–30) domains [15] at 1, 3, 6, 9 and 12 months; the change from baseline in the IPSS, BPH Impact Index (BII) and Patient Perception of Study Medication questionnaire (PPSM) at 0.5, 1, 3, 6, 9, and 12 months.

Safety evaluations included: the incidence of AEs, serious AEs (SAEs), drug-related AEs, serious drug-related AEs, and AEs leading to discontinuation of the study medication or study withdrawal. AEs of special interest were also assessed (including sexual and breast AEs, prostate cancer and cardiovascular AEs). Any abnormal laboratory test results or other safety assessments were recorded as AEs or SAEs.

A 6-month follow-up telephone call was conducted for men with unresolved sexual AEs at the end of the study (after discontinuation of treatment).

Statistical Analysis

Sample size was based on the change in the total MSHQ score. Assuming a 6-unit treatment difference with a standard deviation (SD) of 18 units, 190 patients per treatment group were required to provide a 90% power at a 0.05 significance level. Assuming a 20% withdrawal rate, 238 patients were randomised per treatment group.

The change in MSHQ score from baseline was analysed using a mixed model repeated measures (MMRM) analysis. The primary treatment comparison was the change from baseline in total MSHQ score with DUT-TAM FDC therapy vs placebo at Month 12 (primary endpoint) for the intention-to-treat (ITT) population. A two-sided 95% CI was calculated for the treatment difference in the change from baseline to Month 12.

The MMRM analysis method was also used to compare the change from baseline in the total MSHQ (Months 1, 3, 6 and 9) and domains, and scores on the IPSS, BII and PPSM with DUT-TAM FDC therapy vs placebo.

For the secondary endpoints that were assessed at multiple time points (MSHQ, IPSS, BII, and PPSM scores), a step-down procedure for interpreting the *P* values was adopted; therefore, the final time point was analysed first. Provided significance ($P \leq 0.05$) was seen at this time point, then the preceding time point was interpreted for formal statistical significance and continued step-wise through all time points. If no significance was seen, then the formal interpretation of significance was discontinued. However, testing for nominal significance continued for preceding time points.

The number and percentage of patients reaching each of the defined thresholds of change from baseline in total MSHQ

score at Month 12 were computed using an Observed Cases approach.

The proportion of patients with AEs was compared between treatment groups using Fisher's exact test.

Results

Study Population and Patient Disposition

The ITT population included 489 patients (243 in the DUT-TAM FDC therapy group and 246 in the placebo group; Fig. 1). Demographic and baseline characteristics were similar across both treatment groups and indicative of a population at increased risk of disease progression (Table 1).

Efficacy Results

Primary Efficacy Results

DUT-TAM FDC therapy resulted in a statistically significant ($P < 0.001$) reduction (worsening) in total MSHQ score at Month 12 compared with placebo, with an adjusted mean change from baseline of -8.7 (standard error [SE] 0.81) in the DUT-TAM FDC therapy group vs -0.7 (0.78) in the placebo group (Table 2; Fig. 2a). A greater change in mean MSHQ total score was seen from baseline to Month 12 with DUT-TAM FDC therapy (baseline: 60.6, Month 12: 53.1) compared with placebo (baseline: 61.8, Month 12: 61.6) (Fig. 3a).

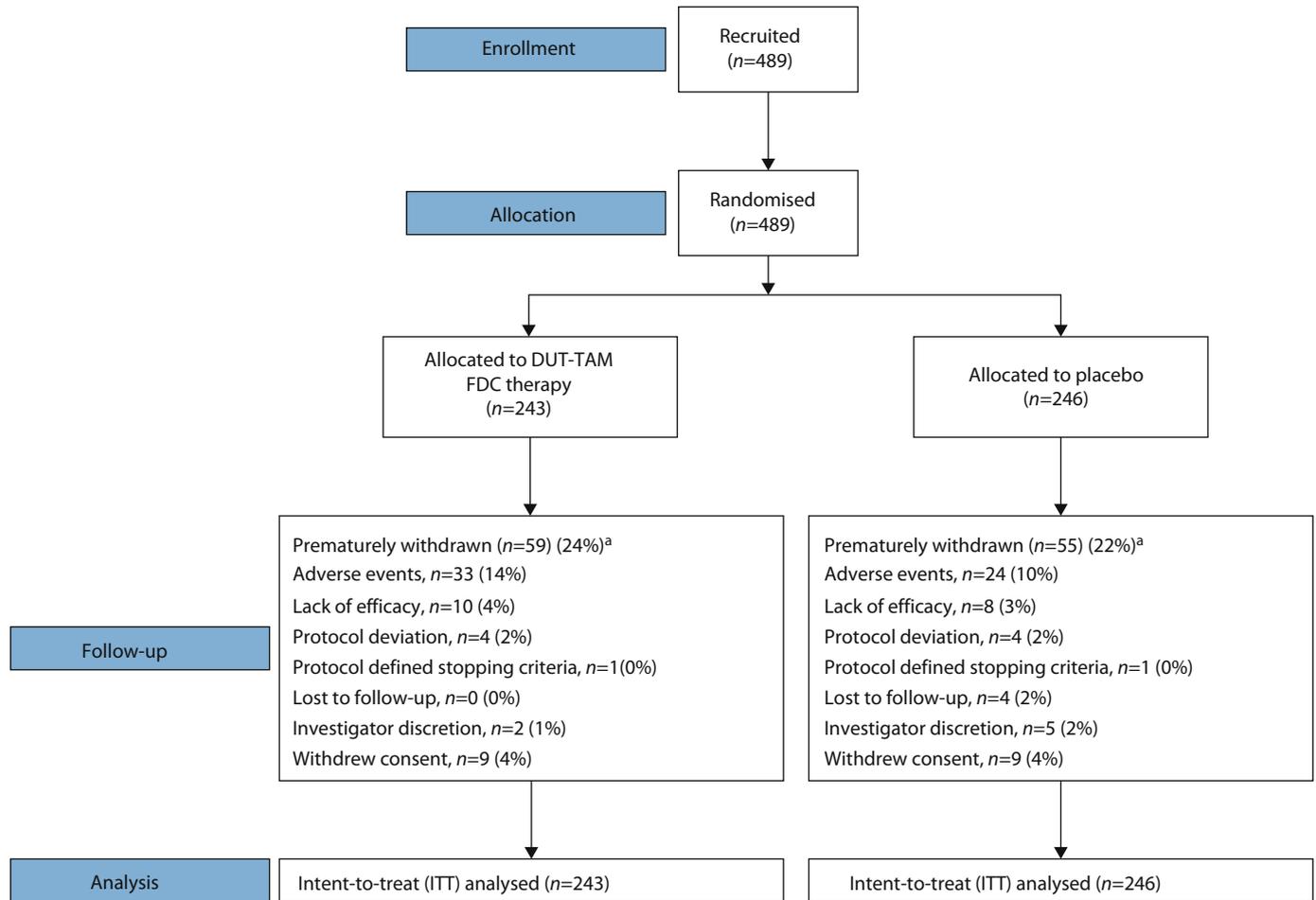
Secondary Efficacy Results

At Months 1, 3, 6 and 9, DUT-TAM FDC therapy resulted in a statistically significant ($P < 0.001$) reduction (worsening) in the total MSHQ score compared with placebo (Table 2; Fig. 2a).

Generally, the proportion of patients with an increase in the total MSHQ score at Month 12 from baseline was lower in the DUT-TAM FDC therapy group than the placebo group. Furthermore, the proportion of patients with a reduction (worsening) in the total MSHQ from baseline to Month 12 was higher in patients receiving DUT-TAM FDC therapy compared with placebo (≤ 1 point: 72% vs 52%; ≤ 5 points, 60% vs 30%; 10 points, 40% vs 15%; 15 points, 27% vs 6%; 20 points, 13% vs 2%; and 25 points, 9% vs 2%; Fig. S1).

The mean scores on the MSHQ erection and ejaculation domains decreased from baseline (worsened) at all post-treatment visits in both groups (Fig. 3b,c). The mean scores for the MSHQ satisfaction domain decreased from baseline (worsened) in the DUT-TAM FDC therapy group, but not in the placebo group, at all post-treatment visits (Fig. 3d). The mean (SE) change in score from baseline at Month 12 was -1.0 (0.19) with DUT-TAM FDC therapy compared with

Fig. 1 Patient disposition diagram. ^aPercentages of patients who prematurely withdrew from the study were calculated with respect to the ITT population (DUT-TAM FDC: $n = 243$; placebo $n = 246$).



–0.5 (0.19) with placebo on the erection domain, –7.5 (0.56) and –0.6 (0.55), respectively, on the ejaculation domain, and –0.6 (0.3) and +0.3 (0.29), respectively, on the satisfaction domain (Fig. 2b–d).

For the erection domain, there were no significant between-group differences in the mean change in MSHQ scores from baseline at Months 1, 3, 6, 9 and 12 (Fig. 2b), compared with placebo. DUT-TAM FDC therapy resulted in statistically significant greater reductions in MSHQ scores for the ejaculation domain at all post-baseline visits ($P < 0.001$; Fig. 2c) compared with placebo. For the satisfaction domain, significant differences in MSHQ scores were also seen at all post-baseline visits ($P = 0.012$ at Month 1, $P = 0.017$ at Month 3, $P < 0.001$ at Month 6, $P = 0.009$ at Month 9, and $P = 0.047$ at Month 12; Fig. 2d), compared with placebo.

Patients in the DUT-TAM FDC therapy group showed statistically significant greater reductions (improvements) in IPSS compared with placebo, at 3 ($P = 0.006$), 6 ($P < 0.001$),

9 ($P = 0.013$) and 12 months ($P < 0.001$; Table 3; Fig. S2). Statistically significant greater reductions in BII score, were seen in the DUT-TAM FDC therapy group compared with placebo at Month 12 ($P = 0.023$; Table 3; Fig. S3), but not at any other time points. Patients in the DUT-TAM FDC therapy group had statistically significant greater reductions in PPSM score, compared with placebo, at 0.5 ($P < 0.001$), 1 ($P < 0.001$), 3 ($P < 0.001$), 6 ($P < 0.001$), 9 ($P = 0.042$) and 12 months ($P < 0.001$; Table 3; Fig. S4).

Safety

The proportion of patients with any AEs, SAEs, and drug-related AEs was significantly higher in the DUT-TAM FDC therapy group than in the placebo group (Table 4). The most common drug-related AEs were those in the reproductive system and breast disorder categories. The proportion of patients with drug-related AEs was highest during the first 6 months of treatment in both treatment groups. No fatal SAEs were reported in this study.

Table 1 Summary of demographics and baseline characteristics (ITT population).

Variable	Placebo (N = 246)	DUT-TAM FDC therapy (N = 243)	Total (N = 489)
Age, years			
<i>n</i>	246	243	489
Mean (SD)	65.4 (6.49)	65.7 (6.59)	65.5 (6.53)
Median (range)	65.0 (50–87)	66.0 (50–84)	65.0 (50–87)
Time from clinical BPH diagnosis to treatment start, years			
<i>n</i>	243	239	482
Mean (SD)	3.4 (4.13)	3.8 (4.57)	3.6 (4.35)
Median (range)	2.2 (0–24.9)	2.3 (0–23.9)	2.3 (0–24.9)
Time from first LUTS to treatment start, years			
<i>n</i>	239	238	477
Mean (SD)	5.1 (4.57)	5.5 (5.46)	5.3 (5.03)
Median (range)	3.8 (0.1–24.2)	3.9 (0.1–34.0)	3.8 (0.1–34.0)
Prostate volume, mL			
<i>n</i>	246	243	489
Mean (SD)	59.0 (23.47)	54.9 (21.38)	57.0 (22.52)
Median (range)	52.1 (30–150)	50.4 (30–152)	51.2 (30–152)
Baseline total MSHQ score			
<i>n</i>	218	206	424
Mean (SD)	61.8 (11.56)	60.6 (12.76)	61.2 (12.16)
Median (range)	64.0 (14–78)	63.0 (14–78)	63.5 (14–78)
Baseline total erection score			
<i>n</i>	232	228	460
Mean (SD)	10.4 (3.30)	10.0 (3.22)	10.2 (3.26)
Median (range)	11 (2–15)	10 (2–15)	11 (2–15)
Baseline total ejaculation score			
<i>n</i>	230	222	452
Mean (SD)	27.7 (6.10)	26.8 (7.31)	27.3 (6.73)
Median (range)	30 (1–34)	30 (1–35)	30 (1–35)
Baseline total satisfaction score			
<i>n</i>	223	209	432
Mean (SD)	23.4 (4.94)	23.4 (5.16)	23.4 (5.05)
Median (range)	24 (7–30)	24 (9–30)	24 (7–30)
Baseline total IPSS			
<i>n</i>	243	242	485
Mean (SD)	14.8 (5.31)	14.7 (5.14)	14.7 (5.22)
Median (range)	15.0 (3–33)	15.0 (1–30)	15 (1–33)
Baseline total BII score			
<i>n</i>	237	233	470
Mean (SD)	3.8 (2.39)	4.4 (2.87)	4.1 (2.65)
Median (min–max)	4.0 (0–12)	4.0 (0–12)	4 (0–12)
Baseline total PPSM score			
<i>n</i>	237	233	470
Mean (SD)	26.4 (5.40)	26.3 (4.93)	26.4 (5.17)
Median (range)	28.0 (11–42)	28.0 (11–42)	28 (11–42)
Baseline total PSA level, ng/mL			
<i>n</i>	246	243	489
Mean (SD)	4.0 (2.16)	3.7 (1.98)	3.9 (2.08)
Median (range)	3.6 (0.7–15.5)	3.2 (1.5–10.0)	3.4 (0.7–15.5)

A similar proportion of patients in both the DUT-TAM FDC therapy and placebo groups had serious drug-related AEs (Table 4). There was no significant difference between groups in the proportion of patients with AEs leading to study medication discontinuation or study withdrawal (Table 4).

The proportion of patients with any sexual and breast AEs of special interest was higher in the DUT-TAM FDC therapy group than in the placebo group (33% vs 14%, respectively; Table 5). At the end of treatment (Month 12), a total of 85 and 31 sexual and breast AEs of special interest were not resolved in the DUT-TAM FDC group and placebo group, respectively (Table 6). Of these AEs, 37 (44%) were resolved

at the end of the study (Month 18) in the DUT-TAM FDC group compared with seven (23%) in the placebo group. Sexual and breast AEs of special interest that were not resolved after 18 months (after the follow-up period) were primarily ejaculation disorders (five cases in the placebo group and 23 in the DUT-TAM FDC group) and altered libido (six cases in the placebo group and 12 in the DUT-TAM FDC group; Table 6). The number of unresolved erection disorders at 18 months was similar between the placebo (12 cases) and the DUT-TAM FDC (13 cases) groups (Table 6).

One patient (<1%) in the DUT-TAM FDC group and two patients in the placebo group (<1%) experienced AEs of

Table 2 Summary of MMRM analysis for change from baseline in total MSHQ scores and scores for the MSHQ domains (erection, ejaculation and satisfaction) (ITT population).

Visit	Treatment difference (DUT-TAM FDC therapy vs placebo)											
	Erection domain score		Ejaculation domain score		Satisfaction domain score							
	Estimate*	95% CI	P	Estimate*	95% CI	P						
Month 1	-4.11	-6.01 to -2.21	<0.001	-0.20	-0.62 to 0.23	0.37	-2.89	-4.07 to -1.70	<0.001	-0.94	-1.67 to -0.21	0.012
Month 3	-6.43	-8.45 to -4.41	<0.001	-0.24	-0.71 to 0.24	0.33	-5.24	-6.59 to -3.90	<0.001	-0.93	-1.69 to -0.17	0.017
Month 6	-9.04	-11.31 to -6.77	<0.001	-0.37	-0.88 to 0.15	0.16	-6.82	-8.30 to -5.34	<0.001	-1.73	-2.57 to -0.88	<0.001
Month 9	-8.82	-10.96 to -6.67	<0.001	-0.68	-1.19 to -0.17	0.009 [†]	-7.05	-8.51 to -5.59	<0.001	-1.15	-2.01 to -0.30	0.009
Month 12	-8.00	-10.22 to -5.79	<0.001	-0.46	-0.99 to 0.07	0.091	-6.92	-8.47 to -5.38	<0.001	-0.83	-1.65 to -0.01	0.047

*A positive treatment difference indicates a benefit of DUT-TAM FDC therapy relative to placebo. [†]This value could not be interpreted as statistically significant due to the step-down multiplicity criteria.

prostate cancer (neither of which were high-grade cancers or related to the study medication). Cardiovascular AEs were experienced by five patients in the DUT-TAM FDC therapy group (all considered SAEs; two events led to study withdrawal) and four patients in the placebo group (SAEs, $n = 3$; considered drug-related, $n = 1$; led to study withdrawal, $n = 1$). The cardiovascular AEs were resolved in four out of the five patients in the DUT-TAM FDC group and in all patients in the placebo group.

Discussion

The present study is the first to prospectively assess the domains of sexual function in men with LUTS secondary to BPH, treated with DUT-TAM FDC therapy, using validated numerical scores. The results from the present study offer both surprising insights and reassuring corrections of previously held opinions based on sexual AEs reported spontaneously in earlier 5ARI studies.

Sexual or breast AEs reported during the study were not resolved in about two-thirds of patients in the DUT-TAM FDC treatment group at the end of the study treatment period. The extended follow-up (6 months) of patients with unresolved spontaneously reported sexual AEs at the end of the 12-month treatment period also provided novel insights. At 6 months after cessation of either placebo or DUT-TAM FDC therapy, seven of 31 (23%; placebo) vs 37/85 (44%; DUT-TAM FDC) of sexual and breast AEs present at the end of the study had resolved, which may suggest a strong placebo discontinuation effect. Alternatively, these findings may provide reassurance that drug-induced AEs do resolve after discontinuation of treatment in a large number of patients. Focusing on individual AEs, only three of 15 cases of ED in the placebo group had resolved after 18 months, whilst in the DUT-TAM FDC therapy group, five of 18 cases had resolved. Therefore, the number of unresolved cases of ED after 18 months was remarkably similar between the two study groups. This is a crucial finding suggesting that persistent ED after 5ARI treatment and discontinuation of such treatment is not observed in the present study. In contrast, 6 months after cessation of treatment, five and 23 cases of ejaculation disorders remained unresolved in the placebo and DUT-TAM FDC therapy groups, respectively.

In the present study, the change in the total MSHQ score appeared to be driven largely by changes in the scores for the ejaculation domain, which reduced by 8 points on average from baseline to Month 12 in the DUT-TAM FDC therapy group ($P < 0.001$). At the end of the study there were 44 persistent ejaculatory AEs reported by 41 patients in the DUT-TAM FDC therapy group. These AEs included decreased semen volume, retrograde ejaculation, and ejaculation failure. Although we may not be able to fully explain the reasons for these persistent AEs and differentiate between the causes, some considerations

Fig. 2 Adjusted mean (\pm SE) change in: (a) total MSHQ score, (b) erection domain score, (c) ejaculation domain score, and (d) satisfaction domain score, from baseline through to Month 12 (ITT population). *This *P* value for Month 9 could not be interpreted as statistically significant due to the step-down multiplicity criteria.

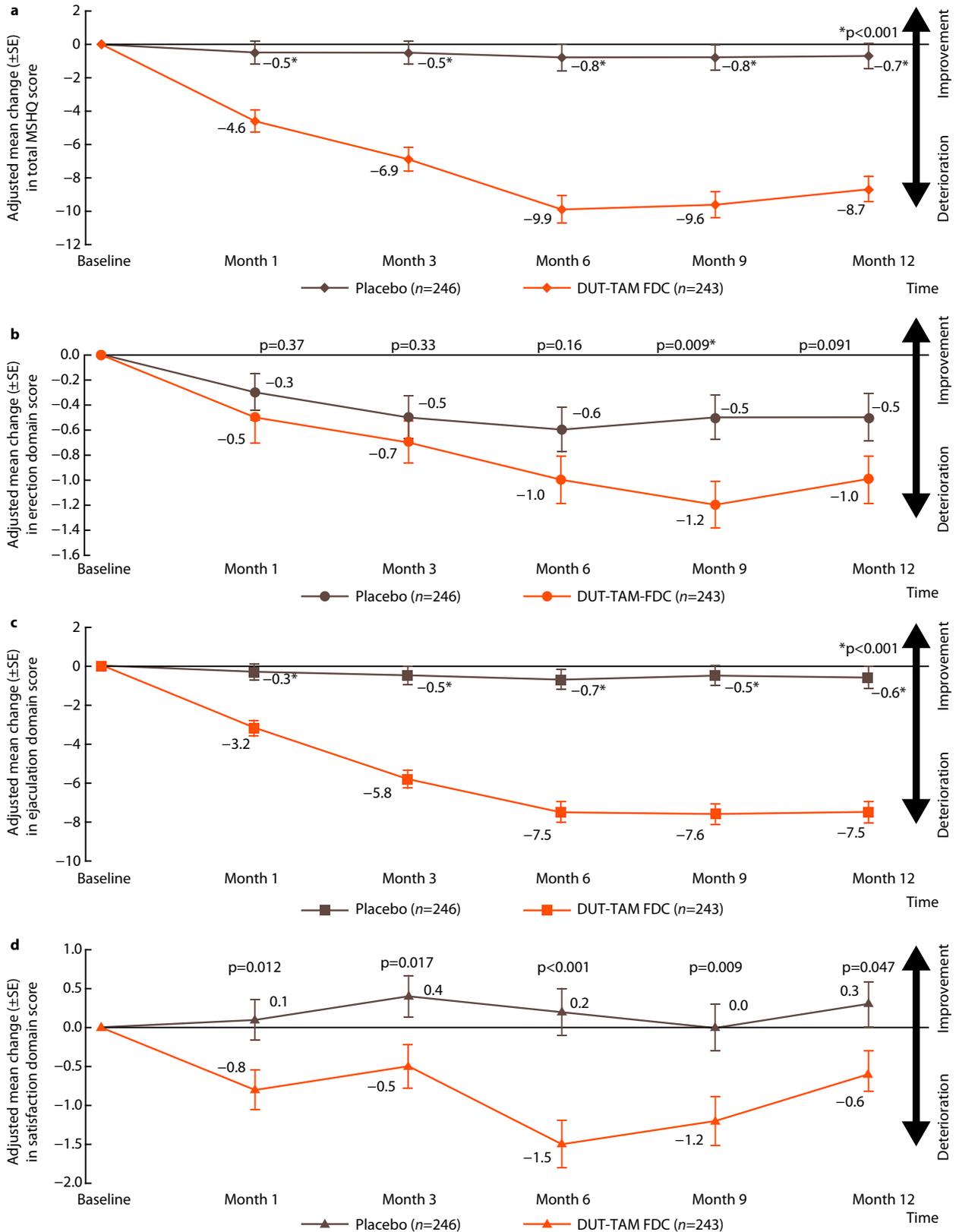


Fig. 3 Mean (\pm SE): (a) total MSHQ score (range 7–80), (b) erection domain score (range 0–15), (c) ejaculation domain score (range 1–35), and (d) satisfaction domain score (range 6–30), from baseline through to Month 12 at each post-baseline visit (observed cases).

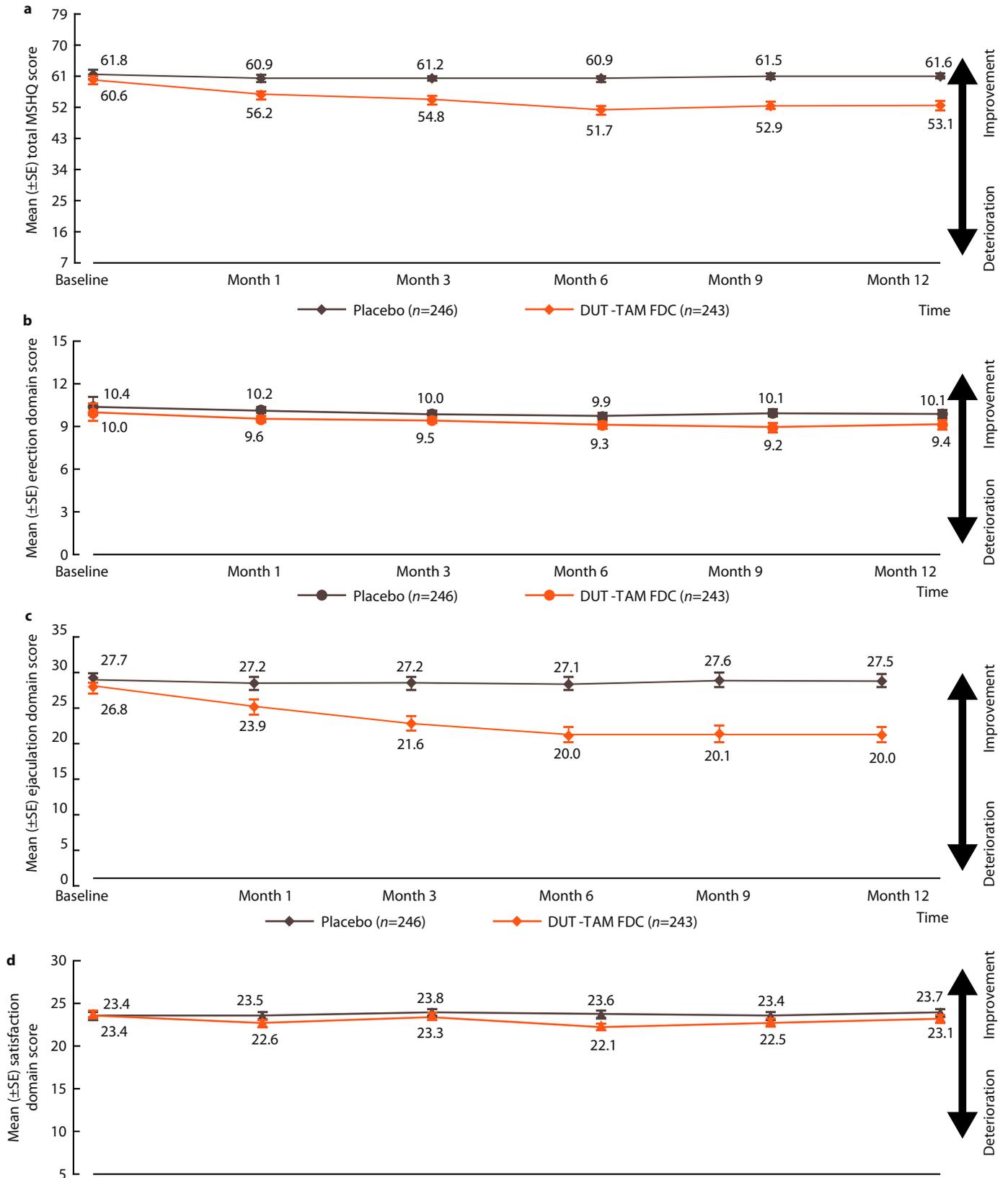


Table 3 Summary of MMRM analysis for change from baseline in total IPSS, BII and PPSM scores at Month 12 (ITT population).

Visit	Treatment	ITT, n	Adjusted mean (SE)	Treatment difference (DUT-TAM FDC therapy vs placebo)		
				Estimate*	95% CI	P
Month 12 IPSS	Placebo	246	-3.2 (0.41)	-1.97	-3.12 to -0.83	<0.001
	DUT-TAM FDC	243	-5.2 (0.41)			
Month 12 BII score	Placebo	246	-0.6 (0.18)	-0.58	-1.08 to -0.08	0.023
	DUT-TAM FDC	243	-1.2 (0.18)			
Month 12 PPSM score	Placebo	246	-1.0 (0.49)	-3.51	-4.87 to -2.14	<0.001
	DUT-TAM FDC	243	-4.6 (0.49)			

*A negative treatment difference indicates a benefit of DUT-TAM FDC therapy relative to placebo.

Table 4 Summary of AEs (ITT population).

AE type, n (%)	Placebo (N = 246)	DUT-TAM FDC therapy (N = 243)
Any AE	116 (47)	139 (57)*
Any SAE	9 (4)	27 (11) [†]
Any drug-related AE [§]	42 (17)	86 (35) [‡]
ED	15 (6)	21 (9)
Retrograde ejaculation	3 (1)	20 (8)
Ejaculation disorder	2 (<1)	15 (6)
Ejaculation failure	2 (<1)	6 (2)
Gynaecomastia	3 (1)	2 (<1)
Decreased libido	12 (5)	19 (8)
Decreased semen volume	2 (<1)	11 (5)
Dizziness	0 (0)	4 (2)
Any serious drug-related AE	2 (<1)	2 (<1)
Any AE leading to study medication discontinuation	20 (8)	33 (14)
Any AE leading to study withdrawal	23 (9)	33 (14)

*P = 0.03; [†]P = 0.002; [‡]P < 0.001. [§]≥1% in any group.

Table 5 Number of patients with unresolved sexual or breast AEs of special interest on treatment and at 12 months (end of treatment).

AE type	Placebo (N = 246)	DUT-TAM FDC therapy (N = 243)
Patients with any sexual or breast AE of special interest (on treatment), n (%)	34 (14)	79 (33)
Patients with any sexual or breast AE of special interest at 12 months (end of treatment), n (%)	23 (9)	58 (24)

Table 6 Number and type of unresolved AEs and sexual or breast AEs of special interest at 12 months (end of treatment) and 18 months (after follow-up).

AEs not resolved	Placebo (N = 246) Number of events		DUT-TAM FDC therapy (N = 243) Number of events	
	12 months	18 months	12 months	18 months
Total number of AEs	31	24	85	48
ED	15	12	18	13
Ejaculation disorders	7	5	44	23
Altered (decreased) libido	7	6	21	12
Breast disorders	2	1	2	0

can be offered. It has been previously observed that tamsulosin induces anejaculation in a substantial number of patients [16,17] and this is likely to contribute to both spontaneously

reported AEs and changes in the MSHQ score. Owing to drug clearance, tamsulosin, however, cannot contribute to the residual ejaculatory AEs reported at 6 months after the end of

treatment [18]. Over time, dutasteride therapy has been associated with shrinkage of the prostate gland by 25–30% [19], by inducing atrophy in the glandular epithelial component (i.e. the location of the production of prostatic secretions accompanying the sperm in the ejaculate), hence the decrease in the volume of fluid in the ejaculate, or the semen volume. Amory *et al.* [19] studied the change in semen volume in healthy volunteers undergoing dutasteride therapy for 52 weeks and found an overall decrease of ~30%. However, the changes in semen volume ranged from a 50% increase to a 100% decrease, i.e. no semen fluid at all. At least a 50% decrease in semen volume was seen in ~20% of patients undergoing dutasteride therapy (JK Amory, C Wang, RS Swerdloff, BD Anawalt, AM Matsumoto, WJ Bremner, SE Walker, LJ Haberer, RV Clark, unpublished). Amory *et al.* [19] also showed that 6 months after drug cessation in dutasteride-treated patients, there was still a measurable decrease in semen volume (at least 50%) in 15% of patients (Amory *et al.*, data not published). Thus, the residual spontaneously reported ejaculatory AEs at 6 months after the end of treatment reported in the present study may be due to the residual reduction in semen volume induced by dutasteride. Further evaluation of the reduction in semen volume and its relation to ejaculatory disorders, reported in patients receiving 5ARIs as monotherapy or in combination with α -blockers, is needed to understand the clinically relevant impact of these AEs.

Focusing on the changes seen using the validated numerical scores, a substantial decrease in the total MSHQ score of 8.7 points occurred from baseline to Month 12 in the DUT-TAM FDC therapy group (compared with -0.7 in the placebo group), indicating worsening of sexual function. The change in the total MSHQ score appeared to be driven largely by changes in the scores for the ejaculation domain, which decreased by 7.5 points from baseline to Month 12 in the DUT-TAM FDC therapy group ($P < 0.001$). The reduction (worsening) in both total MSHQ and ejaculation domain scores, caused by DUT-TAM FDC therapy, seemed to stabilise at Month 6, remaining substantially unchanged beyond this time point.

In contrast, the absolute changes from baseline and the differences at 12 months between placebo and the DUT-TAM FDC therapy group, for the erection and overall satisfaction domains, were numerically very small and unlikely to be clinically relevant. Previous studies have shown the sensitivity of total MSHQ scale scores to both diagnostic status and treatment conditions [2,20,21]. The ejaculation domain subscale of the MSHQ has shown treatment sensitivity to pharmacological and other treatments of BPH [22,23], although a minimum clinically meaningful change in ejaculation has yet to be determined.

In a small study evaluating the change in sexual function in 22 men treated with dutasteride therapy or placebo for 12 months, there was no significant difference between

treatment groups in the International Index of Erectile Dysfunction (IIEF) and MSHQ scores [24]. However, there was a numerical reduction in the total MSHQ scores in patients treated with DUT-TAM FDC therapy. As above, further research into the correlation of IIEF and MSHQ domain score trajectories over time and their relation to the reporting of AEs, will aid our understanding of the clinically relevant impact of 5ARIs and α -blockers in combination with 5ARIs on sexual dysfunction.

A limitation of the present study is that the clinical relevance of the observed changes in total MSHQ score and the individual domain scores is uncertain. However, the magnitude of change in both the MSHQ total and ejaculation dysfunction domains compared to placebo was considerable and was clinically correlated with spontaneous AEs reported. Furthermore, whilst the present study assessed sexual satisfaction, quality of life, and satisfaction with treatment using the MSHQ, BII and PPSM questionnaires, there was no in-depth assessment of quality of life (e.g. using a dedicated quality-of-life questionnaire, such as the WHO Quality of Life or 36-Item Short Form Survey). The study duration was 12 months, and as such, the long-term effects of dutasteride and tamsulosin combined treatment on sexual function could not be evaluated. A further limitation is the lack of tamsulosin-only and dutasteride-only arms, which would be valuable in establishing the impact of monotherapies on sexual function (as assessed by the MSHQ, a validated questionnaire).

Despite evidence showing higher levels of ED in patients treated with combined therapy [3,9,10], recent research has found that the risk of ED was not increased with the use of 5ARIs, alone or in combination with α -blockers, compared with α -blockers alone, in patients with symptomatic BPH [25]. However, current knowledge of 5ARIs with regard to safety is largely based on spontaneous reporting and may be inaccurate [3,7–10]. Factors, such as age [26], co-medications [27], patients' and physician's perceptions [28], comorbidities [29,30], and how information is collected in clinical studies (at baseline, during the trial and follow-up) [31,32] may affect the onset and reporting of sexual dysfunction. Additionally, given that ED is a progressive disorder, the development of this condition in some men may only be seen in longitudinal studies and may not be attributed to medication but rather the natural decline in erectile function.

A recent meta-analysis reported that ejaculatory dysfunction was significantly more common with 5ARIs compared with placebo (odds ratio [OR]: 2.73; $P < 0.001$) [33]. It was also reported that ejaculatory dysfunction was significantly more common with the use of combined therapy compared with 5ARIs alone (OR 2.76; $P = 0.02$) or α -blockers alone (OR 3.75; $P < 0.001$) [33]. Another study examined the effects of doxazosin, finasteride and combined therapy among men

with LUTS associated with BPH on sexual function assessed by the Brief Male Sexual Function Inventory (an 11-item validated, self-administered questionnaire assessing sexual drive, erectile function, ejaculatory function, sexual problems, and overall sexual satisfaction) over 4 years [34]. The results from that study revealed that men treated with combined therapy experienced statistically significant worsening of erectile and ejaculatory function compared with placebo; however, there was no comparable decrease in overall sexual satisfaction [34].

Consistent with these findings, results from the present study provide evidence for the association of ejaculatory dysfunction with combined therapy in a population of patients with symptomatic BPH. In the present study, the MSHQ has been used for the first time to prospectively assess ejaculatory disorders in patients treated for LUTS associated with BPH. These findings provide more detail than spontaneously reported AEs from earlier dutasteride studies. AEs documented in the present study were similar in incidence to those reported in previous studies of combined therapies for BPH [3,9,10], where ED and retrograde ejaculation are the most commonly reported. In the present study, retrograde ejaculation was reported in 9% of patients in the DUT-TAM FDC therapy group vs 1% in the placebo group, although this should be more accurately described as anejaculation as described by Wolters and Hellstrom [35].

Treatment with DUT-TAM FDC therapy was associated with a significant improvement in the patient's BPH-related quality of life at Month 12, as measured using the BII. DUT-TAM FDC therapy also resulted in significantly greater BPH symptom improvement, as measured by the IPSS, at Months 3, 6, 9 and 12, compared with placebo. Patients in the DUT-TAM FDC therapy group also showed statistically significant greater reductions in PPSM scores, compared with placebo, at 0.5, 1, 3, 6, 9 and 12 months. Therefore, combined therapy was beneficial relative to placebo in treating LUTS in sexually active men with BPH. These findings may help to inform clinicians and their patients when considering combined therapy to treat BPH.

The present study is the first prospective study to give a domain-specific assessment of the effects of 5ARI (dutasteride) and α_1 -adrenoceptor antagonist (tamsulosin) combined treatment on sexual function and to provide direct comparison with a placebo population. The changes in total MSHQ score were driven by changes in the scores for the ejaculation domain. From the present study, it is implied that both 5ARIs and α -blockers may contribute to ejaculation disorders. These findings will help provide more context to the sexual function AEs reported spontaneously in earlier 5ARI studies.

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Conflicts of interest

Claus G. Roehrborn was previously employed as a consultant to GSK. Michael J. Manyak and Juan Manuel Palacios-Moreno are employees of GSK. Janet Plastino is an employee of GSK and owns stocks/shares in GSK. Javier Cambronero Santos is a principal investigator for Astellas Pharma, GSK. Timothy H. Wilson is an employee of PARAXEL International (Durham, NC, USA) and owns stocks/shares in GSK. Francois Giuliano is a consultant for Pfizer, Sanofi, Menarini, Recordati, Ipsen and Noveltor. Raymond C. Rosen received research support from Bayer Healthcare, Shionogi and Pfizer. Erik P.M. Roos and Dimitrios Karanastasis have nothing to disclose.

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Abbreviations: (S)AE, (serious) adverse event; 5ARI, 5 α -reductase inhibitor; BII, BPH Impact Index; ED, erectile dysfunction; FDC, fixed-dose combination; IIEF, International Index of Erectile Dysfunction; ITT, intention-to-treat; MMRM, mixed model repeated measures; MSHQ, Male Sexual Health Questionnaire; OR, odds ratio; PPSM, Patient Perception of Study Medication (questionnaire).

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Percentage of patients reaching various thresholds of change in total MSHQ from baseline at 12 months.

Figure S2. Adjusted mean change (\pm SE) in IPSS from baseline (ITT population).

Figure S3. Adjusted mean change (\pm SE) in BII score from baseline (ITT population).

Figure S4. Adjusted mean change (\pm SE) in PPSM score from baseline (ITT population).

Table S1. Ethics and good clinical practice.