Long-term sustained improvement in symptoms of benign prostatic hyperplasia with the dual 5α-reductase inhibitor dutasteride: results of 4-year studies

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OBJECTIVE

To report additional analyses of efficacy over the initial 2 years and during a 2-year open-label extension of the three pivotal phase 3 studies in which dutasteride, a dual inhibitor of type 1 and 2 5α-reductase, was shown to be effective and well tolerated.

PATIENTS AND METHODS

All patients in the placebo and active groups were eligible for entry into the 2-year open-label extension, with all receiving dutasteride 0.5 mg daily. Mean changes from baseline were calculated for the American Urologic Association Symptom Index (AUA-SI) score at each scheduled time in the double-blind and open-label phase. The additional analyses included a breakdown of the AUA-SI score, including stratifying patients by symptom severity, assessment by baseline age and prostate volume, and the evaluation of symptoms responders.

RESULTS

There was a clinically meaningful improvement in AUA-SI in patients on dutasteride in the double-blind phase, but not in those on placebo. At 48 months, patients on dutasteride in both study phases had greater improvements in AUA-SI score and individual question scores than those on dutasteride in the open-label phase only. The proportion of patients with severe symptoms declined in both study groups, although these changes were more profound in those receiving dutasteride for the 4-year duration of the study.

CONCLUSION

In men with symptomatic benign prostatic hyperplasia, long-term (4-year) treatment with the dual isozyme 5α-reductase inhibitor dutasteride resulted in sustained and continued improvements in symptoms and flow rate. For 4 vs 2 years, longer dutasteride therapy resulted in greater symptom improvement.

KEYWORDS

BPH, symptoms, long-term effects, dutasteride

INTRODUCTION

LUTS secondary to BPH are a common reason for consulting primary-care physicians and urologists [1,2], with increasing symptom severity correlating with heightened health-seeking behaviour [3]. It is well documented that LUTS are associated with a lower quality of life for both men [1,4–7] and their partners [8,9]. Also, in the absence of complications such as acute urinary retention (AUR), symptoms and associated bother remain a major cause of referral for surgical intervention in men with BPH [10–12].

The availability of medical therapies for managing BPH has led to an overall decline in the use of TURP [13], with the disease now being managed pharmacologically rather than surgically in many men. The two classes of available medical therapy for BPH, i.e. α-adrenoceptor antagonists (α-blockers) and 5α-reductase inhibitors, differ in their profile of effect on LUTS and the underlying BPH. Treatment with α-blockers is typically associated with an onset of symptom improvement within 1–4 weeks, an improvement in peak urinary flow (Q_{max}), and significant improvements in quality-of-life score and BPH Impact Index [14]. Although evidence suggests that the α-blocker doxazosin increases the time to an episode of AUR or the need for invasive therapy for BPH in the short term, it has not been shown to significantly lower the absolute risk of these events in long-term use [15]. By contrast, 5α-reductase inhibitors reduce prostate volume, improve symptoms, urinary flow, quality of life and bother from 3 to 6 months onwards, and significantly reduce the long-term risks of AUR and need for BPH-related surgery [14–17].

The objective of the present analysis was to examine in detail the effects of dual 5α-reductase inhibition with dutasteride on symptoms over 4 years, using data from 2 years of double-blind, placebo-controlled treatment and a further 2 years of open-label therapy with dutasteride.

PATIENTS AND METHODS

Data were analysed from two studies in the USA and one international study, with concordant protocols, i.e. ARIA3001, ARIA3002 and ARIB3003. These were 2-year, randomized, double-blind, placebo-controlled studies of the efficacy and safety of dutasteride in the treatment of men with symptomatic BPH, followed by 2-year open-label extension studies. The design of the double-blind and open-label phases of these studies, and their principle outcomes, have been reported previously [17,18]. At the start of the double-blind phase, patients had a 1-month, single-blind placebo run-in period, and were then randomized to treatment with dutasteride 0.5 mg or placebo once daily for

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FIG. 1. Subject accountability for double-blind and open-label study phases.

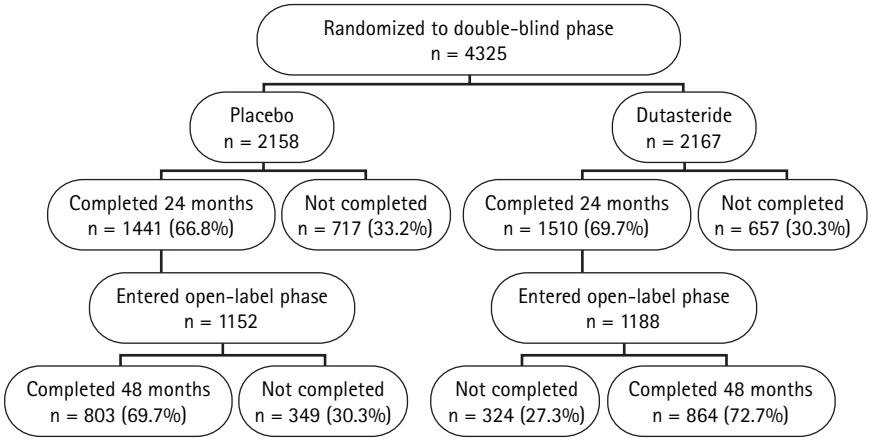


TABLE 1 Comparison of AUA-SI, prostate volume and Q_{max} for patients who entered the open-label phase vs those who did not. Data are derived from the 24-month (double-blind ITT population) and are the mean (SD)

	Placebo		Dutasteride	
	Entered	Did not enter	Entered	Did not enter
N	1152	1006	1188	979
AUA-SI score	14.5 (7.16)	15.5 (7.56)	12.3 (6.68)	12.1 (6.49)
Change from baseline	−2.5 (6.67)	−1.6 (7.30)	−4.4 (6.52)	−4.7 (6.96)
Prostate volume, mL	54.4 (25.31)	53.1 (24.65)	41.3 (20.19)	40.8 (22.24)
Change from baseline, %	1.4 (26.16)	2.8 (24.74)	−26.0 (19.38)	−24.7 (21.03)
Q_{max} , mL/s	11.3 (4.60)	10.9 (5.48)	12.5 (5.57)	12.7 (5.75)
Change, mL/s	0.6 (4.57)	0.9 (5.12)	2.2 (5.15)	2.3 (5.42)

2 years. Patients who completed 2 years of double-blind treatment were eligible to participate in the 2-year open-label phase during which patients initially receiving dutasteride continued on dutasteride (D/D group), and those initially receiving placebo were converted to open-label dutasteride (P/D group). Men eligible for inclusion at the start of the double-blind phase were ≥ 50 years old, with a diagnosis of BPH by history and physical examination, an AUA Symptom Index (SI) score of ≥12, a prostate volume measured by TRUS of ≥30 mL, a PSA level of ≥1.5 and <10 ng/mL, and a Q_{max} of ≤15 mL/s. Patients with previous prostate surgery for BPH, history or evidence of prostate cancer, or who had used an α-blocker within 2 weeks or a 5α-reductase inhibitor at any time, were excluded. The AUA-SI was evaluated at baseline and at 1, 3, 6, 12, 18, 24, 30, 36, 42 and 48 months.

The data from the three trials were pooled for analysis. For effects on AUA-SI, results from the open-label intent-to-treat (ITT) population, who received at least one dose of study medication during the open-label phase, and the 'completer population', those patients who completed 48 months of study medication treatment, are reported (D/D vs P/D). Changes in AUA-SI score were calculated from a baseline established at the start of the double-blind phase. In addition, changes to individual symptom scores, the obstructive symptom score (using the incomplete emptying, intermittency, weak stream, and straining questions from the AUA-SI, with a maximum score of 20) and the irritative score (frequency, urgency, and nocturia questions; maximum score 15) were examined.

Mean (SD) changes from baseline were calculated for the AUA-SI score at each scheduled time in the double-blind and open-label phases. The two treatment groups (P/D and D/D) at the scheduled open-label times in terms of the change from baseline were compared statistically using a general linear model with effects for baseline, treatment, protocol and investigator cluster. A Mantel-Haenszel test, stratified by protocol, was used to compare the treatment groups in terms of the proportion of patients achieving a defined AUA-SI improvement. Within each treatment group, the difference between the 48- and 24-month values was compared using a *t*-test, with significance indicated at $P < 0.05$.

The clinical relevance of improvements in AUA-SI score was judged using the criteria of Barry *et al.* [19], who defined a decrease of 2 points for men with a score of <20 points (mild to moderate symptoms) and 6 points for men with a score of ≥20 points (severe symptoms) as a minimum clinically meaningful improvement in symptoms. Patients were therefore classified as symptom responders if their symptom score decreased by ≥2 points from a baseline AUA-SI of <20, or ≥6 points from a baseline AUA-SI of ≥20 points. Symptom categories were assigned at baseline and reassessed and graded at 24 and 48 months as: 0–7 mild, 8–19 moderate, 20–35 severe.

RESULTS

Of the 363 study centres that participated in the double-blind phase, 265 participated in the open-label phase. Although 98 study centres elected not to participate in the open-label phase, 16 of the 19 countries that contributed patients to the double-blind phase also did so for the open-label phase. Of the 4325 men who were randomized, 2340 entered the open-label phase (Fig. 1), in which all 2340 men were treated with dutasteride and of these, 1188 had previously received dutasteride (D/D group) and 1152 had received placebo (P/D group) during the double-blind phase. There were no significant differences at the start of the double-blind phase in baseline variables between patients randomized to treatment with dutasteride or placebo, except for a higher mean Q_{max} in the placebo group. Men who entered the open-label phase had characteristics that were not significantly different from those who elected not to continue with the study, indicating that there was no selection or responder bias (Table 1). In dutasteride-treated patients, changes in efficacy variables during the double-blind phases did not appear to predict who would enter the open-label phase. The

mean AUA-SI score, prostate volume and Q_{max} at 24 months, and mean changes from baseline, were similar between those who enrolled and those who did not.

The proportion of men completing the open-label phase was higher in the D/D than in the P/D group (72.7% vs 69.7%). The most common reason for premature withdrawal from the open-label phase in either treatment group was adverse events, which occurred more frequently in men with no exposure to dutasteride in the double-blind phase of the study (10.2% in P/D-treated men vs 8.8% in D/D-treated men). The proportion of men who withdrew due to lack of efficacy was low in both groups (5.8% in P/D-treated men and 3.9% in D/D-treated men).

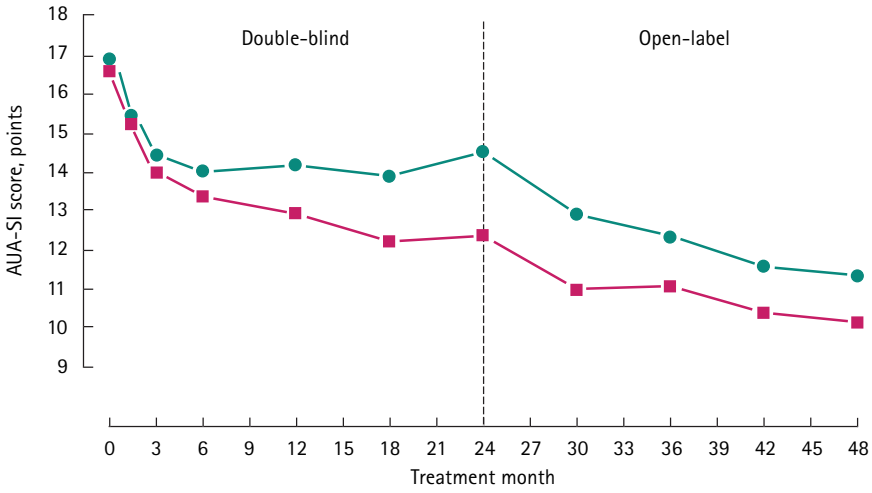
From baseline to 24 months, patients in the D/D group had a mean reduction in AUA-SI score of 4.4 points vs 2.5 points for patients in the P/D group ($P < 0.001$ between treatment groups). The AUA-SI score decreased significantly from 24 to 48 months for D/D-treated patients ($P < 0.001$; Fig. 2), with an overall mean reduction from baseline of 6.5 points. P/D-treated patients also had a significant decrease in symptom score from 24 to 48 months, but the overall change from baseline at 48 months of 5.6 points was significantly smaller than that in the D/D group ($P < 0.001$). For patients in the completer population (who had completed 48 months of study medication treatment), there was a similar decrease in AUA-SI score from baseline at 24 months compared with the ITT population (5.0 points for the D/D group vs 2.7 points for the P/D group; $P < 0.001$).

At 24 and 48 months the proportions of men who had an AUA-SI score of <12 (i.e. below the symptom threshold for study inclusion) differed significantly between the D/D and P/D groups. At 24 months, 51% of D/D-treated men and 40% of P/D-treated men had an AUA-SI score of <12 ($P < 0.001$). At 48 months, the proportions were 63% and 57% respectively ($P = 0.016$).

Treatment-by-country interaction was formally tested for AUA-SI change from baseline to 24 and 48 months; there were no statistically significant interactions.

Patients in the D/D group had greater reductions from baseline in the obstructive and irritative components of the AUA-SI

FIG. 2. Mean AUA-SI scores from baseline to the end of the open-label phase (ITT population). P/D group, green closed squares; D/D group, red closed squares.



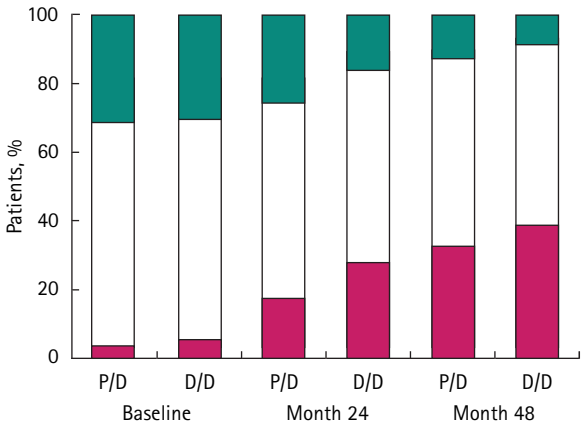


FIG. 3. Proportions of men with mild (AUA-SI 0–7, red), moderate (8–19, open) and severe (20–35, green) symptoms by treatment group (ITT population).

compared to P/D treated patients at 24 and 48 months. At 24 months, D/D-treated patients had mean decreases in obstructive and irritative scores of 2.8 and 1.6, respectively, vs 1.6 and 0.9 for P/D-treated patients ($P < 0.001$ for both comparisons). At 48 months, D/D-treated patients had mean decreases in obstructive and irritative scores of 4.1 and 2.4 respectively, vs 3.6 and 2.0 for P/D-treated patients ($P = 0.004$ and $P = 0.002$ respectively). For each of the seven AUA-SI questions, there was a significant difference between the P/D and D/D groups at 48 months ($P \leq 0.024$).

Over the double-blind and subsequent open-label phase, the proportion of patients with severe symptoms (AUA-SI 20–35) declined in both the P/D and D/D groups (Fig. 3). However, these changes were more profound in the D/D group at 48 months, with the proportion of men with severe symptoms declining by almost 75% from baseline.

Changes in symptom scores in the D/D and P/D groups by baseline age and prostate volume are shown in Fig. 4. There were similar differences between treatment groups for improvements in symptoms in older (≥65 years) and younger (<65 years) men, and in those with a prostate volume of <40 and ≥40 mL ($P = 0.62$ for age, $P = 0.24$ for prostate volume, for the tests of interaction between treatment and baseline values). However, there were differences in response to treatment among men with different baseline symptom scores. In men with a baseline AUA-SI score of <20 (mild to moderate symptoms), there were greater changes in AUA-SI from both baseline to 24 months and from baseline to 48 months, in patients in the D/D group compared to

FIG. 4. Mean change in AUA-SI score from baseline to the end of the double-blind phase (24 months) and the open-label phase (48 months) by baseline age and prostate volume (ITT population). P/D group, green bars; D/D group, red bars.

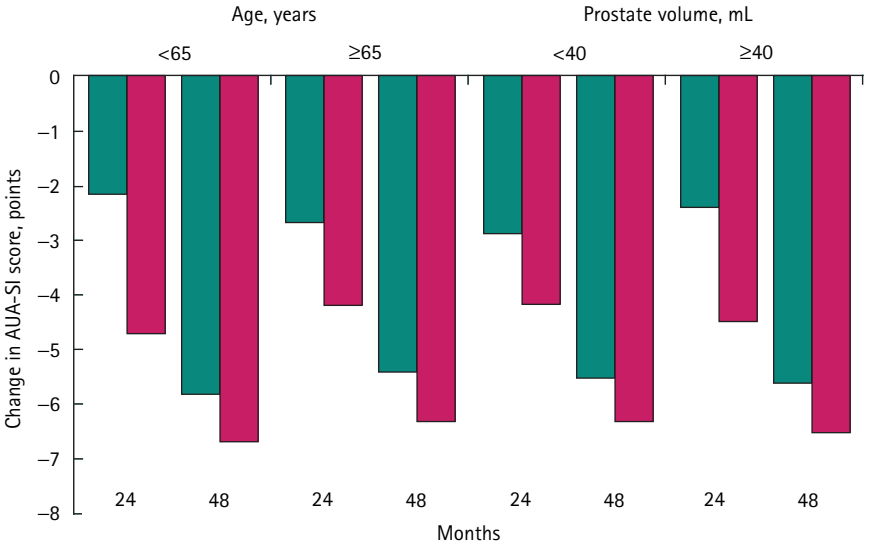


FIG. 5. Mean AUA-SI scores from baseline to the end of the open-label phase for men with moderate (closed symbols) and severe symptoms (open symbols) by treatment group (ITT population). P/D group, green; D/D group, red.

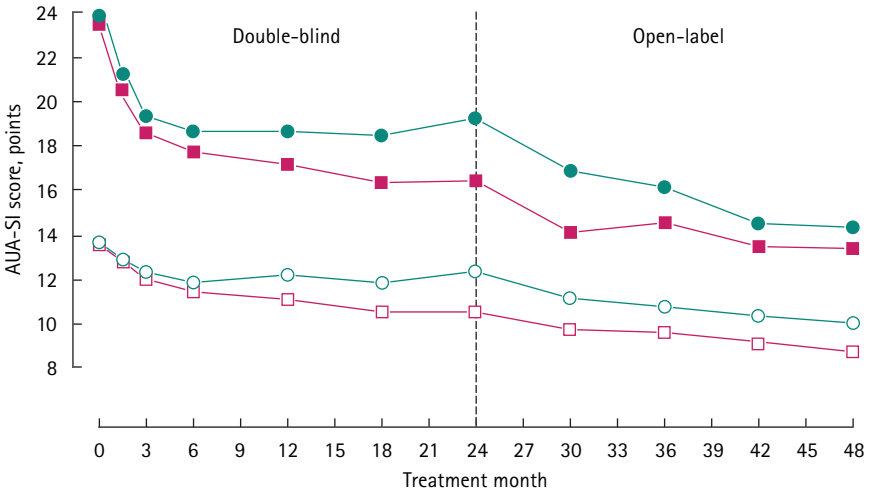
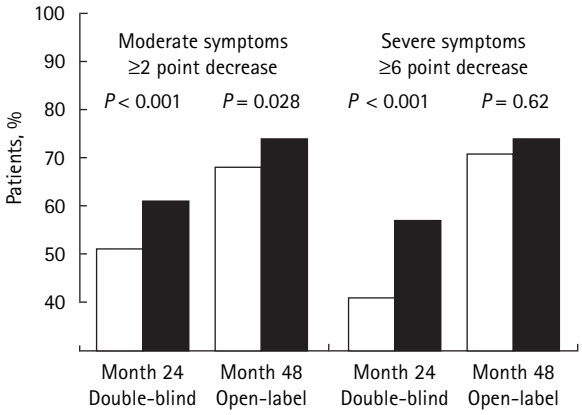


FIG. 6. Proportions of men classified as symptom responders at 24 and 48 months, by baseline symptom severity (ITT population). Open bars, P/D group; black bars, D/D group.



patients in the P/D group (Fig. 5). A similar finding was observed in men with a baseline AUA-SI of ≥20 (severe symptoms), although overall these men had greater improvements in symptom score than men with moderate symptoms.

Men with a baseline score of <20 points in the D/D group (832 men) had a mean decrease from baseline, of 3.2 points at 24 months, compared to 1.5 points for the P/D group (795 men). The decrease at 24 months in the D/D group, but not that in the P/D group, was clinically meaningful (≥2 points). Similarly, the mean decrease in score in men with a baseline score of ≥20 points was 7.2 points in D/D patients (356 men) compared to 4.7 points in P/D patients (355 men); again, only the former change was clinically meaningful (≥6 points). At the end of the open-label phase, patients with a baseline AUA-SI score of <20 points from the D/D group had a decrease in AUA-SI score of 4.9 points, compared to 4.0 points in those from the P/D group. Among men who had severe symptoms at baseline (AUA-SI score of ≥20 points), dutasteride treatment resulted in decreases of 10.1 and 9.4 points, respectively, for the D/D and P/D groups at 48 months.

The proportions of patients classified as symptom responders at 24 and 48 months, by baseline symptom severity, are shown in Fig. 6. At 24 months, significantly more men were classified as responders in the D/D group than in the P/D group in the moderate and severe baseline symptom groups. At 48 months, 74% of D/D patients in both symptom categories had a meaningful response to treatment.

The most common drug-related adverse events were sexual events (impotence, decreased libido and ejaculation disorders) and gynaecomastia (Table 2). The onset of most new drug-related sexual adverse events occurred within the first 6 months of therapy. Among patients who received dutasteride throughout the 48-month study period, the incidence of most drug-related sexual adverse events decreased with duration of treatment. The incidence of drug-related gynaecomastia was low and remained constant over the treatment period. Among patients who received dutasteride in the open-label phase only, the incidence of events was similar to those experienced by D/D-treated patients at the start of therapy. The incidence of events in the P/D group also declined between 36 and

TABLE 2 Onset of double-blind and open-label drug-related adverse events occurring in ≥1% of subjects in either treatment group

	Double-blind phase/ITT population				Open-label phase/ITT population			
	0–12 months		12–24 months		24–36 months		36–48 months	
Variable	P/D	D/D	P/D	D/D	P/D	D/D	P/D	D/D
N	2158	2167	1736	1744	1152	1188	968	1041
Events, %								
Any drug-related event	11.7	15.5	3.7	5.7	10.5	6.4	2.8	2.6
Impotence	3.0	6.0	1.2	1.7	2.8	1.4	0.4	0.4
Decreased libido	1.9	3.7	0.3	0.6	2.4	0.4	0.2	0.1
Ejaculation disorders	0.7	1.8	0.1	0.5	1.2	0.3	0.3	0.1
Gynaecomastia*	0.5	1.3	0.3	1.3	1.3	1.8	0.9	0.7

**Includes breast/nipple tenderness and breast enlargement.*

48 months after 1 year of dutasteride therapy. The incidence of drug-related sexual adverse events that led to withdrawal was < 1% in the open-label phase.

The overall incidence of serious adverse events was similar between the treatment groups during the open-label phase (11% in the P/D group, 13% in the D/D group). Six men (two in the P/D group and four in the D/D group) had serious adverse events during the open-label phase that were considered drug-related by the investigator. Serious adverse events of the cardiovascular system were most frequently reported (5% in the P/D group, 6% D/D group). Prostate cancer was reported in 2% of patients in the P/D and D/D groups during the open-label phase, but none of the cases were considered to be drug-related. One case of breast cancer was reported during the open-label phase (P/D group).

DISCUSSION

This study represents the largest available open-label dataset for the use of 5α-reductase inhibition in men with symptomatic BPH. Furthermore, the finding that men who enrolled in the open-label phase of the study had comparable symptoms, Q_{max} and prostate volume as those who did not enrol shows that the open-label phase data were not significantly biased by the selective recruitment of responders from the double-blind phase. The overall rate of withdrawals from the open-label phase for lack of efficacy was low, and lower still than that in the dutasteride group in the 24-month double-blind phase. The proportion of withdrawals for adverse events during the open-label phase was similar to that in the dutasteride and placebo treatment groups in the double-blind phase.

Dual 5α-reductase inhibition with dutasteride has previously been shown to significantly improve symptoms over a 2-year period [17]. Additional data from the open-label extensions of the studies provide further insight into the pattern of effect of dual 5α-reductase inhibition over both a 2- and a 4-year period. As reported for the double-blind population, men from the open-label population who received dutasteride in the first 24 months had significantly greater reductions in symptom score than placebo-treated men. Furthermore, dutasteride treatment significantly improved both the obstructive and irritative symptom components of the AUA-SI, and there were benefits regardless of baseline age or prostate volume.

The clinical relevance of these improvements in symptoms was examined in more detail by analysing responses to therapy by baseline AUA-SI score. This is important, as the minimum benefit perceptible to patients with severe symptoms is three times as large as that for those with moderate symptoms [19]. For men with moderate or severe symptoms, the mean decrease in symptom score at 24 months was clinically meaningful in the dutasteride group, but not in the placebo group, showing the benefit of dutasteride in both of these symptom groups. Although the mean symptomatic benefit gives an indication of the degree of benefit with dutasteride, the finding that the proportion of symptom responders at 24 months was significantly greater in the dutasteride group than in the placebo group is more clinically relevant.

At 24 months the benefit of dutasteride over placebo for symptom response was particularly marked in men with severe symptoms, as shown both by the mean AUA-SI scores and by the decrease in the proportion of men with severe symptoms, from 30% at baseline to 16% at 24 months.

Previous analyses of the data from these studies show that, for 4 vs 2 years of therapy, longer dutasteride therapy results in greater symptomatic benefits [18]. Four years of therapy is associated with sustained improvements in symptoms, with the magnitude of benefit exceeding that experienced by men who initiated therapy after 24 months. The benefit of longer therapy was apparent regardless of baseline age, prostate volume or symptom severity. The reduction in the proportion of men with moderate or severe symptoms was also greater in the D/D group than in the P/D group at 4 years. The mean benefit of dutasteride treatment over 4 years was a reduction of 6.5 points in the AUA-SI, while overall, 74% of men with moderate or severe symptoms had a clinically meaningful reduction in symptoms after 4 years of therapy.

No new safety issues emerged during the 4-year treatment period. The incidence of drug-related sexual adverse events was consistent with data from the pooled, 2-year dutasteride analysis reported previously [17].

In conclusion, dutasteride therapy over 4 years is associated with significant and

sustained improvements in LUTS, in both obstructive and irritative symptoms, with a significant benefit for longer dutasteride therapy (4 vs 2 years) for each of the seven component questions of the AUA-SI. Three-quarters of men with moderate or severe symptoms had a clinically meaningful reduction in symptoms after 4 years of therapy, and the symptoms improved regardless of baseline age, prostate volume or symptom severity. The magnitude of symptomatic benefit with long-term dutasteride therapy, a mean reduction in AUA-SI score of 6.5 points, suggests that monotherapy with dutasteride is an effective treatment option for men with symptomatic BPH and prostate enlargement (prostate volume ≥ 30 mL).

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CONFLICT OF INTEREST

P. Siami is the principle investigator funded by sponsor; N. Zinner took part in the clinical trial and is on the advisory board for GSK. Source of funding: GSK.

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Abbreviations: **AUA-SI**, AUA Symptom Index; **ITT**, intent to treat (population); **AUR**, acute urinary retention; $\mathbf{Q_{max}}$, peak urinary flow rate.