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Editor's Choice

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Effect of dutasteride, tamsulosin and the combination on patient-reported quality of life and treatment satisfaction in men with moderate-to-severe benign prostatic hyperplasia: 4-year data from the CombAT study

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Disclosures
Francesco Montorsi, Thomas Henkel, Arno Geboers, Vincenzo Mirone and Peio Arrosagaray are investigators in the CombAT study. Francesco Montorsi is an advisor to, and speaker for, GSK. Betsy Morrill and Libby Black are employees of GSK.

SUMMARY

Objective: To investigate the effect of combination therapy with dutasteride plus tamsulosin compared with each monotherapy on patient-reported health outcomes over 4 years in men with moderate-to-severe lower urinary tract symptoms (LUTS) because of benign prostatic hyperplasia (BPH). **Methods:** CombAT was a 4-year international, double-blind, randomised, parallel-group trial in men ($n = 4844$) with moderate-to-severe symptoms of BPH and at increased risk of disease progression [age ≥ 50 years, International Prostate Symptom Score (IPSS) ≥ 12, prostate volume ≥ 30 cc, serum prostate-specific antigen ≥ 1.5 ng/ml to ≤ 10 ng/ml and maximum urinary flow rate 5–15 ml/s with minimum voided volume ≥ 125 ml]. Subjects were randomised to receive 0.5 mg dutasteride, 0.4 mg tamsulosin or the combination once daily for 4 years. The primary endpoint at 4 years was the time to event and proportion of subjects with acute urinary retention or undergoing BPH-related prostate surgery. Secondary endpoints included the health-outcomes measures, BPH Impact Index (BII), IPSS question 8 (IPSS Q8) and the Patient Perception of Study Medication (PPSM) questionnaire. **Results:** At 4 years, combination therapy resulted in significantly superior improvements from baseline in BII and IPSS Q8 than either monotherapy; these benefits were observed from 3 months onwards compared with dutasteride and from 9 months (BII) or 12 months (IPSS Q8) onwards compared with tamsulosin. Also at 4 years, the PPSM questionnaire showed that a significantly higher proportion of patients was satisfied with, and would request treatment with, combination therapy compared with either monotherapy. **Conclusions:** Combination therapy (dutasteride plus tamsulosin) provides significantly superior improvements in patient-reported quality of life and treatment satisfaction than either monotherapy at 4 years in men with moderate-to-severe BPH symptoms.

What's known
Current guidelines recommend alpha-blockers and 5-alpha reductase inhibitors, either alone or in combination, as appropriate treatment options for BPH/LUTS. Both classes of drug have been shown to improve QoL in addition to symptoms, although data on the effects of combination therapy on patient-reported QoL and treatment satisfaction are more limited.

What's new
In men with moderate-to-severe BPH, combination therapy with dutasteride plus tamsulosin significantly improves patient-reported, disease-specific QoL and treatment satisfaction compared with either monotherapy. The significant superiority of combination therapy over both monotherapies was observed at 2 years and was sustained out to 4 years.

Introduction

Lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH) have a significant negative impact on the quality of life (QoL) of affected men (1). Several studies have shown that increasing severity of LUTS is associated with decreasing QoL (2,3). Moderate LUTS have a similar negative impact on QoL (measured using Short-Form 12) to serious conditions such as diabetes, hypertension and cancer; severe LUTS have a similar negative impact to having a heart attack or stroke (2).

The major goals of BPH treatment include improvement of symptom scores, lowering the risk of disease progression and improving patient-reported QoL and treatment satisfaction (4). The importance of patient perceptions and preferences is increasingly recognised as part of the clinical decision-making process (5–7), and patient satisfaction with treatment has implications for compliance and overall treatment success. Current guidelines recommend alpha-blockers and 5-alpha reductase inhibitors (5ARIs), either alone or in combination, as appropriate treatment options for BPH/LUTS (5,8).

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Both classes of drug have been shown to improve QoL in addition to symptoms (9–11), although data on the effects of combination therapy on patient-reported QoL and treatment satisfaction are more limited (12).

The Combination of Avodart® and Tamsulosin (CombAT) study was initiated to assess the efficacy and safety of combining dutasteride and an α-blocker (tamsulosin) in men (n = 4844) with moderate-to-severe symptoms of BPH and at increased risk of disease progression (13). Two-year analyses of CombAT showed that dutasteride plus tamsulosin provided significantly greater improvements in symptoms, patient-reported QoL and treatment satisfaction vs. either monotherapy (4,14).

At 4 years, combination therapy was significantly superior to tamsulosin monotherapy but not dutasteride monotherapy at reducing the relative risk of acute urinary retention (AUR) or BPH-related surgery. Combination therapy was significantly superior to both monotherapies at reducing the relative risk of BPH clinical progression (defined as one of the following: symptom deterioration by IPSS ≥ 4 points on two consecutive visits; BPH-related AUR; BPH-related urinary incontinence; recurrent BPH-related urinary tract infection or urosepsis; BPH-related renal insufficiency) and provided significantly greater symptom benefit than either monotherapy (15).

Here we present 4-year data on the effects of dutasteride plus tamsulosin compared with each monotherapy on the patient-reported health outcomes, International Prostate Symptom Score question 8 (IPSS Q8), BPH Impact Index (BII) and Patient Perception of Study Medication (PPSM).

Methods

The rationale and design of the CombAT study have been previously described in detail (13). Briefly, the study evaluated the efficacy and safety of combining the dual 5ARI dutasteride and the α-blocker tamsulosin in men with moderate-to-severe BPH symptoms (IPSS ≥ 12) at increased risk of disease progression [age ≥ 50 years, prostate volume ≥ 30 cc, serum prostate-specific antigen (PSA) ≥ 1.5 ng/ml to ≤ 10 ng/ml and maximum urinary flow rate 5–15 ml/s with minimum voided volume ≥ 125 ml]. Following screening, all eligible patients were entered into a single-blind run-in period during which they received dutasteride and tamsulosin placebos for 4 weeks. All subjects were then randomised in a 1 : 1 : 1 ratio to receive once-daily treatment with 0.5 mg dutasteride plus 0.4 mg tamsulosin, 0.5 mg dutasteride plus tamsulosin-matched placebo or 0.4 mg tamsulosin plus dutasteride-matched placebo for 4 years.

Separate primary and secondary endpoints were analysed at 2 and 4 years (13). The primary endpoint for the preplanned analysis at 2 years was mean change from baseline in IPSS; secondary endpoints at 2 years included changes from baseline in peak urinary flow, BII, IPSS Q8 and PPSM. At 4 years, the primary endpoint was the time to event and proportion of subjects with AUR or undergoing BPH-related prostate surgery; secondary endpoints included all 2-year primary and secondary endpoints.

The BII is a disease-specific four-item instrument that measures the overall impact of LUTS on the general well-being of patients (see Appendix). It yields a total score ranging from 0 to 13, with higher scores indicating a greater impact on patients' well-being. It has acceptable test-retest and internal consistency reliability, construct and discriminant validity, and responsiveness (16). BII was assessed at baseline and at every 3-month visit.

Responses to IPSS Q8 (If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?) were assessed at baseline and at every 3-month visit. Scores range from 0 (delighted) to 6 (terrible). The validity of the IPSS is widely accepted (17).

The PPSM is a 12-item questionnaire that assesses patient satisfaction with treatment. The US English version of the PPSM has been validated for use in men with BPH (18). For questions 1 to 11, patients respond on a 7-item scale. For question 12 (Would you ask your doctor for the medication you received in this study?) the possible responses are yes, no and not sure. PPSM was assessed at baseline and at every 3-month visit. The PPSM total score analysed the summed responses to questions 1–4 and 9–11. Questions 5–8, which relate to pain, were excluded from the PPSM total score analysis because of the low prevalence of pain in BPH patients in general, and the fact that only half of patients had pain before and during urination at any time in this study. The exclusion of these pain items has been shown to have no impact on the psychometric performance of the PPSM (18). The score for Question 12 (Would you ask your doctor for the medication you received in this study?) is not included in the total score as this question does not assess patient satisfaction or perception of improvement, but rather a patient's willingness to ask for study medication.

The primary analysis population was the intent-to-treat population, using a last observation carried forward approach. The change from baseline in IPSS Q8 scores, BII total scores and BII individual question scores with combination therapy vs. each monotherapy was assessed using t-tests from a general linear model with effects for treatment, cluster and

baseline value at $\alpha = 0.01$; the individual questions of the BII were analysed *post hoc*. Responses to the 12 individual questions of the PPSM were categorised as either positive or negative; positive responses were any improvement for questions on improvement, any satisfaction for questions on satisfaction and yes for question 12; negative responses were no change or worsening for questions on improvement, neutral or dissatisfaction for questions on satisfaction and no or not sure for question 12. Comparisons between combination therapy and each monotherapy were performed using a Mantel-Haenszel test controlling for cluster at $\alpha = 0.01$, selected to ensure a statistically powerful finding. PPSM total score was analysed *post hoc*, after the scoring of the questionnaire had been confirmed by psychometric testing.

Results

Demographics and baseline characteristics were generally similar between the treatment groups and consistent with a moderate-to-severe BPH population (Table 1).

Benign Prostatic Hyperplasia Impact Index (BII)

The mean change from baseline in BII at 4 years was −2.2 with combination therapy, −1.8 with dutasteride and −1.2 with tamsulosin ($p < 0.001$ for combination therapy vs. each monotherapy) (Figure 1).

Table 1 Baseline demographics and patient characteristics. Data presented as mean (SD) unless otherwise stated

	Combination therapy	Dutasteride	Tamsulosin
No. of patients	1610	1623	1611
Age, years	66.0 (7.05)	66.0 (6.99)	66.2 (7.00)
IPSS	16.6 (6.35)	16.4 (6.03)	16.4 (6.10)
IPSS Q8	3.6 (1.28)	3.6 (1.27)	3.6 (1.27)
BII	5.3 (3.06)	5.3 (2.99)	5.3 (3.07)
PPSM total score	25.0 (6.20)	25.3 (6.21)	25.1 (6.28)
PV (screening), cc	54.7 (23.51)	54.6 (23.02)	55.8 (24.18)
PSA (screening), ng/ml	4.0 (2.05)	3.9 (2.06)	4.0 (2.08)
Q_{max}, ml/s	10.9 (3.61)	10.6 (3.57)	10.7 (3.66)
Postvoid residual volume, ml	68.2 (66.12)	67.4 (63.49)	67.7 (65.14)
Previous α-blocker use, *n* (%)	805 (50)	820 (51)	819 (51)
Previous 5ARI use, *n* (%)	171 (11)	188 (12)	172 (11)

IPSS, International Prostate Symptom Score; BII, BPH Impact Index; LUTS, lower urinary tract symptoms; PPSM, patient perception of study medication; PSA, prostate-specific antigen; PV, prostate volume; Q_{max}, peak urinary flow rate; 5ARI, 5α-reductase inhibitor.

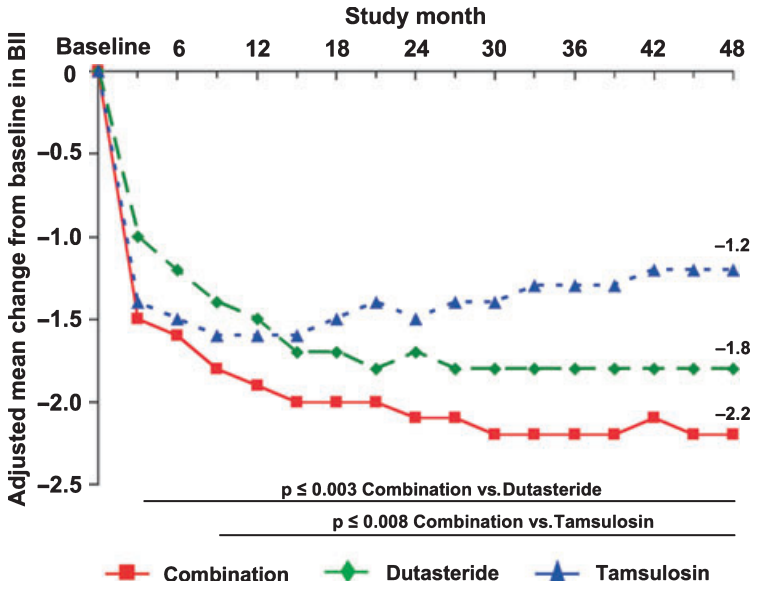

Figure 1 Adjusted mean change from baseline in BII

Improvement in BII from baseline with combination therapy was significantly superior to that with dutasteride from 3 months onwards, and significantly superior to that with tamsulosin from 9 months onwards. The improvement in BII with combination therapy appeared to increase relative to that with tamsulosin from month 24 onwards and stayed constant relative to that with dutasteride.

The mean baseline scores for the individual BII questions were 1.3, 1.4, 1.6 and 1.0 for questions 1 (physical discomfort), 2 (worry), 3 (level of bother) and 4 (effect on normal activities), respectively. For each individual BII question, the improvement from baseline at 4 years was significantly greater with combination therapy than with either monotherapy (Table 2).

International Prostate Symptom Score Question 8 (IPSS Q8)

At 4 years, the mean change in IPSS Q8 from baseline was −1.5 with combination therapy, −1.3 with dutasteride and −1.1 with tamsulosin ($p < 0.001$ for combination therapy vs. each monotherapy) (Figure 2). Improvement in IPSS Q8 from baseline with combination therapy was significantly superior to that with dutasteride from 3 months onwards, and significantly superior to that with tamsulosin from 12 months onwards.

Patient Perception of Study Medication (PPSM)

At baseline, the proportion of patients reporting a positive response to each of the 12 questions in the PPSM was similar between the treatment groups (Table 3).

At 2 years, the proportion of patients reporting an improvement, satisfaction or desire to request study treatment in response to each of the 12 PPSM questions was significantly higher with combination therapy than with either monotherapy, except for Q5 on pain before urination (superiority of combination therapy did not reach statistical significance vs. tamsulosin). The superiority of combination therapy observed at 2 years was sustained out to 4 years (Table 3). In addition, combination therapy was significantly superior to tamsulosin at month 48 for Q5 (pain before urination).

Table 2 Mean change from baseline in scores for individual questions of the BII at 4 years

Question	Combination therapy	Dutasteride	Tamsulosin
1 (physical discomfort)	−0.52*†	−0.42	−0.31
2 (worry)	−0.58*†	−0.50	−0.33
3 (level of bother)	−0.66*†	−0.59	−0.41
4 (effect on normal activities)	−0.41*†	−0.34	−0.19

*$p \leq 0.008$ combination therapy vs. dutasteride.
†$p < 0.001$ combination therapy vs. tamsulosin.

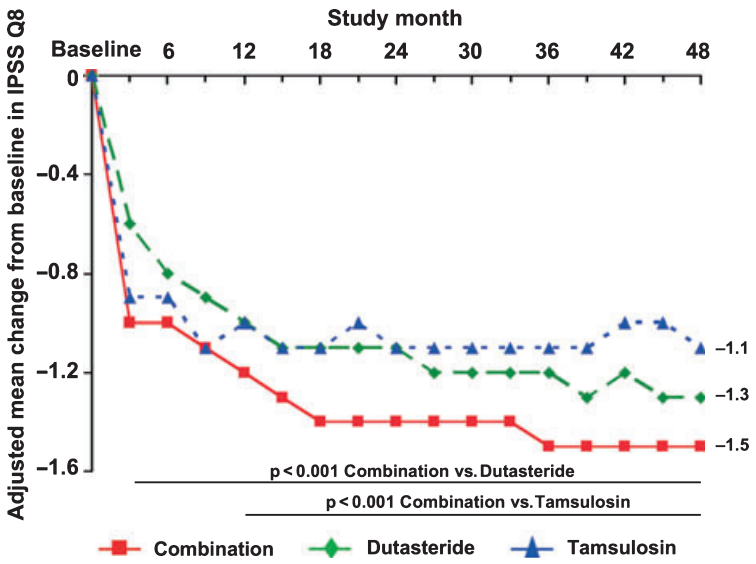

Figure 2 Adjusted mean change from baseline in IPSS Q8

Table 3 Responses to the 12 individual PPSM questions by treatment group at baseline, 24 months and 48 months

	% of patients with any improvement/satisfaction		
PPSM question	**Combination therapy**	**Dutasteride**	**Tamsulosin**
Q1. Improvement in control of urinary problems			
Baseline	44	41	45
24	81*†	75	76
48	81*†	76	72
Q2. Satisfaction with control of urinary problems			
Baseline	45	41	43
24	80*†	73	73
48	80*†	74	69
Q3. Improvement in strength of urinary stream			
Baseline	40	38	39
24	77*†	67	67
48	76*†	68	64
Q4. Satisfaction with change in strength of urinary stream			
Baseline	40	37	39
24	76*†	67	66
48	77*†	68	65
Q5. Improvement in pain before urination			
Baseline	39	37	39
24	75*	67	69
48	75*†	67	65
Q6. Satisfaction with change in pain before urination			
Baseline	41	38	39
24	71*†	64	65
48	71*†	65	64
Q7. Improvement in pain during urination			
Baseline	38	35	39
24	75*†	67	69
48	75*†	66	65
Q8. Satisfaction with change in pain during urination			
Baseline	40	38	39
24	71*†	63	66
48	72*†	64	63
Q9. Improvement in the level of interference with daily activities			
Baseline	32	30	31
24	73*†	66	66
48	73*†	67	64
Q10. Satisfaction with change in the level of interference with daily activities			
Baseline	39	35	37
24	77*†	70	69
48	77*†	70	66
Q11. Overall satisfaction with improvement in urinary problems			
Baseline	46	43	44
24	81*†	75	74
48	80*†	74	69
Q12. Would you ask your doctor for the medication you received in the study? Yes			
Baseline	38	35	37
24	65*†	60	60
48	64*†	58	55

*$p < 0.01$ combination therapy vs. dutasteride.
†$p < 0.01$ combination therapy vs. tamsulosin.

The proportion of patients reporting any satisfaction with treatment in response to Q11 at 4 years was significantly higher with combination therapy (80%) than with dutasteride (74%) or tamsulosin (69%) (Table 3). Satisfaction was significantly higher with combination therapy than with dutasteride from 3 months and with tamsulosin from 15 months (Figure 3). In addition, satisfaction remained relatively stable in the groups receiving combination therapy or dutasteride, but appeared to decrease in the tamsulosin group from 9 months onwards.

At 4 years, the mean change from baseline in PPSM total score (questions 1–4 and 9–11) was −7.0 with combination therapy, −5.5 with dutasteride and −4.1 with tamsulosin ($p < 0.001$ for combination therapy vs. each monotherapy) (Figure 4). Improvement in PPSM total score from baseline with combination therapy was significantly superior to that with dutasteride from 3 months onwards, and significantly superior to that with tamsulosin from 12 months onwards.

Discussion

Clinical practice guidelines for the management of BPH recognise the importance of assessing patient-reported health outcomes in addition to objective measures such as improvement in LUTS (5,6). A

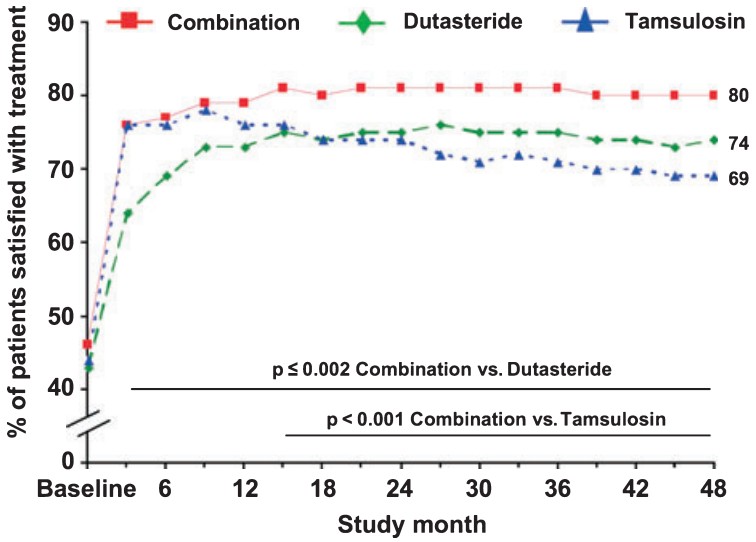

Figure 3 Proportion of patients reporting satisfaction overall with treatment and its effect on their urinary symptoms (Q11 of the PPSM)

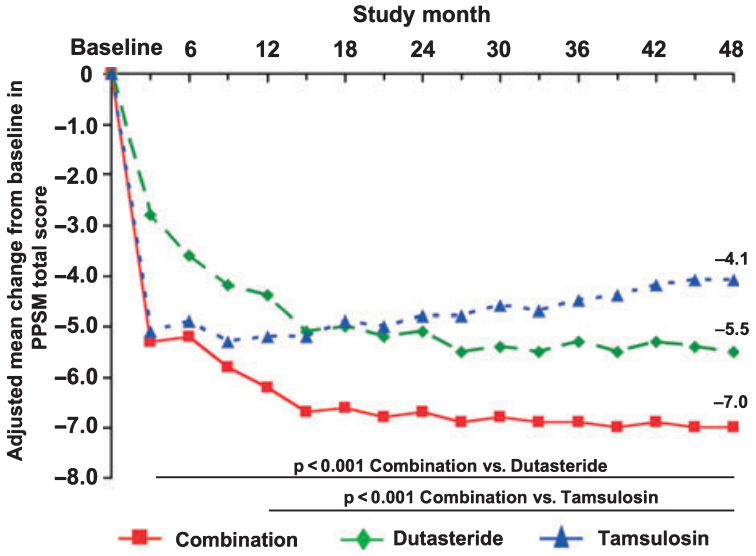

Figure 4 Adjusted mean change from baseline in PPSM total score

previous report from the CombAT study showed that combination therapy with dutasteride plus tamsulosin was significantly superior to either monotherapy for improving patient-reported QoL and treatment satisfaction at 2 years (4). The data presented here confirm and extend these findings, demonstrating the superiority of combination therapy over a longer term (4 years).

CombAT is the first study to show superiority of combined 5ARI plus alpha-blocker therapy over both monotherapies on BPH-related QoL. The Medical Therapy of Prostatic Symptoms (MTOPS) study, which included combination therapy with finasteride and doxazosin, did not assess disease-specific QoL in any detail (19). In the Veteran Affairs Cooperative study, 12 months' treatment with finasteride plus terazosin was superior to finasteride but not terazosin monotherapy for improving BII and global rating of improvement (12). In CombAT, which used the dual 5ARI dutasteride, combination therapy was significantly better than the alpha-blocker (tamsulosin) for improving BII score from 9 months and for improving IPSS Q8 from 12 months, and this superiority was sustained out to 4 years.

In a previous study, over a treatment period of 13 weeks, mean improvements in BII from baseline of −0.5, −1.1 and −2.2 were associated with slight, moderate and marked improvements as perceived by patients (16). In CombAT, the improvement in BII in the combination group reached the threshold for marked improvement at 30 months, and this was maintained out to 48 months (except for month 42, when the improvement was −2.1).

The 12 questions of the PPSM assess treatment satisfaction over several domains (control of urinary symptoms, strength of urinary stream, pain of urination, effect on daily activities and overall satisfaction). For each domain, there is one question on the perceived change and another on the level of satisfaction with that change. The final question assesses the patient's desire to receive study medication after the trial (18). After 4 years in the CombAT study, patients receiving combination therapy were significantly more satisfied with their treatment than those receiving either monotherapy. The proportion of patients who responded positively was significantly higher with combination therapy than with either monotherapy for each of the 12 questions. In addition, improvement in PPSM total score from baseline was statistically greater with combination therapy than with either monotherapy (from 3 months onwards compared with dutasteride, and from 12 months onwards compared with tamsulosin); the superiority of combination therapy was sustained out to 4 years. This greater satisfaction with combination therapy was reflected in the fact that significantly more patients in the combination group said they would request their study medication once the trial was over compared with those receiving either monotherapy (PPSM question 12).

It is interesting to note the similarities over the course of the study between the change from baseline in PPSM total score reported here and the change from baseline in the IPSS reported previously (15), particularly with respect to the combination and tamsulosin arms. The detection of a significant difference in symptom (IPSS) improvement between the two treatments (from month 9 onwards) is followed closely by a significant difference in patient-perceived satisfaction with treatment (PPSM total score; from month 12 onwards). This observation of an apparent correlation between IPSS and PPSM is worthy of further investigation.

The lack of a placebo arm in CombAT was based on ethical considerations, as included men were at increased risk of disease progression and each study drug has been show to be superior to placebo in earlier studies. While this represents a potential limitation of the study (as it may have resulted in overestimated responses), any such effect would apply equally to each of the treatment arms. The consistent effects observed across all questionnaires, as well as symptom measures (15), increase confidence in the study results even in the absence of a placebo group.

In conclusion, in men with moderate-to-severe BPH, combination therapy with dutasteride plus tamsulosin reduced the impact of BPH (BII), improved overall QoL (IPSS Q8) and improved treatment satisfaction (PPSM) to a significantly greater extent than either monotherapy. The significant superiority of combination therapy over both monotherapies was observed at 2 years and was sustained out to 4 years, and the improvement in BII with combination therapy met a previously defined threshold for patient-perceived marked improvement.

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Author contributions

All authors contributed to the concept/design of the article and were responsible for critical revision and final approval of the article.

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Appendix

BII

Q1. During the last month, how much physical discomfort did any urinary problems cause you?

None	Only a little	Some	A lot
0	1	2	3

Q2. During the last month, how much did you worry about your health because of any urinary problems?

None	Only a little	Some	A lot
0	1	2	3

Q3. Overall, how bothersome has any trouble with urination been during the last month?

Not at all	A little	Some	A lot
0	1	2	3

Q4. During the last month, how much of the time has any urinary problem kept you from doing the kinds of things you would usually do?

None	A Little	Some of the time	Most of the time	All of the time
0	1	2	3	4

IPSS Q8

If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?

Delighted						Terrible
0	1	2	3	4	5	6

PPSM questionnaire

1. Since you began taking the study medication, how has control of your urinary problems changed?

Much improved	Improved	Somewhat improved	No change	Somewhat worse	Worse	Much worse

2. How satisfied are you with the effect of the study medication on control of your urinary problems?

Very satisfied	Satisfied	Somewhat satisfied	Neutral	Somewhat dissatisfied	Dissatisfied	Very dissatisfied

3. Since you began taking the study medication, how has the strength of your urinary stream changed?

Much improved	Improved	Somewhat improved	No change	Somewhat worse	Worse	Much worse

4. How satisfied are you with the effect of the study medication on the strength of your urinary stream?

Very satisfied	Satisfied	Somewhat satisfied	Neutral	Somewhat dissatisfied	Dissatisfied	Very dissatisfied

5. Since you began taking the study medication, how has your pain prior to urinating changed?

Much improved	Improved	Somewhat improved	No change	Somewhat worse	Worse	Much worse

6. How satisfied are you with the effect the study medication has on your pain prior to urinating?

Very satisfied	Satisfied	Somewhat satisfied	Neutral	Somewhat dissatisfied	Dissatisfied	Very dissatisfied

7. Since you began taking the study medication, how has your pain during urination changed?

Much improved	Improved	Somewhat improved	No change	Somewhat worse	Worse	Much worse

8. How satisfied are you with the effect the study medication has on your pain during urination?

Very satisfied	Satisfied	Somewhat satisfied	Neutral	Somewhat dissatisfied	Dissatisfied	Very dissatisfied

Appendix (Continued)

9. Since you began taking the study medication, how has the way your urinary problems interfere with your ability to go about your usual activities changed?

Much improved	Improved	Somewhat improved	No change	Somewhat worse	Worse	Much worse

10. How satisfied are you with the effect the study medication has on your ability to go about your usual activities without interference with your usual activities?

Very satisfied	Satisfied	Somewhat satisfied	Neutral	Somewhat dissatisfied	Dissatisfied	Very dissatisfied

11. Overall, how satisfied are you with the study medication and its effect on your urinary problems?

Very satisfied	Satisfied	Somewhat satisfied	Neutral	Somewhat dissatisfied	Dissatisfied	Very dissatisfied

12. Would you ask your doctor for the medication you received in this study?

Yes	No	Not sure

