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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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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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Francesco Montorsi^{1*}, Thomas Henkel², Arno Geboers³, Vincenzo Mirone⁴, Peio Arrosagaray⁵, Betsy Morrill⁶, Libby Black⁶

¹Universita' Vita Salute San Raffaele, Milan, Italy; ²Consultant Urologist, Berlin, Germany; ³Slingeland Hospital, Doetinchem, The Netherlands; ⁴Università Federico II di Napoli, Naples, Italy; ⁵Hospital de Mendaro, Guipuzkoa, Spain;

⁶GlaxoSmithKline, NC, USA

**Corresponding author:*

Prof. Francesco Montorsi
Professor of Urology
Universita' Vita Salute San Raffaele
Via Olgettina 60
20132 Milan
Italy

Ph: +39 0226437286

Fax: +39 0226437298

Email: montorsi.francesco@hsr.it

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.

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) due to 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 AUR 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.

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). 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 versus 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 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

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3 urinary tract infection or urosepsis; BPH-related renal insufficiency), and provided
4 significantly greater symptom benefit than either monotherapy (15).
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8 Here we present 4-year data on the effects of dutasteride plus tamsulosin compared
9 with each monotherapy on the patient-reported health outcomes, International
10 Prostate Symptom Score question 8 (IPSS Q8), BPH Impact Index (BII) and Patient
11 Perception of Study Medication (PPSM).
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15 16 **Methods**

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18 The rationale and design of the CombAT study has been previously described in
19 detail (13). Briefly, the study evaluated the efficacy and safety of combining the dual
20 5ARI dutasteride and the α -blocker tamsulosin in men with moderate-to-severe BPH
21 symptoms (IPSS ≥ 12) at increased risk of disease progression (age ≥ 50 years,
22 prostate volume ≥ 30 cc, serum prostate-specific antigen [PSA] ≥ 1.5 ng/ml to ≤ 10
23 ng/ml and maximum urinary flow rate 5–15 ml/s with minimum voided volume ≥ 125
24 ml). Following screening, all eligible patients were entered into a single-blind run-in
25 period during which they received dutasteride and tamsulosin placebos for 4 weeks.
26 All subjects were then randomised in a 1:1:1 ratio to receive once-daily treatment
27 with 0.5 mg tamsulosin plus 0.4 mg tamsulosin, 0.5 mg dutasteride plus tamsulosin-
28 matched placebo, or 0.4 mg tamsulosin plus dutasteride-matched placebo for 4
29 years.
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41 Separate primary and secondary endpoints were analysed at 2 and 4 years (13).
42 The primary endpoint for the pre-planned analysis at 2 years was mean change from
43 baseline in IPSS; secondary endpoints at 2 years included changes from baseline in
44 peak urinary flow, BII, IPSS Q8 and PPSM. At 4 years, the primary endpoint was the
45 time to event and proportion of subjects with AUR or undergoing BPH-related
46 prostate surgery; secondary endpoints included all 2-year primary and secondary
47 endpoints.
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54 The BII is a disease-specific four-item instrument that measures the overall impact of
55 LUTS on the general well-being of patients. It yields a total score ranging from 0 to
56 13, with higher scores indicating a greater impact on patient well-being. It has
57 acceptable test-retest and internal consistency reliability, construct and discriminant
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3 validity, and responsiveness (16). BII was assessed at baseline and at every 3-
4 month visit.
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8 Responses to IPSS Q8 (If you were to spend the rest of your life with your urinary
9 condition just the way it is now, how would you feel about that?) were assessed at
10 baseline and at every 3-month visit. Scores range from 0 (delighted) to 6 (terrible).
11 The validity of the IPSS is widely accepted (17).
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16 The PPSM is a 12-item questionnaire that assesses patient satisfaction with
17 treatment. The US English version of the PPSM has been validated for use in men
18 with BPH (18). For questions 1 to 11 patients respond on a 7-item scale. For
19 question 12 (Would you ask your doctor for the medication you received in this
20 study?) the possible responses are yes, no and not sure. PPSM was assessed at
21 baseline and at every 3-month visit. The PPSM total score analysed the summed
22 responses to questions 1–4 and 9–11. Questions 5–8, which relate to pain, were
23 excluded from the PPSM total score analysis due to the low prevalence of pain in
24 BPH patients in general, and the fact that only half of patients had pain before and
25 during urination at any time in this study. The exclusion of these pain items has been
26 shown to have no impact on the psychometric performance of the PPSM (18). The
27 score for Question 12 (Would you ask your doctor for the medication you received in
28 this study?) is not included in the total score as this question does not assess patient
29 satisfaction or perception of improvement, but rather a patient's willingness to ask for
30 study medication.
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44 The primary analysis population was the intent-to-treat population, using a last
45 observation carried forward approach. The change from baseline in IPSS Q8 scores,
46 BII total scores and BII individual question scores with combination therapy versus
47 each monotherapy was assessed using *t*-tests from a general linear model with
48 effects for treatment, cluster and baseline value at $\alpha=0.01$; the individual questions of
49 the BII were analysed post-hoc. Responses to the 12 individual questions of the
50 PPSM were categorised as either positive or negative; positive responses were any
51 improvement for questions on improvement, any satisfaction for questions on
52 satisfaction, and yes for question 12; negative responses were no change or
53 worsening for questions on improvement, neutral or dissatisfaction for questions on
54 satisfaction, and no or not sure for question 12. Comparisons between combination
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3 therapy and each monotherapy were performed using a Mantel-Haenszel test
4 controlling for cluster at $\alpha=0.01$, selected to ensure a statistically powerful finding.
5 PPSM total score was analysed post-hoc, after the scoring of the questionnaire had
6 been confirmed by psychometric testing.
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10 11 **Results**

12 Demographics and baseline characteristics were generally similar between the
13 treatment groups, and consistent with a moderate-to-severe BPH population (Table
14 1).
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20 **BII**

21 The mean change from baseline in BII at 4 years was -2.2 with combination therapy,
22 -1.8 with dutasteride and -1.2 with tamsulosin ($p<0.001$ for combination therapy
23 versus each monotherapy) (Figure 1). Improvement in BII from baseline with
24 combination therapy was significantly superior to that with dutasteride from 3 months
25 onwards, and significantly superior to that with tamsulosin from 9 months onwards.
26 The improvement in BII with combination therapy appeared to increase relative to
27 that with tamsulosin from month 24 onwards, and stayed relatively constant relative
28 to that with dutasteride.
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38 The mean baseline scores for the individual BII questions were 1.3, 1.4, 1.6 and 1.0
39 for questions 1 (physical discomfort), 2 (worry), 3 (level of bother) and 4 (effect on
40 normal activities), respectively. For each individual BII question, the improvement
41 from baseline at 4 years was significantly greater with combination therapy than with
42 either monotherapy (Table 2).
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50 **IPSS Q8**

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

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 versus 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 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

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3 at 2 years (4). The data presented here confirm and extend these findings,
4 demonstrating the superiority of combination therapy over a longer term (4 years).
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8 CombAT is the first study to show superiority of combined 5ARI plus alpha-blocker
9 therapy over both monotherapies on BPH-related QoL. The Medical Therapy of
10 Prostatic Symptoms (MTOPS) study, which included combination therapy with
11 finasteride and doxazosin, did not assess disease-specific QoL in any detail (19). In
12 the Veteran Affairs Cooperative study, 12 months' treatment with finasteride plus
13 terazosin was superior to finasteride but not terazosin monotherapy for improving BII
14 and global rating of improvement (12). In CombAT, which used the dual 5ARI
15 dutasteride, combination therapy was significantly better than the alpha-blocker
16 (tamsulosin) for improving BII score from 9 months and for improving IPSS Q8 from
17 12 months, and this superiority was sustained out to 4 years.
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22 In a previous study, over a treatment period of 13 weeks, mean improvements in BII
23 from baseline of -0.5 , -1.1 and -2.2 were associated with slight, moderate and
24 marked improvements as perceived by patients (16). In CombAT, the improvement
25 in BII in the combination group reached the threshold for marked improvement at 30
26 months and this was maintained out to 48 months (except for month 42, when the
27 improvement was -2.1).
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32 The 12 questions of the PPSM assess treatment satisfaction over several domains
33 (control of urinary symptoms, strength of urinary stream, pain of urination, effect on
34 daily activities and overall satisfaction). For each domain, there is one question on
35 the perceived change and another on the level of satisfaction with that change. The
36 final question assesses the patient's desire to receive study medication after the trial
37 (18). After 4 years in the CombAT study, patients receiving combination therapy
38 were significantly more satisfied with their treatment than those receiving either
39 monotherapy. The proportion of patients who responded positively was significantly
40 higher with combination therapy than with either monotherapy for each of the 12
41 questions. In addition, improvement in PPSM total score from baseline was
42 statistically greater with combination therapy than with either monotherapy (from 3
43 months onwards compared with dutasteride, and from 12 months onwards compared
44 with tamsulosin); the superiority of combination therapy was sustained out to 4 years.
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47 This greater satisfaction with combination therapy was reflected in the fact that
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3 significantly more patients in the combination group said they would request their
4 study medication once the trial was over compared with those receiving either
5 monotherapy (PPSM question 12).
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10 It is interesting to note the similarities over the course of the study between the
11 change from baseline in PPSM total score reported here and the change from
12 baseline in the IPSS reported previously (15), particularly with respect to the
13 combination and tamsulosin arms. The detection of a significant difference in
14 symptom (IPSS) improvement between the two treatments (from month 9 onwards)
15 is followed closely by a significant difference in patient-perceived satisfaction with
16 treatment (PPSM total score; from month 12 onwards). This observation of an
17 apparent correlation between IPSS and PPSM is worthy of further investigation.
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25 The lack of a placebo arm in CombAT was based on ethical considerations, since
26 included men were at increased risk of disease progression and each study drug has
27 been shown to be superior to placebo in earlier studies. While this represents a
28 potential limitation of the study (as it may have resulted in over-estimated responses),
29 any such effect would apply equally to each of the treatment arms. The consistent
30 effects observed across all questionnaires, as well as symptom measures (15),
31 increase confidence in the study results even in the absence of a placebo group.
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39 In conclusion, in men with moderate-to-severe BPH, combination therapy with
40 dutasteride plus tamsulosin reduced the impact of BPH (BII), improved overall QoL
41 (IPSS Q8), and improved treatment satisfaction (PPSM) to a significantly greater
42 extent than either monotherapy. The significant superiority of combination therapy
43 over both monotherapies was observed at 2 years and was sustained out to 4 years,
44 and the improvement in BII with combination therapy met a previously defined
45 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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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, yrs | 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) |
| Qmax, 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; Qmax=peak urinary flow rate; 5ARI=5 α -reductase inhibitor

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

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

| PPSM question | % of patients with any improvement/satisfaction | | |
|---|---|-------------|------------|
| | Combination therapy | Dutasteride | Tamsulosin |
| <i>Q1. Improvement in control of urinary problems</i> | | | |
| Baseline | 44 | 41 | 45 |
| 24 | 81*† | 75 | 76 |
| 48 | 81*† | 76 | 72 |
| <i>Q2. Satisfaction with control of urinary problems</i> | | | |
| Baseline | 45 | 41 | 43 |
| 24 | 80*† | 73 | 73 |
| 48 | 80*† | 74 | 69 |
| <i>Q3. Improvement in strength of urinary stream</i> | | | |
| Baseline | 40 | 38 | 39 |
| 24 | 77*† | 67 | 67 |
| 48 | 76*† | 68 | 64 |
| <i>Q4. Satisfaction with change in strength of urinary stream</i> | | | |
| Baseline | 40 | 37 | 39 |
| 24 | 76*† | 67 | 66 |
| 48 | 77*† | 68 | 65 |
| <i>Q5. Improvement in pain before urination</i> | | | |
| Baseline | 39 | 37 | 39 |
| 24 | 75* | 67 | 69 |

| | | | |
|---|------|----|----|
| 48 | 75*† | 67 | 65 |
| <i>Q6. Satisfaction with change in pain before urination</i> | | | |
| Baseline | 41 | 38 | 39 |
| 24 | 71*† | 64 | 65 |
| 48 | 71*† | 65 | 64 |
| <i>Q7. Improvement in pain during urination</i> | | | |
| Baseline | 38 | 35 | 39 |
| 24 | 75*† | 67 | 69 |
| 48 | 75*† | 66 | 65 |
| <i>Q8. Satisfaction with change in pain during urination</i> | | | |
| Baseline | 40 | 38 | 39 |
| 24 | 71*† | 63 | 66 |
| 48 | 72*† | 64 | 63 |
| <i>Q9. Improvement in the level of interference with daily activities</i> | | | |
| Baseline | 32 | 30 | 31 |
| 24 | 73*† | 66 | 66 |
| 48 | 73*† | 67 | 64 |
| <i>Q10. Satisfaction with change in the level of interference with daily activities</i> | | | |
| Baseline | 39 | 35 | 37 |
| 24 | 77*† | 70 | 69 |
| 48 | 77*† | 70 | 66 |
| <i>Q11. Overall satisfaction with improvement in urinary problems</i> | | | |
| Baseline | 46 | 43 | 44 |

| | | | |
|---|------|----|----|
| 24 | 81*† | 75 | 74 |
| 48 | 80*† | 74 | 69 |
| <i>Q12. Would you ask your doctor for the medication you received in the study? Yes</i> | | | |
| 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

For Peer Review Only

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3 **Figure 1. Adjusted mean change from baseline in BII**
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9 **Figure 2. Adjusted mean change from baseline in IPSS Q8**
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14 **Figure 3. Proportion of patients reporting satisfaction overall with treatment**
15 **and its effect on their urinary symptoms (Q11 of the PPSM)**
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21 **Figure 4. Adjusted mean change from baseline in PPSM total score**
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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 |
|----------------|-----------|--------------------|---------|-----------------------|--------------|-------------------|

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 |
|----------------|-----------|--------------------|---------|-----------------------|--------------|-------------------|

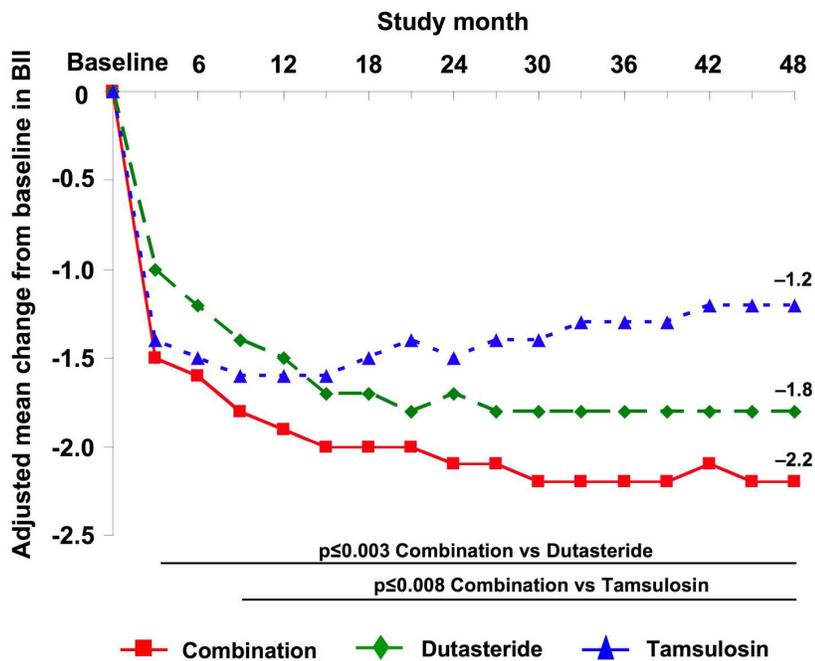
11. Overall how satisfied are you with the study medication and its effect on your urinary problems?

| | | | | | | |
|----------------|-----------|--------------------|---------|-----------------------|--------------|-------------------|
| 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 |
|-----|----|----------|

Figure 1

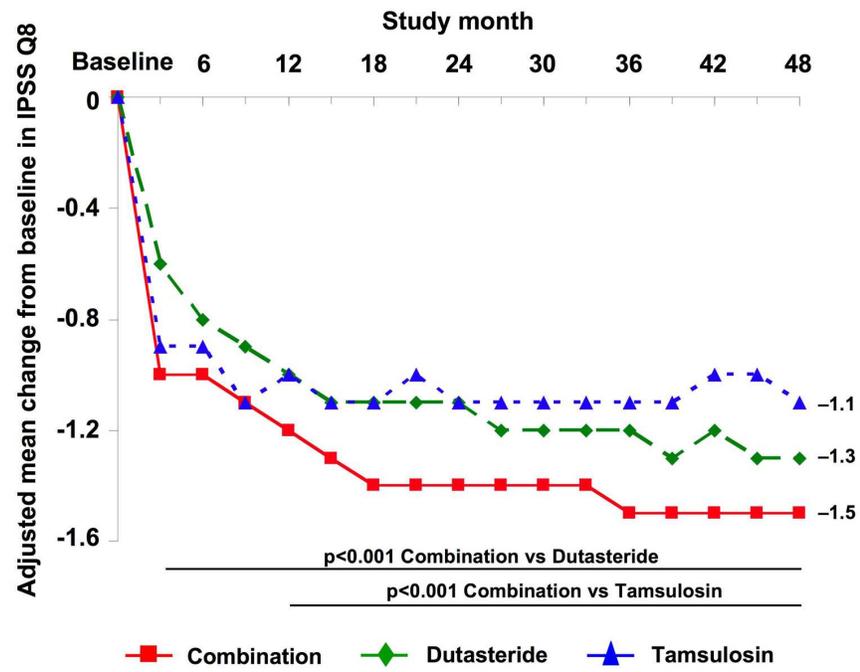


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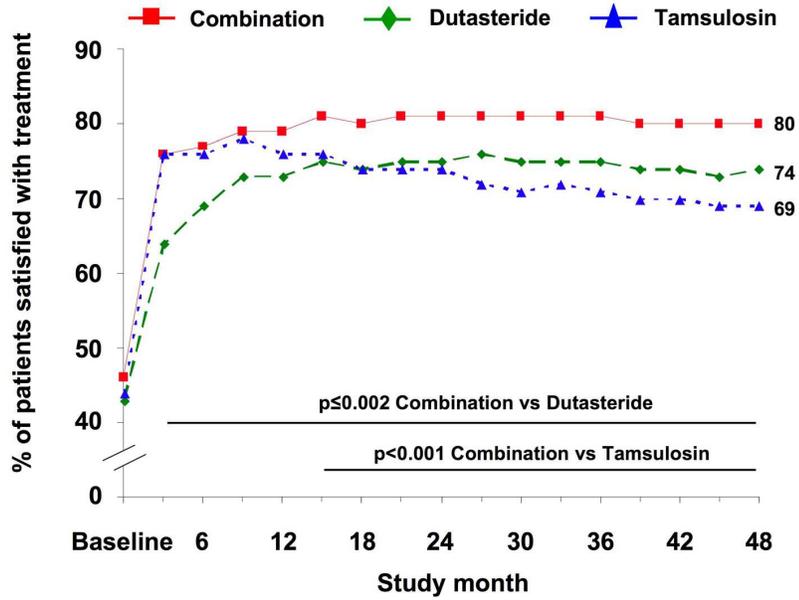
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Figure 2



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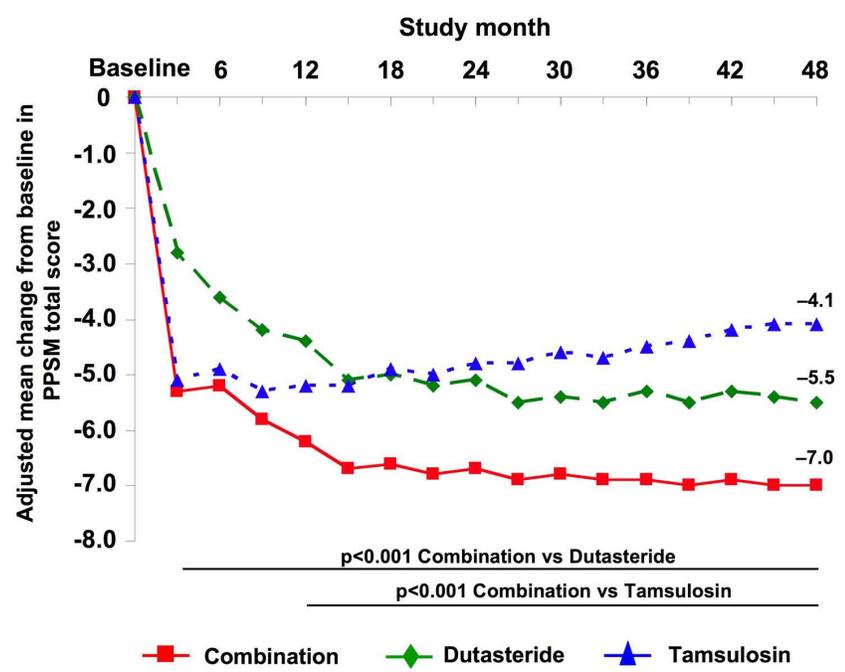
Figure 3



150x112mm (300 x 300 DPI)

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Figure 4



150x112mm (300 x 300 DPI)