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The effects of combination therapy with dutasteride plus tamsulosin on clinical outcomes in men with symptomatic benign prostatic hyperplasia: 4-year *post hoc* analysis of European men in the CombAT study

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Running title: CombAT study: analysis of European men

Abstract

CombAT was a randomised, double-blind study in men (n=4844) aged ≥ 50 years with a clinical diagnosis of benign prostatic hyperplasia (BPH). Patients were randomised to daily tamsulosin 0.4 mg, dutasteride 0.5 mg or both for 4 years. The primary endpoint was time to acute urinary retention (AUR) or BPH-related surgery. Secondary endpoints included BPH clinical progression, symptoms and maximum urinary flow rate. A *post-hoc* analysis of data from the European subgroup was conducted.

A total of 2925 men were randomised to treatment in Europe as part of CombAT (tamsulosin, n=972; dutasteride, n=970; combination, n=983). Combination therapy significantly reduced the relative risk of AUR or BPH-related surgery compared with either monotherapy at 4 years, and also significantly reduced the risk of BPH clinical progression. Combination therapy also provided significantly greater symptom improvement than either monotherapy at 4 years. Safety and tolerability of dutasteride plus tamsulosin was consistent with previous experience of this combination and with the monotherapies.

These data provide further evidence to support the use of long-term combination therapy (dutasteride plus tamsulosin) in men with moderate-to-severe LUTS due to BPH and prostatic enlargement. The results in the European subgroup are generally consistent with those in the overall study population.

Keywords: benign prostatic hyperplasia; CombAT; dutasteride; tamsulosin; combination therapy

Introduction

Benign prostatic hyperplasia (BPH) is a common condition in older men and lower urinary tract symptoms (LUTS) associated with BPH can have a significant impact on the quality of life of patients. BPH is a progressive disease and the risk of bothersome LUTS and complications such as acute urinary retention (AUR) or BPH-related surgery may increase if BPH is untreated.¹⁻³

Current treatment guidelines recommend alpha-blockers and 5-alpha reductase inhibitors (5ARIs), either alone or in combination, as appropriate treatment options for BPH/LUTS.^{4,5} Both classes of drug have been shown to improve LUTS, but have different effects in terms of influencing BPH disease progression.⁶⁻⁸ Alpha-blockers provide rapid symptom relief and reduce the risk of symptomatic progression, while 5ARIs provide long-term symptom relief and a reduction in the risk of progression to worsening symptoms and complications.

CombAT (Combination of Avodart[®] and Tamsulosin) was a global study initiated to assess the efficacy and safety of combining dutasteride (a dual 5ARI) and an alpha-blocker (tamsulosin) in men (n=4844) with moderate-to-severe symptoms of BPH at increased risk of disease progression (age ≥ 50 years, prostate volume ≥ 30 cc and serum prostate-specific antigen [PSA] ≥ 1.5 ng/ml).⁹ Two-year analyses of CombAT data showed that dutasteride plus tamsulosin provided significantly greater improvements in symptoms and patient-reported quality of life versus either monotherapy.^{10,11} 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 also significantly superior to both monotherapies at reducing the relative risk of BPH clinical

progression, and provided significantly greater symptom benefit than either monotherapy.¹²

Here we present 4-year data from a *post-hoc* analysis of the pan-European subgroup from CombAT, which represented 60% of the total study population. This analysis was conducted to determine if there were any differences in outcomes in the European subgroup compared with the overall study population, which also included men from sites in North and Latin America and Asia-Pacific. In addition to age and genetics, it is becoming increasingly recognised that modifiable lifestyle and cultural factors (e.g. obesity, diabetes, physical activity, alcohol intake) may contribute to the development and progression of BPH/LUTS.^{13,14} Therefore, an analysis of the pan-European subgroup from CombAT is of interest. To our knowledge, the present analysis represents the largest assessment of combination therapy in a European population.

Methods

The rationale and design of the CombAT study has been described in detail previously.⁹ Briefly, eligible patients were randomised in a 1:1:1 ratio to receive once-daily double-blind 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. Occurrence of AUR, BPH-related surgery, urinary tract infection, urosepsis and overflow or urge incontinence was assessed every 3 months. The International Prostate Symptom Score (IPSS) questionnaire (including question 8, BPH-related health status) was completed at screening, baseline, and every 3 months, and maximum urinary flow rate (Q_{max}) was measured at screening, baseline,

and every 6 months. Transrectal ultrasound was performed at screening and once a year thereafter to document changes in total prostate volume.

Men aged ≥ 50 years with a BPH clinical diagnosis were eligible for inclusion if they had an IPSS ≥ 12 points, prostate volume ≥ 30 cc, total serum prostate-specific antigen (PSA) ≥ 1.5 ng/ml, and $Q_{\max} > 5$ ml/s and ≤ 15 ml/s with a minimum voided volume ≥ 125 ml. The main exclusion criteria were total serum PSA > 10 ng/ml, history or evidence of prostate cancer, previous prostatic surgery, history of AUR within 3 months of study entry, 5-ARI use within 6 months (or dutasteride use within 12 months) before study entry, or use of an alpha-blocker or phytotherapy for BPH within 2 weeks before study entry.

The primary end point at 4 years was time to first event of AUR or BPH-related surgery, defined as the number of days from the date of first dose of randomised study drug to the date of the initial event. The proportion of subjects experiencing AUR or BPH-related surgery was a supportive end point to the primary analysis. Secondary endpoints at 4 years included BPH clinical progression (defined as one of the following: symptom deterioration by IPSS ≥ 4 points on two consecutive visits; AUR related to BPH; overflow or urge incontinence, recurrent urinary tract infection or urosepsis; or renal insufficiency related to BPH), and changes from baseline in Q_{\max} , International Prostate Symptom Score (IPSS) and IPSS Q8. The primary analysis population was the intent-to-treat population, using a last observation carried forward approach. Similar endpoints were analysed for the pan-European subgroup. These analyses were performed *post-hoc*, and were not part of the protocol-specified primary and secondary endpoint hierarchy ($p < 0.05$).

Results

A total of 2925 men were randomised to treatment in Europe (tamsulosin, n=972; dutasteride, n=970; combination, n=983). Demographics and baseline characteristics of the pan-European subgroup were similar to those of the total study population, except for a higher representation of Caucasian ethnicity in Europe (Table 1).

AUR or BPH-related surgery

AUR or BPH-related surgery occurred in 3.5% of patients treated with combination therapy, 11.9% of patients receiving tamsulosin and 5.8% of patients receiving dutasteride. Combination therapy significantly reduced the relative risk of AUR or BPH-related surgery compared with tamsulosin monotherapy (RRR 72.0% [95% CI: 58.9–80.9%], $p<0.001$) or dutasteride monotherapy (relative risk reduction [RRR] 39.6% [95% CI: 7.6–60.6%], $p=0.019$) (Figure 1).

When AUR and BPH-related surgery were considered separately, combination therapy significantly reduced the relative risk of AUR compared with tamsulosin (RRR 70.3%; $p<0.001$), and non-significantly reduced the relative risk compared with dutasteride (RRR 30.1%; $p=0.23$) (Figure 1). For BPH-related surgery, combination therapy significantly reduced the relative risk compared with both tamsulosin (RRR 76.0%; $p<0.001$) and dutasteride (RRR 47.5%; $p=0.018$).

BPH clinical progression

Combination therapy was also significantly superior to both monotherapies in reducing the incidence of BPH clinical progression (Figure 1). The RRR with combination therapy was 43.0% (95% CI: 27.7–55.1%, $p<0.001$) versus tamsulosin and 32.1% (95% CI: 13.2–46.9%, $p=0.002$) versus dutasteride.

Change in IPSS

The adjusted mean change in IPSS from baseline after 4 years was –6.4 for combination therapy, –4.2 for tamsulosin ($p < 0.001$ versus combination) and –5.7 for dutasteride ($p = 0.007$ versus combination) (Figure 2). Superiority of combination therapy over tamsulosin was observed from month 12, and superiority over dutasteride was observed from month 3.

The adjusted mean change from baseline in BPH-related health status (IPSS Q8) was –1.5 for combination therapy, –1.2 for tamsulosin and –1.3 for dutasteride. The improvement with combination therapy was significantly greater with combination therapy than with tamsulosin ($p < 0.001$) and dutasteride ($p = 0.001$).

Change in Q_{max}

At 4 years, the adjusted mean increase from baseline in Q_{max} was 2.5 ml/s with combination therapy, 0.8 ml/s with tamsulosin ($p < 0.001$ versus combination) and 2.2 ml/s with dutasteride ($p = 0.25$ versus combination) (Figure 3). As a result of these changes, the mean Q_{max} values at month 48 were 13.4, 11.6 and 13.0 in the combination, tamsulosin and dutasteride groups, respectively.

Total prostate volume

The adjusted mean percentage change from baseline in total prostate volume after 4 years was –27.1% with combination therapy, +3.1% with tamsulosin ($p < 0.001$ versus combination) and –27.1% with dutasteride ($p = 1.00$ versus combination).

Safety and tolerability

The occurrence of any adverse event (AE) and serious AEs was similar in the three treatment groups (Table 2). The occurrence of drug-related AEs was significantly

greater with combination therapy than with either monotherapy; however, rates of withdrawal due to drug-related AEs were similar in the three groups. Prostate cancer was reported as an AE in 21 men (2.1%) in the combination therapy group, 27 men (2.8%; $p=0.33$ versus combination) in the tamsulosin group and 17 men (1.8%; $p=0.51$ versus combination) in the dutasteride group. Serum PSA decreased from baseline by a median of 56.8% in the combination group and 55.9% in the dutasteride group, and increased by 18.4% in the tamsulosin group.

There was no difference in overall cardiovascular AEs across the three treatment groups. The incidence of the composite term of cardiac failure was higher in the combination (0.7%) and tamsulosin monotherapy (0.7%) groups than in the dutasteride monotherapy group (0.3%).

Discussion

Combination therapy with dutasteride plus tamsulosin significantly reduced the risk of AUR or BPH-related surgery compared with either monotherapy after 4 years in European men with moderate-to-severe LUTS due to BPH at increased risk of disease progression. In addition, combination therapy significantly reduced the relative risk of BPH clinical progression compared with both monotherapies, and provided significantly greater symptom improvement. These improvements in clinical outcomes with combination therapy are reflected by the significantly greater improvement in BPH-related health status with combination therapy compared with either monotherapy. The results in the pan-European subgroup are generally consistent with those previously reported for the overall study population,¹² and further support the use of dutasteride and tamsulosin combination therapy as a

treatment option in men with LUTS due to BPH and prostatic enlargement at increased risk of disease progression.

Inconsistent with the results from the overall study population, in the present analysis the reduction in the risk of BPH-related surgery with combination therapy achieved statistical significance compared with dutasteride monotherapy. It is possible that this difference reflects the *post-hoc* nature of the present analysis, which involves a smaller number of patients (n=2925) than the overall study group (n=4844) and a different significance level, although the relative risk reduction was higher in the European subgroup (47.5%) than in the overall population (31.1%). Another explanation for this difference is that it reflects regional differences in the patient-physician decision-making process regarding when to perform surgery.

Combination therapy provided significantly greater improvements in IPSS from month 3 versus dutasteride and from month 12 versus tamsulosin, which were maintained until the end of the study at 4 years. Symptom improvement in the first 3 months was more rapid with combination therapy or tamsulosin monotherapy than with dutasteride monotherapy. This is expected, since the clinical effects of 5ARIs are largely thought to be mediated by reductions in prostate volume whereas alpha-blockers improve symptoms by the inhibition of α 1-adrenoceptor-mediated sympathetic stimulation and relaxation of smooth muscle in the prostate and bladder neck.

In addition, there was a reduction in symptom benefit in the tamsulosin group from around one year onwards whereas the levels of symptom benefit observed with combination therapy and dutasteride monotherapy were maintained for the duration of the 4-year study. This may be attributed to the increase in prostate volume

observed in the tamsulosin group. However, the difference in symptom benefit between combination therapy and dutasteride alone at 4 years suggests that tamsulosin remains a significant contributor to long-term symptom benefits when used in combination. A possible explanation for this is that dutasteride allows tamsulosin to maintain its maximum effect on symptoms by preventing the prostate growth that occurs with tamsulosin alone.

Combination therapy significantly improved Q_{max} at month 48 compared to tamsulosin, while the difference compared to dutasteride monotherapy was not statistically significant. The improvement in Q_{max} at month 24 was maintained to month 48 with combination therapy and dutasteride monotherapy, but decreased with tamsulosin monotherapy. These findings are consistent with those from the overall study population.¹²

Combination therapy was generally well tolerated. The most common types of AEs were consistent with previous experience for dutasteride and tamsulosin monotherapies. The significantly greater rate of drug-related AEs in the combination group appears to be largely driven by an increased incidence of ejaculatory disorders, consistent with previous data.^{10,12} However, withdrawal rates due to drug-related AEs were similar across the three treatment groups. The higher incidence of the composite term cardiac failure in the combination and tamsulosin groups is consistent with data from the overall study population.¹² As with the overall study group, the rates of cardiac failure in the present analysis were <1% in all three treatment arms; these rates are lower than the event rate in the placebo arm at year 2 of the pivotal phase 3 studies of dutasteride monotherapy (1.3%), in which alpha-blocker use was not permitted.

A number of studies have assessed the use of drug therapies for the treatment of BPH/LUTS in European men.^{15,16} however, they were observational in nature and therefore are of limited value for evaluation of efficacy. Such studies have shown marked national differences in prescribing patterns, both in individual drug choice and in the use of combination therapies. Future studies will be of interest to determine the impact of data from CombAT on the management of men with BPH/LUTS.

As indicated above, the *post-hoc* nature of this subgroup analysis and the reduced sample size (40% fewer subjects than the overall study group) may be a limitation. Nevertheless, the 2925 subjects included represent a substantial sample size. As suggested previously, the lack of a placebo arm in CombAT represents another possible limitation of the study,¹² raising the theoretical potential for enhanced reporting of subjective outcomes. However, this limitation would apply to all study arms and is unlikely to impact clinical outcomes.

In conclusion, this 4-year analysis of European men in the CombAT study supports the long-term use of combination therapy (dutasteride plus tamsulosin) in men with moderate-to-severe LUTS due to BPH and prostatic enlargement at increased risk of disease progression, in order to provide rapid and durable improvement in symptoms and reduce the risk of BPH disease progression.

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Conflicts of interest: Drs Hailot, Fraga, Maciukiewicz, Pushkar, Tammela, Höfner and Chantada have been investigators in studies sponsored by GlaxoSmithKline. Dr Tammela has acted as an advisor to GlaxoSmithKline. Paul Gagnier and Betsy Morrill are employees of GlaxoSmithKline.

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

	All patients	European subgroup
No. of patients	4844	2925
Mean (SD) age, yrs	66.1 (7.01)	66.0 (6.74)
No. white ethnicity (%)	4259 (88)	2921 (>99)
Mean (SD) IPSS	16.4 (6.16)	16.1 (5.68)
Mean (SD) yrs since first LUTS	5.4 (4.84)	5.1 (4.22)
Prostate volume, cc		
Mean (SD)	55.0 (23.58)	53.6 (20.62)
Median	48.9	48.1
Mean (SD) PSA, ng/ml	4.0 (2.08)	4.0 (2.06)
Mean (SD) Qmax, ml/sec	10.7 (3.62)	10.8 (3.58)
No. sexually active (%)	3529 (73)	2142 (73)
No. previous α -blocker use (%)	2444 (50)	1455 (50)
No. previous 5ARI use (%)	531 (11)	260 (9)

IPSS=International Prostate Symptom Score; LUTS=lower urinary tract symptoms; PSA=prostate-specific antigen; 5ARI=5 α -reductase inhibitor

Table 2. Summary of adverse events

	Combination, % (n=983)	Dutasteride, % (n=970)	Tamsulosin, % (n=972)
Any AE	65	66	63
Any serious AE	18	20	20
Any drug-related AE	23	17*	14*
Any serious drug-related AE	<1	<1	<1
Any AE leading to study withdrawal	12	10	11
Any drug-related AE leading to study withdrawal	5	3	3
Drug-related AEs occurring in $\geq 1\%$ of subjects in any treatment group			
Erectile dysfunction	8	6	4
Retrograde ejaculation	3	<1	<1
Decreased libido	3	3	2
Ejaculation failure	2	<1	<1
Gynaecomastia	2	2	<1
Loss of libido	2	<1	1
Dizziness	2	<1	1
Breast tenderness	1	1	<1
Nipple pain	1	<1	<1
Decreased semen volume	1	<1	<1

*p<0.05 vs Combination

Figure 1. Effect of combination therapy compared with monotherapies on AUR or BPH-related surgery and BPH clinical progression

Figure 2. Adjusted mean change from baseline in IPSS

Figure 3. Adjusted mean change from baseline in Qmax

Figure 1

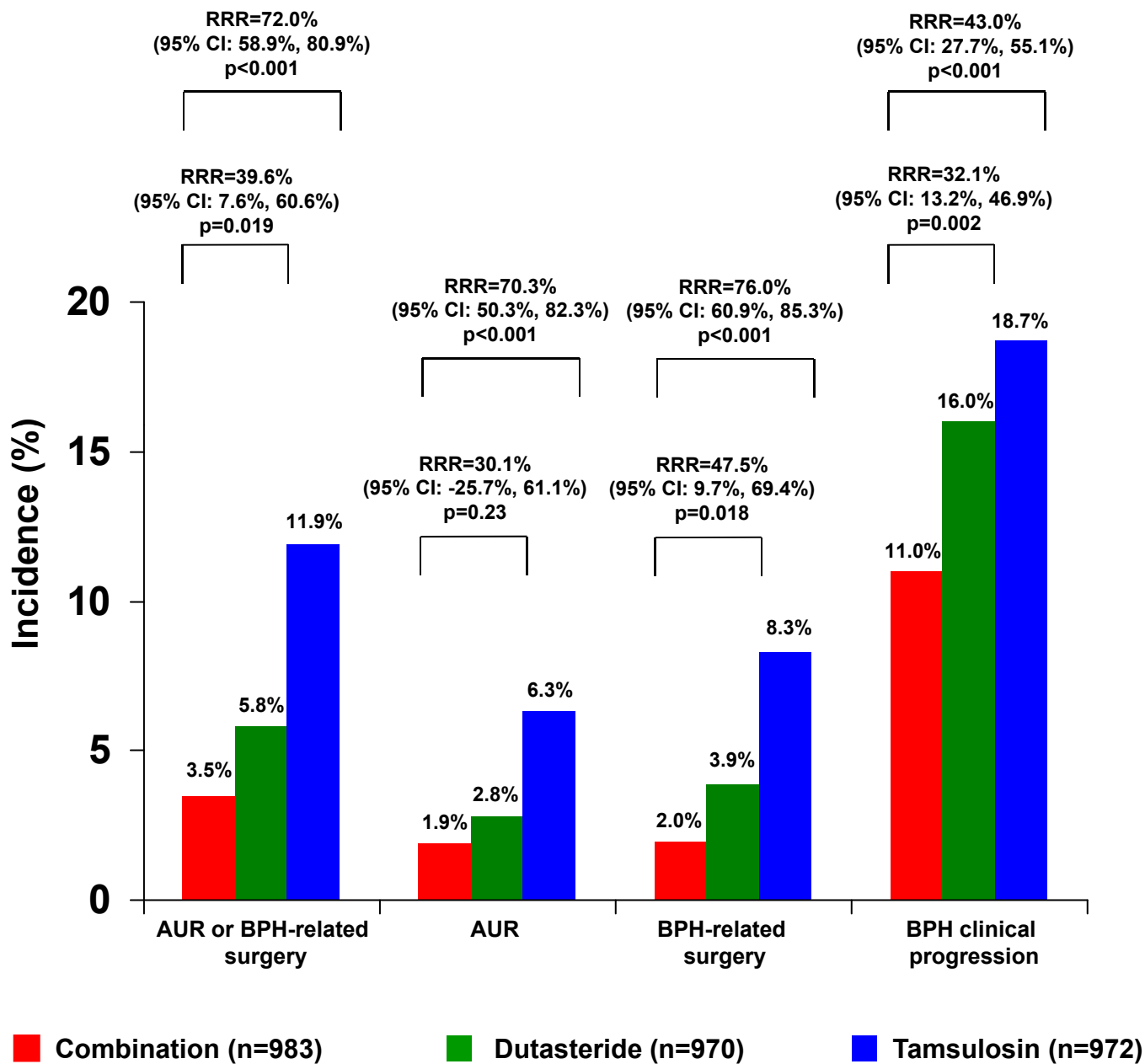


Figure 2

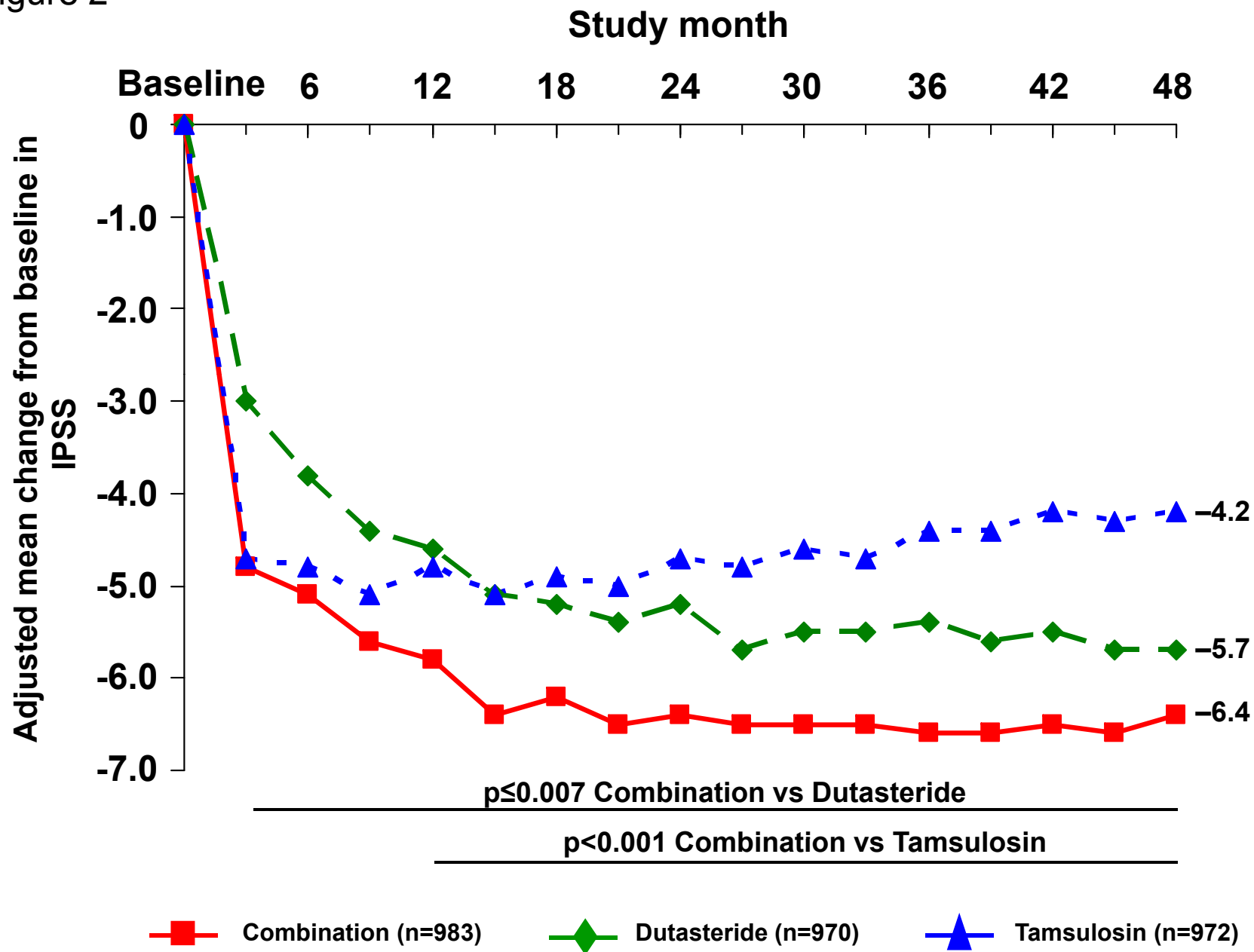


Figure 3

