**European Association of Urology**

Benign Prostatic Hyperplasia

# The Effects of Combination Therapy with Dutasteride and Tamsulosin on Clinical Outcomes in Men with Symptomatic Benign Prostatic Hyperplasia: 4-Year Results from the CombAT Study

*Claus G. Roehrborn [a],\*, Paul Siami [b], Jack Barkin [c], Ronaldo Damião [d], Kim Major-Walker [e], Indrani Nandy [e], Betsy B. Morrill [e], R. Paul Gagnier [e], Francesco Montorsi [f]*
*on behalf of the CombAT Study Group*

[a] Department of Urology, UT Southwestern Medical Center, Dallas, Texas, USA
[b] Deaconess Clinic, Evansville, Indiana, USA
[c] Department of Urology, University of Toronto, Toronto, Ontario, Canada
[d] Urology Department, State University of Rio de Janeiro, Rio de Janeiro, Brazil
[e] Research and Development, GlaxoSmithKline, Research Triangle Park, North Carolina, USA
[f] Department of Urology, Universita Vita Salute San Raffaele, Milan, Italy

## Article info

## Abstract

*Background:* Combination therapy with dutasteride and tamsulosin provides significantly greater benefit than either monotherapy for various patient-reported outcomes in men with moderate-to-severe lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) and prostatic enlargement.
*Objective:* To investigate whether combination therapy is more effective than either monotherapy in reducing the relative risk for acute urinary retention (AUR), BPH-related surgery, and BPH clinical progression over 4 yr in men at increased risk of progression.
*Design, setting, and participants:* The Combination of Avodart® and Tamsulosin (CombAT) study was a 4-yr, multicenter, randomised, double-blind, parallel-group study in 4844 men ≥50 yr of age with a clinical diagnosis of BPH, International Prostate Symptom Score ≥12, prostate volume ≥30 $cm^3$, prostate-specific antigen 1.5–10 ng/ml, and maximum urinary flow rate ($Q_{max}$) >5 and ≤15 ml/s with minimum voided volume ≥125 ml.
*Intervention:* Oral daily tamsulosin, 0.4 mg; dutasteride, 0.5 mg; or a combination of both.
*Measurements:* The 4-yr primary end point was time to first AUR or BPH-related surgery. Secondary end points included BPH clinical progression, symptoms, $Q_{max}$, prostate volume, safety, and tolerability.
*Results and limitations:* 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. Combination therapy provided significantly greater symptom benefit than either monotherapy at 4 yr. Safety and tolerability of combination therapy was consistent with previous experience with dutasteride and tamsulosin monotherapies, with the exception of an imbalance in the composite term of cardiac failure among the three study arms. The lack of placebo control is a study limitation.
*Conclusions:* The 4-yr CombAT data provide support for the long-term use of dutasteride and tamsulosin combination therapy in men with moderate-to-severe LUTS due to BPH and prostatic enlargement.
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\* Corresponding author. Department of Urology, The University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Blvd., J8 142, Moss Clinical Science Building, Dallas, TX 75390-9110, USA. Tel. +1 214 648 2941; Fax: +1 214 648 0365.
E-mail address: claus.roehrborn@utsouthwestern.edu (C.G. Roehrborn).

## 1. Introduction

Benign prostatic hyperplasia (BPH) and associated lower urinary tract symptoms (LUTS) is a progressive disease [1–5]. Medical management of LUTS due to BPH with $\alpha$-blockers and/or 5$\alpha$-reductase inhibitors (5-ARIs) is the first-line treatment; these two drug classes have shown different abilities to influence likelihood of progression [6–8]. The 4-yr Combination of Avodart® and Tamsulosin (CombAT) study was initiated to investigate whether combination therapy with dutasteride and tamsulosin was more effective than either monotherapy in reducing the relative risk for acute urinary retention (AUR), BPH-related surgery, and BPH clinical progression in men with moderate-to-severe LUTS due to BPH who were predicted to be at increased risk of progression by virtue of having a prostate volume $\geq$30 cm$^3$ *and* prostate-specific antigen (PSA) $\geq$1.5 ng/ml [9].

In this paper, we report the 4-yr results of CombAT relating to the risks of AUR, BPH-related surgery, overall clinical progression, and symptom progression, as well as symptom improvement, maximum urinary flow rate ($Q_{max}$) improvement and prostate volume and serum PSA changes.

## 2. Materials and methods

### 2.1. Study design

The design of the multinational, multicenter, randomised, double-blind, parallel-group CombAT study has been previously reported [9–11]. Briefly, eligible subjects were randomised to receive one of the following treatments orally once daily for a period of 4 yr: dutasteride 0.5 mg and tamsulosin 0.4 mg, dutasteride 0.5 mg and tamsulosin-matched placebo, or dutasteride-matched placebo and tamsulosin 0.4 mg. Details of AUR and BPH-related prostatic surgery episodes were recorded at every visit, and the occurrence of recurrent urinary tract infection or urosepsis and/or first episode of incontinence (overflow or urge) was assessed at baseline and every 3 mo. The International Prostate Symptom Score (IPSS) questionnaire (including question 8, BPH-related health status) was implemented at screening, baseline, and every 3 mo, and $Q_{max}$ was measured at screening, baseline, and every 6 mo. Transrectal ultrasound (TRUS) was performed at screening and annually to document change in total prostate volume.

### 2.2. Study population

Men $\geq$50 yr of age with a BPH clinical diagnosis by medical history and physical examination, an IPSS $\geq$12 points, prostate volume $\geq$30 cm$^3$ by TRUS, total serum PSA $\geq$1.5 ng/ml, and $Q_{max}$ >5 ml/s and $\leq$15 ml/s with a minimum voided volume $\geq$125 ml were eligible for inclusion. Principal exclusion criteria were total serum PSA > 10.0 ng/ml, history or evidence of prostate cancer, previous prostatic surgery, history of AUR within 3 mo prior to study entry, 5-ARI use within 6 mo (or dutasteride within 12 mo) prior to entry, or use of an $\alpha$-blocker or phytotherapy for BPH within 2 wk prior to entry.

### 2.3. Study end point and statistical analyses

The primary end point at 4 yr was time to first event of AUR or BPH-related prostatic 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. To address multiplicity, secondary end points were analysed in a predefined hierarchy (Table 1). Additionally, all primary and secondary end points defined and initially tested at 2 yr were included as secondary end points at 4 yr and analysed according to the hierarchy at year 2 [10]: We report IPSS, $Q_{max}$, and prostate volume outcomes in this paper.

The intent-to-treat population was the primary population analysed, consisting of all subjects randomised to double-blind study treatment. The primary comparison was combination versus tamsulosin, for which the study was powered at 94%; a comparison of combination versus dutasteride was also performed. The primary analysis used a log rank test stratified by investigative site cluster. Superiority for combination versus tamsulosin and dutasteride was based on a two-sided $p$ value at $\alpha = 0.01$. The relative risk (hazard ratio) for the treatment effect and associated two-sided 95% confidence intervals were estimated using a Cox proportional hazards model with treatment as the only covariate and stratified by investigative site cluster.

## 3. Results

### 3.1. Subject disposition and demographics

Of the 4844 men randomised to treatment, 3195 (66%) completed the month 48 visit (Fig. 1). A numerically higher rate of discontinuation was observed in the tamsulosin group (39%) compared with the combination (31%) or dutasteride (33%) groups, and more patients in the

**Table 1 – Combination of Avodart® and Tamsulosin study secondary end-point hierarchy**

| Comparison of combination vs tamsulosin | Comparison of combination vs dutasteride |
|---|---|
| Time to BPH clinical progression[*] | Time to BPH clinical progression[*] |
| Time to AUR | The proportion of subjects with symptom deterioration of IPSS $\geq$4 points |
| The proportion of subjects with symptom deterioration of IPSS $\geq$4 points | Time to worsening of urinary incontinence |
| Time to BPH-related prostatic surgery | The proportion of subjects with BPH-related macroscopic haematuria |
| Time to worsening of urinary incontinence | Time to recurrent UTI |
| The proportion of subjects with BPH-related macroscopic haematuria | Time to BPH-related renal insufficiency |
| Time to recurrent UTI | Time to AUR |
| Time to BPH-related renal insufficiency | Time to BPH-related prostatic surgery |
| The proportion of subjects with BPH-related macroscopic haematospermia | The proportion of subjects with BPH-related macroscopic haematospermia |

AUR = acute urinary retention; BPH = benign prostatic hyperplasia; IPSS = International Prostate Symptom Score; UTI = urinary tract infection.
[*] Defined as one of the following: symptom deterioration by IPSS $\geq$4 points on two consecutive visits; BPH-related AUR; BPH-related urinary incontinence; recurrent BPH-related UTI or urosepsis; BPH-related renal insufficiency.