Available online at www.sciencedirect.com
ScienceDirect
Contemporary Clinical Trials 28 (2007) 770–779
Contemporary Clinical Trials
www.elsevier.com/locate/conclintrial

Combination therapy with dutasteride and tamsulosin in men with moderate-to-severe benign prostatic hyperplasia and prostate enlargement: the CombAT (Combination of Avodart® and Tamsulosin) trial rationale and study design ☆

Paul Siami [a,*], Claus G. Roehrborn [b], Jack Barkin [c], Ronaldo Damiao [d], Marek Wyczolkowski [e], Annette Duggan [f], Kim Major-Walker [g], Betsy B. Morrill [h] on behalf of the CombAT study group

[a] *Department of Urology, Welborn Clinic, Evansville, IN, USA*
[b] *Department of Urology, UT Southwestern Medical Center, Dallas, TX, USA*
[c] *Department of Urology, University of Toronto and Male Health Center, Toronto, ON, Canada*
[d] *Serviço de Urologia, Hospital Universitário Pedro Ernesto, UERJ, Rio de Janeiro, RJ, Brazil*
[e] *Department of Urology, Rydygier Memorial Hospital, Krakow, Poland*
[f] *Clinical Development, GlaxoSmithKline, Greenford, United Kingdom*
[g] *Clinical Development, GlaxoSmithKline, Research Triangle Park, Raleigh, NC, USA*
[h] *Department of Biostatistics, GlaxoSmithKline, Research Triangle Park, Raleigh, NC, USA*

Received 5 January 2007; accepted 26 July 2007

Abstract

Benign prostatic hyperplasia (BPH) is a highly prevalent condition in aging men, which can be progressive and lead to acute urinary retention (AUR) and the need for surgery. It is commonly treated with α-blockers and 5α-reductase inhibitors (5ARIs), both of which improve the symptoms of BPH. Long-term treatment with 5ARIs can also reduce the risk of developing AUR and the need for surgery. The landmark Medical Therapy of Prostatic Symptoms (MTOPS) trial demonstrated that over 4 years the combination of the type 2-specific 5ARI, finasteride and the α-blocker doxazosin was more effective than either agent alone in reducing overall clinical progression. Since the initiation of MTOPS, it has been shown that patients with larger prostates and higher prostate-specific antigen (PSA) levels are at greater risk of BPH progression, and are therefore arguably more likely to benefit from combination therapy. The Combination of Avodart and Tamsulosin (CombAT) trial is a 4-year, global, multicenter, randomized, double-blind, parallel-group study designed to investigate the benefits of combination therapy with the dual 5ARI dutasteride and the α-blocker tamsulosin compared with each monotherapy in improving symptoms and long-term outcomes in men with moderate-to-severe symptoms of BPH and prostate enlargement. Symptoms and long-term outcomes (AUR and surgery) will be assessed as separate primary endpoints at 2 and 4 years, respectively. Eligible patients were at least 50 years old with

☆ This study was fully funded by GlaxoSmithKline.
* Corresponding author. Dr Paul Siami, Welborn Clinic, 4411 Washington Avenue, Evansville, IN 47714, USA. Tel.: +1 812 474 7171.
E-mail address: siamip@welbornclinic.com (P. Siami).

1551-7144/$ - see front matter
doi:10.1016/j.cct.2007.07.008

prostate volume ≥30 cm^3 and PSA level ≥1.5 ng/mL. A total of 4838 subjects have been enrolled. This paper describes the rationale, design and baseline data of the CombAT study.

Keywords: Clinical trial; Prostatic hyperplasia; BPH; Prostate enlargement Combination drug therapy; Alpha adrenergic antagonist; Testosterone; DHT; 5-alpha-reductase inhibitors; Prostate; Prostate-specific antigen

1. Introduction

Benign prostatic hyperplasia (BPH) is a common condition in aging men, affecting over half of men in their seventh decade and 90% of men in their eighth and ninth decade [1], with bothersome symptoms reported in nearly 50% of men aged ≥50 years in the general population [2]. The condition is characterized histologically by stromal and epithelial hyperplasia and clinically by lower urinary tract symptoms (LUTS), which are typically divided into irritative (storage) symptoms (i.e. increased frequency, nocturia and urgency) and obstructive (voiding) symptoms (i.e. incomplete emptying, weak stream, intermittency and hesitancy).

The disease is progressive in nature and may lead to the worsening of symptoms and flow rate, and serious complications such as acute urinary retention (AUR) and the need for surgery [3–5]. There is a wealth of evidence that both prostate volume (PV) and serum prostate-specific antigen (PSA) levels are effective predictors of BPH progression [6–9].

Current treatment for BPH comprises two main drug classes: the α-blockers and 5α-reductase inhibitors (5ARIs), with surgery reserved for more severe or complicated cases [10,11]. The α-blockers reduce smooth muscle tone in the prostate and bladder neck, providing a rapid onset of symptom relief and improvement in flow rate. Although they delay the onset of AUR and need for surgery, α-blockers do not reduce the overall risk of these events [12,13]. 5ARIs block the conversion of testosterone to dihydrotestosterone, the primary driver of prostate growth. Both the type 2-specific 5ARI, finasteride, and the dual (both type 1 and type 2) 5ARI, dutasteride, have been shown to provide long-term improvements in symptoms and flow rate and to reduce significantly PV and therefore the risk of BPH progression and the risks of AUR and surgery in men with symptomatic BPH and prostate enlargement [4,14].

Due to their distinct and complementary modes of action, there is a strong rationale for the use of α-blocker and 5ARI combination therapy in patients with bothersome LUTS and prostatic enlargement, and this rationale is now recognized in clinical practice guidelines [10,11].

A landmark study assessing the efficacy and safety of the combination of finasteride and the α-blocker doxazosin *versus* either treatment alone was reported in 2003 [12]. The Medical Therapy Of Prostatic Symptoms (MTOPS) study showed that the long-term (4-year) combination of doxazosin and finasteride provided a significantly greater reduction in the overall incidence of clinical progression and a significantly greater reduction in symptom score than either drug alone, and was well tolerated in men with mild-to-severe symptoms of BPH. Combination therapy and finasteride alone also reduced the long-term risk of AUR and the need for invasive therapy. A subsequent analysis demonstrated that the benefits of combination therapy *versus* the monotherapies were significant in all men with a baseline PV of at least 25 cm^3 [15].

The efficacy and safety of combining the dual 5ARI, dutasteride, and the α-blocker, tamsulosin, were investigated over 36 weeks in The Symptom Management After Reducing Therapy (SMART-1) study [16]. In this short-term study, combination therapy was effective in providing rapid symptom relief and was well tolerated.

1.1. Rationale for the CombAT study

The CombAT (*Comb*ination of *A*vodart and *T*amsulosin) trial was initiated following positive findings from the MTOPS study on the benefits of combination therapy with the type 2-specific 5ARI, finasteride and the α-blocker, doxazosin compared with either monotherapy in men with mild-to-severe BPH. Although long-term direct comparator trials are lacking, dutasteride is known to be a more potent inhibitor of both of the 5α-reductase enzymes, type 1 and type 2, and has been shown to provide greater and more consistent DHT suppression than finasteride [17]. Thus, investigation into the benefits of combination therapy with the dual 5ARI dutasteride and an α-blocker in a large-scale,

long-term study is warranted. Analyses of data from the placebo arms of long-term BPH trials, performed after the initiation of MTOPS, demonstrated the prognostic value of PV and PSA in BPH progression [7,9]; a review of these trials concluded that a PV of at least 30 cm^3 and a PSA level of at least 1.5 ng/mL could identify men at risk of BPH progression [18]. This was supported by the finding in MTOPS that the benefit of combination therapy *versus* the monotherapies was significant in men with a baseline PV $\geq$ 25 cm^3. Thus, the aim of CombAT is to investigate the efficacy and safety of the combination of the dual 5ARI, dutasteride, and the α-blocker, tamsulosin, compared with either drug alone, in men with moderate-to-severe BPH and at risk of disease progression — as identified by age $\geq$ 50 years, moderate-to-severe symptoms, PV $\geq$ 30 cm^3 and PSA $\geq$ 1.5 ng/mL.

This article reports on the study design and selected baseline data from the trial.

1.2. Study design

The CombAT trial is a multicenter, randomized, double-blind, parallel-group study designed to investigate whether combination therapy with dutasteride and tamsulosin is superior to each monotherapy in improving symptoms and long-term clinical outcomes in men with moderate-to-severe symptoms of BPH. The study is being conducted in Europe, North America, Latin America, and Asia Pacific.

Following screening for inclusion, eligible subjects received placebo tamsulosin and placebo dutasteride orally for 4 weeks, to minimize any contribution of the placebo effect to the study results. After this single-blind, placebo run-in period, subjects were randomized in a 1:1:1 ratio, in accordance with a computer-generated randomization schedule, to the double-blind phase and will receive one of the following treatments orally for 208 weeks:

- 0.5 mg dutasteride once daily + 0.4 mg tamsulosin once daily
- 0.5 mg dutasteride once daily + placebo tamsulosin
- 0.4 mg tamsulosin once daily + placebo dutasteride.

Subjects will self-administer the oral drugs on a daily basis and return to the clinic for assessment every 13 weeks post-randomization until week 208. Finally, subjects will return at 16 weeks after the last dose of study medication for a safety follow-up.

The total study duration is up to 229 weeks, from placebo run-in to final safety assessment (Fig. 1).

Separate primary and secondary endpoints will be analyzed at 2 and 4 years. The main aim at each of these time points will be to assess improvement in symptoms (2 years) and time to event/proportion of patients with AUR or undergoing AUR or BPH-related surgery (4 years). For all endpoints, superiority of the combination *versus* each monotherapy will be tested.

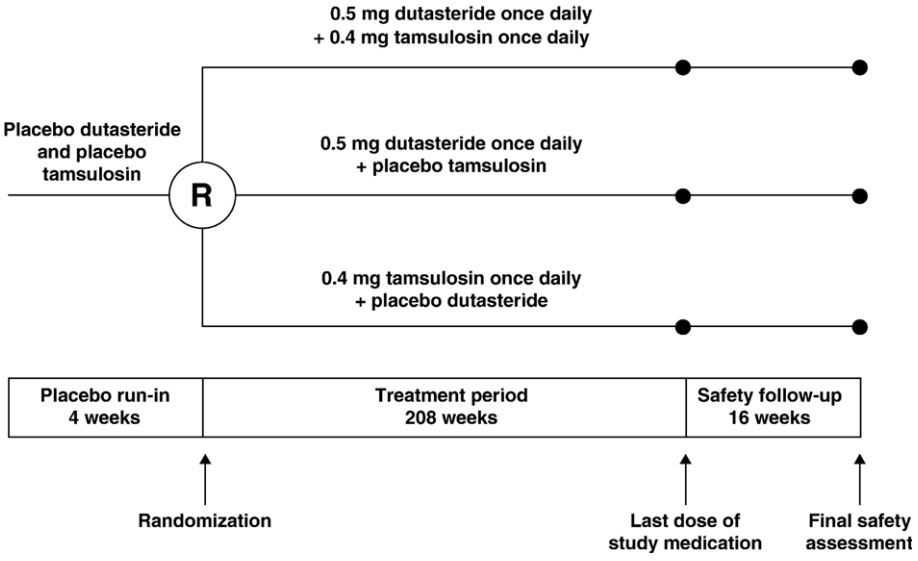

Fig. 1. Schematic of CombAT (Combination of Avodart and Tamsulosin) study design.

1.3. Primary endpoints

At 2 years, the primary endpoint is the change in International Prostate Symptom Score (IPSS) from baseline. The IPSS is essentially the same 7-item instrument as the American Urological Association Symptom Index (AUA-SI) with the addition of an eighth question on quality of life, which is analyzed separately.

At 4 years, the primary endpoint is the time to event and proportion of subjects with AUR or undergoing BPH-related prostatic surgery.

1.4. Secondary endpoints

Secondary endpoints at 2 years are: total PV change from baseline; the proportion of subjects with an IPSS improvement of ≥ 2 and ≥ 3 points from baseline and, separately, a $\geq 25\%$ improvement from baseline in IPSS; change in peak urine flow rate (Q_{max}) from baseline; the proportion of subjects with a Q_{max} improvement of ≥ 3 mL/s and, separately, $\geq 30\%$ improvement from baseline; and changes in transition zone volume from baseline as analyzed in a subset of patients. The within-patient thresholds for improvements in IPSS and Q_{max} are generally considered to be perceptible to an individual patient.

At year 4, secondary endpoints include: time to BPH clinical progression (defined as one of the following: symptom deterioration by IPSS ≥ 4 points on two consecutive visits; AUR related to BPH; incontinence [overflow or urge], recurrent urinary tract infection [UTI] or urosepsis; or renal insufficiency related to BPH); symptom deterioration by IPSS of ≥ 4 units on two consecutive baseline visits; time to event and proportion of subjects with AUR or undergoing BPH-related prostatic surgery; and proportions of patients with BPH-related gross hematuria or hematospermia post-baseline. All 2-year primary and secondary endpoints will also be considered as secondary endpoints at year 4.

Health outcome and safety measures will be assessed at both years 2 and 4.

1.5. Health outcome measures

Health outcomes will be measured using two fully validated instruments, the BPH Impact Index (BII) and BPH-related Health Status (Q8 of IPSS) [10]. In addition, the Patient's Perception of Study Medication (PPSM) questionnaire was developed by GlaxoSmithKline for use in this trial. The PPSM is an instrument designed to quantify patients' expectations and satisfaction with treatment, and will be validated during the study.

All three health outcome measures will be recorded at years 2 and 4. Medical resource use will be captured at every visit, so that at year 4, both 2- and 4-year resource utilization can be analyzed.

1.6. Safety

The following safety parameters will be analyzed: vital signs, clinical laboratory measurements (including hematology, chemistry), change in total serum PSA, post-void residual volume, adverse events, serious adverse events and physical examinations (digital rectal examination [DRE] and evaluation of gynecomastia).

Compliance to study treatment, assessed by capsule count, between visits and the cumulative study drug compliance will be calculated.

1.7. Study management

This study is sponsored and monitored by GlaxoSmithKline. It was designed at GlaxoSmithKline in collaboration with a global panel of BPH experts. The study protocol and any amendments were reviewed and approved by a national, regional or investigational center ethics committee or institutional review board. The protocol has been filed under an Investigational New Drug (IND) application with the FDA and submitted to the national regulatory agency in each of the participating countries. The study is being conducted in accordance with the Good Clinical Practice (GCP) and with the guiding principles of the Declaration of Helsinki. Written informed consent was provided by each subject.

Data management, including validation of the data and quality control, will be performed by Quintiles Ireland Ltd. Adverse events will be recorded and reviewed by the investigators; serious adverse events will be reported to the

regulatory authorities and institutional review board/independent ethics committee in accordance with local regulatory requirements. GlaxoSmithKline will be responsible for the planned statistical analyses of the data.

1.8. Study population

Eight thousand three hundred and eighty eight subjects were screened during a recruitment period of 13 months and 4838 patients with symptomatic BPH have been enrolled and randomized to treatment, with the aim of achieving at least 3150 evaluable subjects. The study is being conducted in 450 centers in 34 countries worldwide, including outpatient clinics, hospital clinics and general surgery practices. Inclusion and exclusion criteria for CombAT can be seen in Table 1. The goal of the inclusion/exclusion criteria was to focus the selection of subjects on those likely to experience BPH progression.

1.9. Study assessments and procedures

Self-administered IPSS and health outcomes questionnaires were administered at Pre-screening (Visit 1a), Baseline (Visit 2) and will be administered at each 13-weekly clinic visit until study completion.

Other key efficacy assessments include the number of episodes of AUR and BPH-related prostatic surgery and resource utilization associated with these events recorded at every visit. Also, urinary flow measurements were made at screening baseline, and every 6 months until the end of the study.

Prostate volume assessments (transrectal ultrasound [TRUS]) will be conducted annually at years 1, 2, 3 and 4 post-randomization. Guidelines for standardized assessment were provided at study start-up and where possible TRUS was performed by the same assessor at each visit for a given patient.

Table 1
Inclusion and exclusion criteria

- **Inclusion criteria**
  - Males, aged ≥50 years
  - Clinical diagnosis of BPH by medical history and physical examination, including a DRE
  - IPSS ≥12 points at screening
  - PV ≥30 cm^3 by TRUS
  - Total serum PSA ≥1.5 ng/mL at screening
  - Q_{max}>5 mL/s and ≤15 mL/s and minimum voided volume of ≥125 mL at screening (based on two voids)
  - Willing and able to give written informed consent and comply with study procedures
  - Fluent and literate in local language with the ability to read, comprehend and record information on the IPSS, BII and PPSM questionnaires.
- **Key exclusion criteria**
  - Total serum PSA>10.0 ng/mL at screening
  - History or evidence of prostate cancer. Patients with suspicious ultrasound or DRE who have had a negative biopsy within the preceding 6 months and stable PSA are eligible for the study
  - Previous prostatic surgery or other invasive procedures to treat BPH
  - History of flexible/rigid cystoscopy or other instrumentation of the urethra within 7 days prior to the screening visit
  - History of AUR within 3 months prior to screening visit
  - Post-void residual volume >250 mL (suprapubic ultrasound) at screening
  - Use of any 5ARI, any drugs with antiandrogenic properties or other drugs noted for gynecomastia effects, or could affect PV, within past 6 months of the historical TRUS or screening visit and throughout the study (other than as study medication). Previous use of dutasteride should not be within 12 months of the baseline or historical TRUS. Chronic use of metronidazole is prohibited
  - Use of phytotherapy for BPH within 2 weeks of screening visit and/or predicted to need phytotherapy during the study
  - Use of any α-adrenoreceptor blockers within 2 weeks of screening visit and/or predicted to need any α blockers other than tamsulosin during the study
  - Use of any α-adrenoreceptor agonists or anticholinergics or cholinergics within 48 h prior to all uroflowmetry assessments
  - History of postural hypotension, dizziness, vertigo or any other signs and symptoms of orthostasis, which in the opinion of the investigator could be exacerbated by tamsulosin and result in putting the subject at risk of injury

BPH=benign prostatic hypertrophy, DRE=digital rectal examination, IPSS=International Prostate Symptom Score, PV=prostate volume, TRUS=transrectal ultrasound, PSA=prostate-specific antigen, Q_{max}=peak urine flow, BII=BPH impact index, PPSM=Patient Perception of Study Medication, AUR=acute urinary retention, 5ARI=5α-reductase inhibitors.

Table 2
Summary of CombAT and MTOPS patient characteristics at baseline

Parameter (mean±SD or %)	CombAT	MTOPS
Number of patients	4838	3047
Age, year	66.1±7.01	62.6±7.3
PV, cm^3	55.0±23.36	36.3±20.1
PSA, ng/mL	4.0±2.06	2.4±2.1
IPSS	16.4±6.19	16.9±5.9
IPSS irritative	7.2±2.94	–
IPSS obstructive	9.2±4.28	–
Q_{max}, mL/s	10.7±3.61	10.5±2.6
Post-void residual volume, mL (range)	67.7±64.83	68.1±82.9
Ethnic origin (%)		
Caucasian	88	82.3
Black	1	8.9
Asian	7	–
American Hispanic	3	7.3
Other	1	1.5
Transition zone volume (cm^3)	29.2±20.43	–
Sexually active (%)	73	–

CombAT=Combination of Avodart and Tamsulosin, MTOPS=Medical Therapy Of Prostatic Symptoms, SD=standard deviation, PV=prostate volume, PSA=prostate-specific antigen, IPSS=International Prostate Symptom Score, Q_{max}=peak urine flow.

Key safety assessments include a physical examination (DRE and qualitative gynecomastia evaluation) at Pre-screening (Visit 1a) and every 6 months until the end of the study. Prostate-specific antigen at screening and annually thereafter, and post-void residual volume at screening (Visit 1a) and every 6 months until the end of the study.

During screening, demographic and baseline data were collected including date of birth, race, height, weight and girth, and a complete physical examination was conducted.

1.10. Statistical analyses

Enrolment of approximately 1500 subjects per treatment group (4500 total) was required to provide 91% power to declare superiority of the combination therapy *versus* both monotherapies at 2 years and 94% power to declare superiority of combination therapy *versus* 0.4 mg tamsulosin at year 4. The power estimate at year 2 is to detect a difference in IPSS change from baseline of 1.0 unit between combination and tamsulosin and 1.5 units between combination and dutasteride, and assumes a withdrawal rate of 25%. These between-group differences were determined based on the reported differences between a number of BPH products and placebo and were considered to

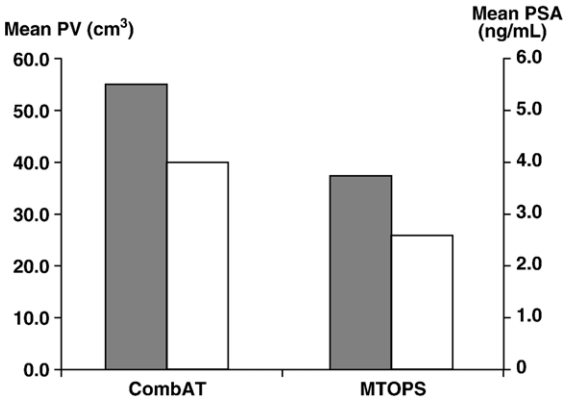

Fig. 2. Comparison of baseline PSA and PV values in the CombAT and MTOPS trials. CombAT=Combination of Avodart and Tamsulosin, MTOPS=Medical Therapy Of Prostatic Symptoms, PSA=prostate-specific antigen, PV=prostate volume.

Table 3
Summary of CombAT patient characteristics at baseline by ethnic group

Parameter (mean±SD or %)	Caucasian (worldwide)	Black	Asian (worldwide)	American Hispanic
Number of subjects	4253	63	325	147
Age, year	66.1±6.98	63.5±6.75	66.7±7.09	65.2±7.60
PV, cm^3	55.7±23.63	49.0±21.13	48.2±18.75	54.2±25.38
Transition zone volume (cm^3)	29.6±21.07	23.0±11.21	27.0±17.19	30.7±20.65
PSA, ng/mL	4.0±2.07	3.5±1.64	4.1±2.13	3.5±1.89
IPSS	16.3±6.07	16.4±6.79	17.8±6.80	17.1±6.75
IPSS irritative	7.1±2.92	7.9±2.97	7.6±3.04	7.2±3.12
IPSS obstructive	9.1±4.21	8.7±4.77	10.0±4.68	9.9±4.66
Q_{max}, mL/s	10.7±3.57	11.7±3.89	10.5±4.05	10.2±3.65
BII	5.2±3.00	5.1±3.18	6.2±3.17	5.6±3.18
Sexually active (%)	74	81	52	78

CombAT=Combination of Avodart and Tamsulosin, SD=standard deviation, PV=prostate volume, PSA=prostate-specific antigen, IPSS=International Prostate Symptom Score, BII=BPH impact index, Q_{max}=peak urine flow.

be clinically meaningful [10]. The power estimate of 94% at year 4 is to detect an incidence of AUR or surgery of 5% with combination compared with 10% with tamsulosin and assumes a withdrawal rate of 35%.

The primary efficacy variable at year 2 is change from baseline IPSS, and at 4 years is time to event/proportion of patients with AUR or undergoing BPH-related surgery. Analysis and reporting of the year 2 data will occur before the completion of the study without breaking the blind.

The primary population of subjects to be analyzed will be the intention-to-treat population, i.e. all subjects randomized to double-blind study treatment after the 4-week placebo run-in.

At year 2, total IPSS, change from baseline IPSS, and percentage change from baseline IPSS will be summarized by treatment group[1] using both the last observation carried forward and At Visit approaches at each scheduled assessment. Changes will be compared using a general linear model with effects for treatment, investigative site cluster and baseline IPSS at alpha=0.01.

At year 4, primary efficacy analyses will be performed using a log rank test stratified by investigative site cluster at alpha=0.01. The hazard ratio for the treatment effect and two-sided 95% confidence intervals will be estimated using a Cox proportional hazards model with treatment as the only covariate.

1.11. Baseline data

Key baseline data are presented in Table 2. Patients have an average age of 66.1 years, ranging from 49.0 to 88.0 years, 73% patients are sexually active and 11% are currently using tobacco. Mean PSA and PV baseline levels are 4.0 ng/mL and 55.0 cm^3, respectively (Fig. 2). Key baseline parameters by ethnic group are displayed in Table 3.

2. Discussion

Rational treatment of BPH should include consideration of symptoms and the associated bother and the risks of long-term outcomes. The CombAT study is designed to investigate the efficacy and safety of the combination of dutasteride and tamsulosin, compared with each monotherapy, in improving symptoms and reducing the risks of AUR and surgery in men with moderate-to-severe symptoms of BPH and at risk of clinical progression. Enrolment in the CombAT trial was completed in 2005.

Prior to MTOPS, a number of combination studies had failed to show a benefit of 5ARI and α-blocker combination treatment over monotherapy, including the Veterans Affairs Study and the Prospective European Doxazosin and Combination Therapy (PREDICT) trial [19,20]. The Veterans Affairs Study, which examined terazosin, finasteride, and the combination of these two agents, also failed to show a significant benefit of finasteride *versus* placebo in improving symptoms and Q_{max} over 1 year of treatment (N=1229). However, the relatively short duration for this type of study compromised the findings. There were similar conclusions for doxazosin and finasteride combination therapy

[1] Investigator is blinded to the treatment.

in PREDICT, with finasteride not providing additional benefit when added to doxazosin, but this study was also limited by the 1-year duration.

The MTOPS study reported that the long-term combination of doxazosin and finasteride resulted in a significantly greater reduction in the risk of overall clinical BPH progression (defined as an increase of ≥4 in AUA symptom score, AUR, urinary incontinence, renal insufficiency, or recurrent UTI) than either drug alone [12]. Combination therapy and finasteride alone also reduced the long-term risk of AUR and the need for invasive therapy. Subsequent analyses of the MTOPS data have confirmed the value of adding a 5ARI to α-blocker therapy, both in terms of improving symptoms and reducing long-term progression, in patients with larger prostates (≥25 cm^3) [15]. However, there is a need for a long-term study examining the combination of a dual 5ARI with an α-blocker in patients at higher than average risk of progression of BPH.

The independent assessment of both symptom relief and risk of AUR and surgery in the CombAT trial, compared with the composite primary endpoint of clinical progression in the MTOPS study, will allow a more transparent examination of which parameter is contributing to the overall effect of treatment. Seventy-eight percent of the total progression events in MTOPS were symptomatic events (worsening of AUA symptom score by ≥4 units), and other components of the composite progression endpoint occurred infrequently (e.g. UTI, renal insufficiency) [12]. Therefore, addressing the BPH endpoints of key interest (IPSS, AUR, surgery) in CombAT is a data-driven and practical approach to assessing benefit. Furthermore, the use (and validation) of the novel PPSM questionnaire in CombAT will provide quantitative data on how changes in symptom scores relate to the way patients feel about their condition. A retrospective psychometric analysis will explore the validity and reliability of the questionnaire, will be completed once the study has been unblinded. The relationship between expectations, clinical efficacy, and treatment satisfaction will also be explored. Futhermore, results from already validated quality of life measures (BII and Q8 of the IPSS) will be available, in addition to a summary of medical resource use at year 2 and year 4.

Based on evidence from a review of clinical trials in the AUA guidelines publication [10], a treatment duration of 4 years was chosen for CombAT. Two years is considered the minimum duration necessary to demonstrate a difference of ≥1 unit between the combination and monotherapy treatment groups in the change in IPSS score from baseline. However, monitoring patients for 4 years will determine whether symptom control is maintained, with no need for data extrapolation. In addition, improvements in symptoms will be assessed at more frequent intervals in CombAT compared with MTOPS thus providing further valuable information on the time of onset of the benefits of combination therapy.

At the time of study initiation, the dose of tamsulosin (0.4 mg/day) used in CombAT was the registered dose for BPH in Europe, and the most frequently prescribed dose in the USA (where 0.4 mg/day and 0.8 mg/day are available but the majority of patients are prescribed the lower dose). The use of doses below this level was not appropriate given the long-term nature of this study. A double-placebo treatment arm was possible for the study; however, it was felt that this would not be ethical as CombAT was specifically designed to recruit men with moderate-to-severe symptoms and a risk of disease progression, and the efficacy and safety profiles of the dutasteride and tamsulosin monotherapies are well defined. The goal of the study is to demonstrate superiority of the combination treatment *versus* the two monotherapies, and the absence of a placebo arm (no placebo effect) may make the findings clearer.

The CombAT study inclusion criteria differ from those of MTOPS in several important ways. Enrolment in MTOPS began in 1993, before baseline PSA and PV were widely recognized as key prognostic factors for BPH progression. In contrast with the MTOPS study and other combination therapy studies, entry thresholds for PV (≥30 cm^3) and PSA (≥1.5 ng/mL) in the CombAT trial have been used to select patients who are at higher risk of clinical progression of BPH (Tables 2 and 4). Thus, mean PSA and PV baseline levels in the CombAT trial were higher than values recorded in the MTOPS trial: 4.0 *versus* 2.4 ng/mL for PSA and 55.0 *versus* 36.3 cm^3 for PV (Table 2, Fig. 2). In MTOPS, the baseline median PV was 31 cm^3 and median PSA was 1.6 ng/mL, which indicates that a significant proportion of men enrolled in that trial would not have qualified for the CombAT study, and with PV and PSA below the thresholds reported to identify men at risk of progression [18], may not, in retrospect, have been ideal candidates for long-term combination therapy [8,10,15]. The CombAT trial therefore provides an opportunity to re-assess the impact of combination therapy in men with enlarged prostates and elevated PSA levels. In other respects, the CombAT and MTOPS populations appear similar, including baseline symptom severity. There were minor differences in ethnic mix as MTOPS was conducted entirely in the USA, while CombAT is a global study.

Differences in key baseline parameters of patients enrolled in CombAT, including PV and PSA, between black and Caucasian study participants are in contrast to the results of several studies, which have reported higher levels in black compared with Caucasian men [21–23]. This may be due to the number of black participants in this study (63) which is too small to draw meaningful conclusions. However, the finding of smaller PV but greater symptom severity in Asian

Table 4
Comparison of entry criteria between CombAT and MTOPS

	CombAT	MTOPS
Age, year	≥50	≥50
Serum PSA, ng/mL	≥1.5 and ≤10	≤10
PV, cm^3	≥30	–
Q_{max}, mL/s	>5 and ≤15	≥4 and ≤15
Minimum voided volume, mL	125	125
Symptom scores		
IPSS	≥12 points	≥8 and ≤30

CombAT=Combination of Avodart and Tamsulosin, MTOPS=Medical Therapy Of Prostatic Symptoms, PSA=prostate-specific antigen, PV=prostate volume, Q_{max}=peak urine flow, IPSS=International Prostate Symptom Score.

men is in agreement with the findings of other studies [24]. In addition, among the four ethnic groups, Asian patients were the least sexually active and had the highest BII and IPSS (obstructive symptom) scores, compared with black patients who had the lowest IPSS (obstructive symptom) score, the highest Q_{max} and were the most sexually active.

A causal relationship between the presence of the metabolic syndrome, its associated components, and BPH, has been postulated [25]. A separate analysis of baseline data from 4820 men enrolled in CombAT found that higher body mass index was associated with other components of the metabolic syndrome such as higher systolic blood pressure and diastolic blood pressure, elevated fasting glucose, insulin, and triglyceride levels [26]. Higher body mass index was also associated with greater total prostate and transition zone volume, higher Q_{max} and more severe irritative LUTS. These findings suggest that there may be a link between high insulin levels (and other aspects of the metabolic syndrome), and LUTS associated with BPH, and warrant further investigation.

In conclusion, the CombAT trial is the first long-term study to investigate the benefits of combination therapy with the dual 5ARI, dutasteride, and α-blocker, tamsulosin, and takes the next major step in assessing the overall value of 5ARI and α-blocker combination therapy compared with the monotherapies in men with symptomatic BPH and prostate enlargement. Given the larger prostates and higher PSA values at baseline in this population compared with the MTOPS population, CombAT may result in a greater understanding of how to manage patients at high risk of clinical progression of BPH.

Acknowledgements

The authors wish to thank their colleagues in the CombAT study research group, including centers in the following countries (number of centers): Argentina (5), Belgium (9), Brazil (6), Bulgaria (5), Canada (32), Czech Republic (6), Denmark (4), Estonia (4), Finland (5), France (57), Germany (47), Greece (5), Hungary (3), Israel (6), Italy (19), Korea (5), Lithuania (3), Mexico (4), Netherlands (18), Norway (9), Philippines (2), Poland (5), Portugal (5), Puerto Rico (2), Romania (6), Russian Federation (9), Slovakia (7), South Africa (4), Spain (31), Taiwan (7), Thailand (4), Turkey (3), United Kingdom (9), United States (99).

Medical writing support was provided by Cheryl Wright at Prime Medica during the preparation of this paper, supported by GlaxoSmithKline. Responsibility for opinions, conclusions and interpretation of data lies with the authors.

References

[1] National Kidney and Urologic Diseases Information Clearinghouse (NKUDIC). Information accessed September 2006. Available at: http://kidney.niddk.nih.gov/kudiseases/pubs/prostateenlargement.
[2] Napalkov P, Maisonneuve P, Boyle P. Worldwide patterns of prevalence and mortality from benign prostatic hyperplasia. Urology 1995;46(3 Suppl A):41–6.
[3] Barry MJ, Fowler Jr FJ, Bin L, et al. The natural history of patients with benign prostatic hyperplasia as diagnosed by North American urologists. J Urol 1997;157(1):10–4.
[4] McConnell JD, Bruskewitz R, Walsh P, et al. The effect of finasteride on the risk of acute urinary retention and the need for surgical treatment among men with benign prostatic hyperplasia. Finasteride long-term efficacy and safety study group. N Engl J Med 1998;338(9):557–63.
[5] Jacobsen SJ, Jacobson DJ, Girman CJ, et al. Natural history of prostatism: risk factors for acute urinary retention. J Urol 1997;158(2):481–7.
[6] Marberger M, Harkaway R, de la Rosette J. Optimising the medical management of benign prostatic hyperplasia. Eur Urol 2004;45(4):411–9.
[7] Roehrborn CG, Boyle P, Bergner D, et al. Serum prostate-specific antigen and prostate volume predict long-term changes in symptoms and flow rate: results of a four-year, randomized trial comparing finasteride versus placebo. PLESS Study Group. Urology 1999;54(4):662–9.

[8] Crawford ED, Wilson SS, McConnell JD, et al. Baseline factors as predictors of clinical progression of benign prostatic hyperplasia in men treated with placebo. J Urol 2006;175(4):1422–6.
[9] Roehrborn CG. Definition of at-risk patients: baseline variables. BJU Int 2006;97(Suppl 2):7–11.
[10] American Urological Association. Management of BPH clinical guideline. 2003. Updated 2006. Accessed March 2006. Available at: http://www.auanet.org/guidelines/bph.cfm.
[11] European Association of Urology. EAU guidelines on benign prostatic hyperplasia. 2004. Accessed March 2006. Available at: http://www.uroweb.org/files/uploaded_files/BPHDec2004webversion.pdf.
[12] McConnell JD, Roehrborn CG, Bautista OM, et al. The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia. N Engl J Med 2003;349(25):2387–98.
[13] Roehrborn CG. Alfuzosin 10 mg once daily prevents overall clinical progression of benign prostatic hyperplasia but not acute urinary retention: results of a 2-year placebo-controlled study. BJU Int 2006;97(4):734–41.
[14] Roehrborn CG, Boyle P, Nickel JC, Hoefner K, Andriole G. Efficacy and safety of a dual inhibitor of 5-alpha-reductase types 1 and 2 (dutasteride) in men with benign prostatic hyperplasia. Urology 2002;60(3):434–41.
[15] Kaplan SA, McConnell JD, Roehrborn CG, et al. Combination therapy with doxazosin and finasteride for benign prostatic hyperplasia in patients with lower urinary tract symptoms and a baseline total prostate volume of 25 ml or greater. J Urol 2006;175(1):217–20.
[16] Barkin J, Guimaraes M, Jacobi G, et al. Alpha-blocker therapy can be withdrawn in the majority of men following initial combination therapy with the dual 5alpha-reductase inhibitor dutasteride. Eur Urol 2003;44(4):461–6.
[17] Clark RV, Hermann DJ, Cunningham GR, et al. Marked suppression of dihydrotestosterone in men with benign prostatic hyperplasia by dutasteride, a dual 5alpha-reductase inhibitor. J Clin Endocrinol Metab 2004;89(5):2179–84.
[18] Bartsch G, Fitzpatrick JM, Schalken JA, et al. Consensus statement: the role of prostate-specific antigen in managing the patient with benign prostatic hyperplasia. BJU Int 2004;93(Suppl 1):27–9.
[19] Lepor H, Williford WO, Barry MJ, Haakenson C, Jones K. The impact of medical therapy on bother due to symptoms, quality of life and global outcome, and factors predicting response. Veterans Affairs Cooperative Studies Benign Prostatic Hyperplasia Study Group. J Urol 1998;160(4):1358–67.
[20] Kirby RS, Roehrborn C, Boyle P, et al. Efficacy and tolerability of doxazosin and finasteride, alone or in combination, in treatment of symptomatic benign prostatic hyperplasia: the Prospective European Doxazosin and Combination Therapy (PREDICT) trial. Urology 2003;61(1):119–26.
[21] Fowler Jr JE, Bigler SA, Kilambi NK, Land SA. Relationships between prostate-specific antigen and prostate volume in black and white men with benign prostate biopsies. Urology 1999;53(6):1175–8.
[22] Kaplan SA, Reis RB, Staimen VB, Te AE. Is the ratio of transition zone to total prostate volume higher in African-American men than in their Caucasian or Hispanic counterparts? Br J Urol 1998;82(6):804–7.
[23] Roehrborn C, Ray P, Gittelman M, et al. Racial differences in prostate volume and PSA measures: analysis of baseline data from the Phase III dutasteride studies. J Urol 2003;169:365.
[24] Platz EA, Kawachi I, Rimm EB, Willett WC, Giovannucci E. Race, ethnicity and benign prostatic hyperplasia in the health professionals follow-up study. J Urol 2000;163(2):490–5.
[25] Hammarsten J, Hogstedt B, Holthuis N, Mellstrom D. Components of the metabolic syndrome-risk factors for the development of benign prostatic hyperplasia. Prostate Cancer Prostatic Dis 1998;1(3):157–62.
[26] Roehrborn C, Schulman C, Arrosagarai P, et al. Baseline data from the Combination of Avodart and Tamsulosin (CombAT) trial: relationships between body mass index (BMI) and LUTS/BPH measures. Eur Urol Suppl 2006;5:195.