Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Dutasteride

Proprietary Product Name: Avodart

Sponsor: GlaxoSmithKline Australia Pty Ltd

January 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	Extension of Indications
Decision:	Approved
Date of Decision:	22 September 2010
Active ingredient(s):	Dutasteride
Product Name(s):	Avodart
Sponsor's Name and Address:	GlaxoSmithKline Australia Pty Ltd PO Box 18095 Melbourne Vic 3067
Dose form(s):	Capsules
Strength(s):	500 µg
Container(s):	Blister packs
Pack size(s):	Packs of 30 and 90
Approved Therapeutic use:	Use as monotherapy for the management of symptomatic benign prostatic hyperplasia (BPH) or as combination therapy with an alpha blocker which is approved for use in BPH and which has been dose titrated in accordance with the relevant recommendations in the product information for that alpha blocker.
Route(s) of administration:	Oral
Dosage:	The recommended dose is one 500 µg capsule daily.
ARTG Number (s)	90434

Product Background

Benign prostatic hyperplasia (BPH) is a chronic and progressive disease, and is the most common benign neoplasm in ageing males. Pathological changes were found in 88% of men ≥80 years, and symptoms have been reported in nearly 50% of men over 50 years of age.[1] The cause of BPH is age related prostate growth which is stimulated by dihydrotestosterone (DHT), which is formed from testosterone by the action of 5α-reductase isoenzymes type 1 and 2. This prostatic growth may eventually lead to urethral obstruction, causing lower urinary tract symptoms (LUTS), including both voiding symptoms (for example, hesitancy, weak stream, terminal dribbling) and storage symptoms (urgency, frequency, nocturia).

The progressive nature of the disease leads to increased need for surgery and episodes of acute urinary retention (AUR).[2] There are two components that lead to symptoms. There is a static component that is attributed to the increased pressure in the prostatic urethra secondary

[1] Napalkov P, Maisonneuve P, Boyle P. Worldwide patterns of prevalence and mortality from benign prostatic hyperplasia. Urology 1995; 46: 41-46.
[2] 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. N Eng J Med 1998; 338: 557-563.

to obstruction caused by hyperplasia of the prostatic tissue. There is also a dynamic component which is influenced by the adrenergic tone of the prostatic stromal smooth muscle and bladder neck.

The aim of therapy is to improve symptoms and quality of life, and also to prevent complications such as AUR and upper urinary tract dilatation. Current treatment modalities include pharmacotherapy, minimally invasive therapy and conventional surgical therapy.[3,4]

Current pharmacological treatments recommended by guidelines include alpha blockers and 5α-reductase inhibitors (5ARIs). Alpha blockers target the dynamic component of the disease by inhibiting alpha-1 adrenergic receptors in the prostate smooth muscle and bladder neck, thereby relaxing constriction around the prostatic urethra. This leads to improvement in LUTS and the onset is relatively rapid, usually within 2-4 weeks.[5,6]Alpha blockers can therefore provide rapid relief of symptoms, but have not been shown to delay disease progression.

5ARIs inhibit the conversion of testosterone to DHT, which is the primary stimulator of prostate growth. Lowering DHT leads to reduction of prostate volume, leading to improvement in symptoms, improvement in urinary flow, reduction in the risk of longer term complications such as AUR, and reduction in need for BPH related surgery.[7] Dutasteride is a potent and selective inhibitor of type 1 and type 2 5α-reductase isoenzymes, and has been shown to reduce intraprostate and serum DHT by up to 90% within 2 weeks. However, it may take up to 6 months for improvement in symptoms to be noted.[8]

Therefore combining an alpha blocker with a 5ARI is considered an option for providing early onset of symptom relief and prolonged clinical benefit. The combination of an a 5ARI (finasteride) and an alpha blocker (doxazosin) over 4 years has been shown in a double blind placebo controlled study to improve symptoms and reduce risk of overall progression significantly more than placebo or either drug alone, in men with mild to severe BPH.[9] Similarly, co-administration of dutasteride 500 µg and tamsulosin 400 µg has been shown to provide a greater degree of symptom improvement compared with either monotherapy over 1-year and 2-year periods.[10] The Current European Association of Urology (EAU) guidance

[3] 'Minimally invasive therapy' refers to laser therapy, transurethral needle ablation of the prostate (TUNA), transurethral electrovaporization of the prostate, hyperthermia, high intensity focused ultrasound (HIFU), intraurethral stents and transurethral balloon dilatation of the prostate.

[4] 'Conventional surgical therapy' refers to transurethral resection of the prostate (TURP), transurethral incision of the prostate (TUIP) and open simple prostatectomy.

[5] Beduschi M, Beduschi R, Oesterling JE. Alpha-blockade therapy for benign prostatic hyperplasia: from a nonselective to a more selective alpha1a-adrenergic antagonist. Urology 1998; 51: 861-872.

[6] Clifford GM, Farmer RDT. Medical therapy for benign prostatic hyperplasia: a review of the literature. Eur Urol 2000; 38: 2-19.

[7] Kirby R, Fitzpatrick J, Kirby M, Fitzpatrick A. Development of prostatic disease. In: Shared care for prostatic disease. Isis Medical Media 1994: 21-35.

[8] Avodart (dutasteride): Summary of Product Characteristics, 2008.

[9] McConnel 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 Eng J Med 2004; 340: 2387-2398.

[10] Roehrborn CG, Saimi P, Barkin J et al. The effects of dutasteride, tamsulosin and combination therapy on lower urinary tract symptoms in men with benign prostatic hyperplasia and prostatic enlargement: 2-year results from the CombAT study. Urology 2008; 179: 616-621.

states "Recommendation: The combination therapy with 5ARIs and alpha blockers seems to be more beneficial and durable than monotherapy by either one of these drugs".[11]

The drug related symptom relief obtained from 5ARIs takes longer to be perceived by the patient than that which is attainable with an alpha blocker. Therefore there is a possibility that patients may not persist with a 5ARI for long enough to obtain the benefits of longer term delay of disease progression. Combining dutasteride with an alpha blocker does not only provide the additive benefit of the two drugs, but could ensure that the patient associates both medications with early symptomatic relief, and would therefore persevere with treatment for sufficient time for the 5ARI to modify the underlying condition and reduce risk of disease progression.

The current approved indications for dutasteride are:

Treatment of patients with symptomatic benign prostatic hyperplasia (BPH) with an enlarged prostate.

The recommended dose is one capsule of dutasteride (500 µg) taken orally per day, alone or in combination with the alpha-1 blocker tamsulosin (400 µg).

The proposed wording of the new indication is:

Avodart, as monotherapy or in combination with an alpha blocker, is indicated for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate.

This submission is closely related to another submission, PM-2009-01559-3-3, evaluated by the TGA at the same time, for the registration of a new fixed-dose combination of dutasteride 500 µg and tamsulosin 400 µg in the one capsule, Duodart, again to assist in the treatment of BPH.

Regulatory Status

The product received initial ARTG Registration on 14 November 2002 for the treatment of BPH.

The application to register the new indication for the co-administration of dutasteride and tamsulosin (an alpha blocker) has been approved in the USA on 19 June 2008, the European Union (EU) (via the mutual recognition procedure) on 18 April 2008, Canada on 23 November 2009 and Switzerland on 16 December 2008.

The indication in the EU is:

- *Treatment of moderate to severe symptoms of benign prostatic hyperplasia (BPH).*
- *Reduction in the risk of acute urinary retention (AUR) and surgery in patients with moderate to severe symptoms of BPH.*

The indication in the USA is:

In combination with the alpha blocker tamsulosin is indicated for the treatment of symptomatic BPH in men with an enlarged prostate.

The indication in other international markets is:

[11] Maderbacher S, Allivizatos G, Nordling J et al. EAU 2004 Guidelines on assessment, therapy and follow-up of men with lower urinary tract symptoms suggestive of benign prostatic obstruction (BPH guidelines). Eur Urol 2004; 46: 547-554.

In combination with the alpha blocker tamsulosin, treats and prevents progression of benign prostatic hyperplasia (BPH) by reducing prostate size, alleviating symptoms and improving urinary flow.

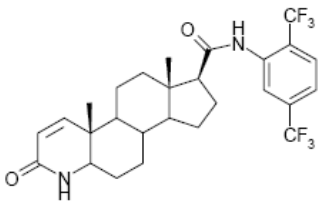
Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Drug Product

There is no proposed change in formulation. It is supplied as soft gelatine capsules containing 500 µg of dutasteride for oral administration. Dutasteride is a white to pale yellow powder, insoluble in water and soluble in organic solvents, dimethyl sulfoxide, acetone, methanol, ethanol and isopranol. The chemical structure is:



Dutasteride

CAS No.: 164656-23-9

Quality Summary and Conclusions

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical Findings

Introduction

The sponsor's application seeks approval to extend the indications for dutasteride (Avodart) to include use as monotherapy or in combination with an alpha blocker for the treatment of BPH in men with an enlarged prostate.

The sponsor has previously submitted a comprehensive dossier of studies supporting the use of dutasteride for the treatment of BPH. New data in the current submission was limited to minor studies examining:
1) plasma-protein binding interactions of dutasteride with various anticoagulants (with supportive analytical methods), and
2) *in vitro* metabolism of dutasteride by SRD5A1 and SRD5A2.[12] The nonclinical package also included an amended toxicology report for a previously evaluated male rat fertility study plus 17 literature references cross-referenced to the sponsor's *Nonclinical Overview.*

No nonclinical studies were submitted that used a combination of dutasteride and an alpha blocker. The sponsor justified the absence of these studies by reference to the European Medicines Agency (EMA) guideline adopted by the TGA and consideration of the following factors:[13]

[12] Steroid 5-alpha-reductase (SRD) catalyzes the conversion of testosterone into the more potent androgen, dihydrotestosterone (DHT). There are 2 isoforms of the enzyme: SRD5A1 and SRD5A2

[13] EMEA, Committee for Medicinal Products for Human Use (CHMP), 24 January 2008. Guideline on the Non-Clinical Development of Fixed Combinations of Medicinal Products, CHMP/SWP/258498/2005.

- Extensive clinical experience; and
- The absence of nonclinical signals that indicate the potential for additive or synergistic toxicity.

The sponsor provided a justification for the absence of combination studies to EU regulatory agencies and it was agreed that additional nonclinical studies were not warranted. One of the EU agencies noted that the age of the tamsulosin data package (many studies pre-1990) meant that many parts of the nonclinical data package were not in accordance with modern standards. It was suggested that any gaps in such data that were not superseded by clinical data should be updated according to scientific and regulatory developments since the time of the original submission. While no original pharmaco-toxicological data for alpha blockers were submitted in this data package, 17 relevant, modern literature references were provided, 13 of which related to alpha blockers, with several pertaining specifically to tamsulosin. Moreover, reference was made to the US Food and Drug Administration (FDA) review of tamsulosin which is available in the public domain.

Pharmacology

Potential pharmacodynamic interactions

Nonclinical pharmacodynamic interaction studies were not performed with dutasteride and an alpha blocker.

Dutasteride and alpha blockers are unlikely to interact pharmacodynamically due to their fundamentally different mechanisms of action which occur at different target sites: dutasteride inhibits SRD5A2 activity (and hence DHT-induced hyperplasia) in prostatic glandular tissue while alpha-1 adrenergic blockers target receptors on prostatic stromal smooth muscle and the bladder neck, thus relaxing the constriction of the prostatic urethra.

The potential for pharmacodynamic interactions on the cardiovascular system between alpha blockers and dutasteride appears to be low. Alpha blockers such as tamsulosin cause well known dose-dependent decreases in blood pressure in experimental animals and humans while dutasteride had little effect on major cardiovascular parameters (including electrocardiogram [ECG]) in dogs at the maximum plasma concentration (C_{max}) levels of 15 to 30 times that anticipated in humans at the maximum recommended human dose (MRHD). QT prolongation with the combination is not expected as tamsulosin causes little hERG inhibition (hERG median inhibitory concentration [IC_{50}] 105 µM) and dutasteride tends to shorten, rather than prolong action potentials in isolated dog Purkinje fibres.

According to the sponsor's *Nonclinical Overview*, clinical studies with the dutasteride/tamsulosin combination have shown no increase in postural hypotension, no QT prolongation and no effect of tamsulosin on dutasteride's suppression of DHT levels.

Pharmacokinetics

Potential Pharmacokinetic interactions

Nonclinical pharmacokinetic interaction studies were not performed with dutasteride and an alpha blocker. The EU guideline adopted by the TGA notes:[14]

"Provided that the pharmacokinetics of the single components are adequately characterised in animals, including the profile for enzyme induction and inhibition and drug-drug interactions,

[14] EMEA, Committee for Medicinal Products for Human Use (CHMP), 13 October 2005. Note for Guidance of Fixed Combination Medicinal Products, CPMP/EWP/240/95.

additional non-clinical documentation on pharmacokinetic interactions is generally not needed."

Protein binding for dutasteride was high (>99.5%) across all species tested, including humans while that for tamsulosin was moderately high (80-82% in rats, 90 to 93% in dogs and 94-99% in humans). *In vitro* studies showed that:
1) dutasteride neither displaced nor was displaced from human serum proteins by warfarin, diazepam or phenytoin, or by acenocoumarol or phenprocoumon; and
2) tamsulosin neither displaced nor was displaced from human serum proteins by amitryptiline, diclofenac, glyburide, simvastatin plus metabolite, warfarin, diazepam, propranolol, trichlormethiazide or chlormadinone.

Previous applications have shown that dutasteride undergoes oxidative metabolism to various hydroxylated metabolites by cytochrome P450 (CYP) 3A4 and CYP3A5 while data in the current application also suggests that SRD5A1 and SRD5A2 may also contribute by generating the metabolite 1,2-dihydrodutasteride. Tamsulosin is metabolised by CYP3A4 and CYP2D6.

Overall, it can be concluded that co-prescription of dutasteride and tamsulosin is unlikely to yield clinically significant pharmacokinetic interactions as neither compound has been shown to be an inducer or inhibitor of hepatic metabolising enzymes and clinical data have shown no effect of dutasteride on the steady-state pharmacokinetics of tamsulosin.

Toxicology

Potential toxicological interactions

Nonclinical toxicological interaction studies were not performed with dutasteride and an alpha blocker. However, the toxicology of the individual components has been previously well characterised in previous applications.

General toxicity

Dutasteride was relatively well tolerated in the rat (and mouse) toxicity studies, with findings primarily reflecting pharmacological activity (that is, prostate/seminal vesicle atrophy and reduced secretion). Reversible neurological signs indicative of central nervous system (CNS) toxicity (for example, unsteady gait, incoordination, shaking/tremors) were observed at higher doses (10-50 mg/kg/day) in the dog studies of 26 and 53 weeks duration, and to a lesser extent in rats. However, such effects were only evident at relative systemic exposure levels (based on the minimum plasma concentration [C_{trough}]) more than 100 to 200 times that anticipated at the maximum recommended human dose.

The toxicity profile of tamsulosin in animals was typical of that observed with other alpha-1-adrenoceptor antagonists currently registered in Australia. Toxic effects such as decreased salivation, intermittent tremors, hypoactivity, reduced heart rates, ECG changes and decreases in body weight gain were only seen in dogs at more than 500 times the anticipated human exposure (based on the area under the plasma concentration time curve [AUC]).

Given that signs of overt toxicity were only observed at very high exposure margins for both drugs, the potential for toxicological interactions should be low with combined use.

Genotoxicity and Carcinogenicity

A standard battery of genotoxicity tests revealed no signals of concern for either drug.

Rodent carcinogenicity studies with dutasteride showed an increase in Leydig cell tumours at high relative systemic exposure margins (123-fold at the No Observable Effect Level [NOEL] in mice) which was attributable to chronic stimulation by elevated luteinising

hormone (LH) resulting from pharmacological perturbation of the hypothalamic-pituitary-testes axis. This effect has also been seen with finasteride and has been shown to be rodent-specific and therefore not relevant to humans.

Rodent carcinogenicity studies with tamsulosin were complicated by tamsulosin's significant dopamine D2-receptor antagonist effects, with much of the treatment-related pathological changes observed in animals (including increased mammary tumours in female rats and mice) being due to the hyperprolactinaemic activity of the drug. Male animals were much less sensitive to the hyperprolactinaemic effects of tamsulosin than females and it is noted that co-prescription of dutasteride and tamsulosin will be contraindicated in women due to the risk of dutasteride exposure to the male fetus (see below).

The overall potential of co-prescribed dutasteride/tamsulosin should be low as the former decreases prostate hypertrophy and is therefore more likely to decrease subsequent carcinogenic activity.

Reproductive Toxicity

Co-prescription of dutasteride and an alpha blocker is only indicated for men; women are not included in this indication and the use of this combination is clearly contraindicated for women. Therefore no combination embryofetal development studies were necessary.

The reversible impairment of male fertility in the rodent by both dutasteride and tamsulosin is consistent with their pharmacological effects. Dutasteride's effect is related to a rodent-specific effect related to the failure to form copulatory plugs and is not relevant to humans. Tamsulosin, like other alpha-1-adrenoceptor antagonists, impairs ejaculation, an effect which has been noted clinically.

Feminisation of male fetuses after treatment of pregnant rats and rabbits with dutasteride was observed in previous studies; an expected response to a SRD5A2 inhibitor. A NOEL was not established in either species and use of dutasteride is contraindicated in pregnancy. Nevertheless, rhesus monkey fetal development was unaffected by low intravenous (IV) maternal doses (about 45-260 ng/kg/day), which were high multiples of likely human female exposure via the semen of treated males.

Tamsulosin, at oral doses causing maternal toxicity, was not embryotoxic or teratogenic when administered during gestation in rats (doses up to 300 mg/kg/day) or rabbits (doses up to 50 mg/kg/day).

Taken together, the results above suggest no additional cause for concern for co-prescription outside of the issues that are currently well known for the individual drugs (for example, impairment of ejaculation by an alpha blocker).

Nonclinical Summary and Conclusions

Nonclinical studies using a combination of dutasteride and an alpha blocker were not submitted. The sponsor's *Nonclinical Overview* and supportive documentation were focused on co-prescription of dutasteride and tamsulosin only (and not any other currently registered alpha blockers).

The sponsor provided an acceptable justification for the absence of nonclinical combination studies by reference to the appropriate TGA-adopted EU guideline and consideration of extensive clinical experience with co-administration of the products. Moreover, both dutasteride and tamsulosin have been previously evaluated individually in nonclinical development programs, and the potential for adverse pharmacodynamic, pharmacokinetic or toxicological interactions would appear to be low.

The proposed indication for use of dutasteride with an alpha blocker is too broad as this submission was focused on the specific co-administration of dutasteride with tamsulosin. Therefore, there are no objections, on nonclinical grounds, to the co-prescription of dutasteride and tamsulosin for the treatment of BPH. The use of dutasteride with other alpha-1-adrenergic blockers is not supported by the current data package.

IV. Clinical Findings

Introduction

The application seeks to extend the current indications for Avodart (dutasteride) to include co-administration of dutasteride with an alpha blocker to assist in treatment of benign prostatic hyperplasia. Support for the role of each of the individual components in the treatment of BPH has been previously established as part of their respective development programs, and is not evaluated in this report.

There was one clinical pharmacology study (ARIA1011) and three Phase III clinical studies to support the efficacy and safety of co-administration of dutasteride and tamsulosin. Study ARI40005 was a pre-determined interim 2-year analysis of a long-term pivotal study. Supporting data was presented in studies ARI40002 and ARI40013.

Tamsulosin was selected as the alpha blocker of choice for co-administration because there is no need for dose titration, it has a more favourable safety profile compared with other alpha blockers, and there are no known pharmacokinetic/pharmacodynamic (PK/PD) interactions between dutasteride and tamsulosin. However, combination therapy with other alpha blockers such as alfuzosin, prazosin and doxazosin were not evaluated.

All studies were undertaken in accordance with standard operating procedures of the GlaxoSmithKline Group, which comply with the principles of Good Clinical Practice. All studies were conducted with the approval of Ethics Committees or Institutional Review Boards. Informed consent was obtained from all subjects and the studies were performed in accordance with the Declaration of Helsinki.

Pharmacodynamics

An open-label, crossover study (ARIA1011) investigated the pharmacokinetic-pharmacodynamic interaction between (1) tamsulosin and dutasteride and (2) terazosin and dutasteride when co-administered to 48 healthy male subjects, aged 19 to 54 years, for 14 days. The secondary objective of the study was to investigate the effects of repeat doses of tamsulosin and terazosin on the dutasteride induced decrease in dihydrotestosterone (DHT).

DHT concentrations decreased markedly from the median DHT levels at baseline (Day 1) of 496 pg/mL and 507 pg/mL for tamsulosin and terazosin groups, respectively. Following the commencement of dutasteride treatment (Day 43), median DHT concentrations decreased to 28 pg/mL and 25 pg/mL for the tamsulosin and terazosin groups, respectively. Following administration of the combination therapy (Day 56), median DHT concentrations remained decreased at 34 pg/mL and 29 pg/mL, respectively.

Testosterone levels at the end of both the dutasteride monotherapy and the combination treatments increased 10 to 37% over baseline levels.

Pharmacokinetics

Plasma protein binding studies

Dutasteride binds extensively to human plasma proteins (>99%) as do the anticoagulants, acenocoumarol and phenprocoumon. Therefore, the potential for displacement of plasma protein bound dutasteride by acenocoumarol and phenprocoumon was investigated *in vitro*

using an ultra-filtration method. In addition, the potential for displacement of acenocoumarol and phenprocoumon bound to plasma protein by dutasteride was also examined.

Protein bound dutasteride (1000 ng/mL) was not displaced by either acenocoumarol (300 ng/mL) or phenprocoumon (1000 ng/mL). In the absence of other drugs or in the presence of either acenocoumarol or phenprocoumon, the unbound fraction of dutasteride in human plasma was 0.1%. The unbound fraction of 100 ng/mL dutasteride in the presence or absence of acenocoumarol and phenprocoumon was below the limit of detection (0.1 ng/mL) and was not determined. Similarly, protein bound acenocoumarol (300 ng/mL) or phenprocoumon (1000 ng/mL) were not displaced by dutasteride (100 or 1000 ng/mL). The unbound fraction of acenocoumarol in human plasma in the absence of any other drug was 0.6%, whereas, the unbound fractions of acenocoumarol in the presence of 100 and 1000 ng/mL dutasteride were 0.5% and 0.6%. The unbound fraction of phenprocoumon in human plasma in the absence of any other drug or in the presence of 100 and 1000 ng/mL dutasteride was 0.5%. These results suggest that dutasteride was neither displaced nor was displaced by acenocoumarol or phenprocoumon at therapeutically relevant concentrations and the authors conclude that protein binding displacement interactions between dutasteride and acenocoumarol or phenprocoumon are not likely to occur *in vivo* in humans.

Metabolite identification

An *in vitro* study investigated the metabolic pathway involved in the formation of the 1,2-dihydro metabolite of dutasteride. The purpose of this study was to determine qualitatively if human 5-alpha-reductases (5αRs) are responsible for the formation of 1,2-dihydrodutasteride from dutasteride. The results of these studies suggest that this was in fact the case as the dihydro metabolite, GI201448, was observed when dutasteride was incubated in microsomal preparations from COS cells separately transfected with cDNA specific for 5αR1 or 5αR2.

PK-PD studies

The primary objective of ARIA1011 (see Pharmacodynamics) was to investigate the effects of repeat doses of dutasteride on the pharmacokinetic characteristics of tamsulosin and terazosin in healthy males.

Dutasteride had little effect on the area under the plasma concentration time curve from time zero to 24 hours (AUC_{24}) and C_{max} of tamsulosin (AUC was 206 and 215 ng/mL.h with tamsulosin alone and in combination, respectively and C_{max} was 17.8 and 18.2 ng/mL, respectively) and terazosin (AUC was 2326 and 2419 ng/mL.h for terazosin alone and in combination, respectively and C_{max} 236 and 246 ng/mL, respectively).

The geometric least squares (LS) means ratios for the primary pharmacokinetic parameters ranged between 0.93 and 1.05 and the 90% confidence intervals (CIs) ranged from 0.82 to 1.18 (Table 1). Therefore, the pharmacokinetics of tamsulosin and terazosin were bioequivalent when administered alone and in combination with dutasteride.

Table 1: Summary of Tamsulosin and Terazosin PK Parameters

	Tamsulosin Drug Group (n=19)		Terazosin Drug Group (n=19)	
	Day 14 Monotherapy	Day 56 Combination	Day 14 Monotherapy	Day 56 Combination
AUC_{24} (ng·h/mL)				
Geo. LSmean	190	199	2285	2340
Geo. LSmean ratio	1.05		1.02	
90% CI	(0.92-1.18)		(0.94-1.11)	
C_{max} (ng/mL)				
Geo. LSmean	16.5	16.9	231	236
Geo. LSmean ratio	1.02		1.02	
90% CI	(0.89-1.18)		(0.93-1.11)	
λ_z (h^{-1})				
Geo. LSmean	0.08	0.07	0.08	0.07
Geo. LSmean ratio	0.94		0.93	
90% CI	(0.82-1.08)		(0.84-1.03)	
t_{max} (h)				
Median	6.00	6.00	1.00	1.00
Median Difference[a]	0.00		-0.25	
90% CI	(-1.00-1.00)		(-0.75-0.25)	

a The comparison is the geometric LSmean ratio between Day 56/Day 14 for all treatments except t_{max}, where the comparison is the Hodges-Lehmann estimate of the median difference between the two treatments.

The monotherapy treatment is the reference in all comparisons.

As expected following a loading dose of 40 mg dutasteride, median trough serum concentrations decreased 29% and 23% after 13 days of combination therapy (from Days 43 to 56) with tamsulosin and terazosin, respectively. In spite of this, dutasteride median serum concentrations remained above the anticipated therapeutic level of 40 ng/mL.

Efficacy

Efficacy Overview

Evidence to support the efficacy of co-administration of dutasteride and tamsulosin in the treatment of BPH was submitted in the data from the pre-defined 2-year analyses of one pivotal long-term study, ARI40005, and from two supporting studies, ARI40002 and ARI40013. A number of different scoring systems were used in these trials to assess symptoms of BPH.

The International Prostate Symptom Score (IPSS) was used as a key outcome measure for all three studies.[15,16] This is a validated 8-item instrument designed to quantify urinary symptoms (essentially the same as the American Urological Association Symptom Index, AUA-SI), but with an independent eighth question related to quality of life (IPSS-QOL). Total score (excluding question 8) ranges from 0 to 35, with higher scores indicating greater impairment.

The BPH Impact Index (BII) was used in studies ARI40005 and ARI40013. This is a validated 4-item instrument to assess the overall impact of BPH on a subject's sense of well

[15] Badia X, Garcia-Losa M, Dal-Re R. Ten-language translation and harmonization of the international prostate symptom score: developing a methodology for multinational clinical trials. Eur Urol 1997; 31: 129-140.
[16] Barry MJ, Fowler FJ, O'Leary MP et al. The American Urological Association Symptom Index for benign prostatic hyperplasia. J Urology 1992: 148: 1549-57.

being, and measures physical discomfort and impact on usual activities.[17] Scores range from 0 to 13, with higher scores reflecting greater impact.

The BPH-related Health Status (BHS) was used in study ARI40005 and it has a total score range of 0 to 6 with higher scores reflecting greater impact of BPH on quality of life.

Pivotal Trial - Study ARI40005

This is a Phase III study designed to assess the efficacy of combination treatment with dutasteride 500 µg and tamsulosin 400 µg over dutasteride 500 µg or tamsulosin 400 µg alone. It is an ongoing international, multicentre, randomised, double-blind, parallel group study on improvement of symptoms and clinical outcome in men aged 50 years or older, with moderate to severe symptomatic BPH. The pre-defined year-2 analysis of this ongoing trial was presented for evaluation. The study period to Year 2 was from November 2003 to January 2007, and the study was performed in accordance with GCP guidelines.

Inclusion criteria were males aged≥50 years, diagnosed with moderate -to-severe BPH, with IPSS at screening ≥12, prostate volume (PV) ≥30 cc, prostate specific antigen (PSA) ≥1.5 ng/mL and ≤10 ng/mL, peak urinary flow rate (Q_{max}) >5 mL/sec and <15 mL/sec and minimum voided volume of≥125 mL. Patients had to be able to tolerate oral medication and be willing to participate in the study for 4 years. Exclusion criteria included, a history or evidence of prostate cancer, previous prostatic surgery, PSA >10ng/mL and other significant, unstable, serious co-existing medical condition.

The study consists of a 4-week single blind placebo run-in period to reduce any subjective 'placebo response' component in subsequent results reported after randomisation to treatment with active medication. This is then followed by a 4 year double-blind treatment period and a 16-week safety follow up period. The total study duration for each patient will be up to 229 weeks. A placebo control group was not included because the treatment benefits from the therapies being studied have been clearly demonstrated and it was therefore deemed inappropriate to expose this population of men with moderate to severe BPH to undue risk of disease progression and symptoms for a period of 4 years.

Treatment compliance was assessed by a capsule count. Prohibited concomitant medication included other alpha blockers, medications that may interact with alpha blockers (for example, cimetidine, warfarin) and drugs with antiandrogenic properties. A total of 5064 men were enrolled, of which all except 12 entered the placebo run-in phase; the 12 subjects were randomised to active treatment without entering the placebo run-in phase. Of subjects who entered the placebo run-in, 220 withdrew prior to randomisation. Reasons for withdrawing were other (67 patients), protocol variation (62), withdrawal of consent (49), adverse events (26), lost to follow up (15), and missing (1). The remaining 4844 patients were assigned to study treatment in accordance with a computer generated randomization schedule. The majority of the patients completed the Year 2 visit, and the number of subjects that withdrew prior to this was similar across the treatment groups. The primary reasons for premature discontinuation were adverse events (AEs) and withdrawal of consent. More patients withdrew due to AEs in the combination group (154/1610, 10%) compared with the tamsulosin group (136/1611, 8%) and dutasteride group (108/1623, 7%). The number of patients with major protocol violations resulting in extension for the per protocol set was low and similar across all three treatments groups. The predominant major violation in all groups were deviations from inclusion criteria of Q_{max} >5mL/sec and ≤ 15mL/sec and minimum voided volume of ≥125mL at screening. The majority of subjects in each treatment group

[17] Barry MJ, Fowler FJ, O'Leary MP, Bruskewitz RC, Holtgrewe L, Mebust WK. Measuring disease-specific health status in men with benign prostatic hyperplasia. Med Care 1995; 33: AS145-AS155.

were compliant having taken >75% and ≤125% of allotted study medication. Mean overall compliance was >96% in all groups.

Baseline demographics were similar across all treatment groups. The majority of the patients were White and 42% were under 65 years of age. Subjects had a diagnosis of BPH for a mean of 3.9 years and the majority of patients were sexually active. Baseline BPH history was similar across the treatment groups. More than half (59%) of the population had concurrent medical conditions, most common being cardiovascular disorders, mainly hypertension, which affected 41% of all patients. At baseline, mean symptom scores, Q_{max}, and PV were similar across the treatment groups and were indicative of a group with moderate to severe symptoms of BPH.

Efficacy Endpoints & Statistical Considerations

The primary efficacy endpoint of interest at Year 2 was improvement in symptoms as determined by change from baseline in International Prostate Symptom Score (IPSS). Previous studies have suggested that 3 units is the minimum within-treatment IPSS change in symptom improvement before a difference is perceived, hence the selection of 2 and 3 unit differences in the secondary outcome measure.[17] For IPSS, the anticipated superiority of combination therapy over dutasteride monotherapy was 1.5 units and for tamsulosin monotherapy was 1.0 unit.

Key secondary outcome measures were change from baseline in PV and Q_{max}; proportion of patients with IPSS improvement from baseline≥2 units, ≥3 units, an d ≥25%; the proportion of subjects with Q_{max} improvements form baseline of≥30% and ≥3mL/sec; and health outcome measures such as BPH Impact Index (BII), BPH-related Health Status (IPSS-QOL) and the Patient Perception of Study Medication (PPSM), which is a tool that was developed by the sponsor specifically for this study to quantify patient perception and satisfaction with the effect of the study treatment.

It was calculated that approximately 4500 enrolled subjects, 1500 per treatment group, would provide 91% power to declare superiority of the combination therapy versus both monotherapies at Year 2. The intention to treat (ITT) population consisted of all patients randomised to the double-blind treatment phase, and was the primary analysis population for efficacy and safety.

The ITT population was the primary population for analysis of efficacy and safety. Statistical testing of the multiple primary, secondary and of multiple time points for each endpoint were performed in a pre-determined hierarchical step down manner at the 0.01 level of significance. Analysis of data was performed using two different approaches for missing data: last observation carried forward (LOCF) and At Visit where missing values were not replaced. Change in baseline IPSS, Q_{max}, BII and BHS were compared at each scheduled assessment point for combination therapy versus monotherapy using t-tests from a general linear model with effects for adjustment, cluster and baseline value at alpha = 0.01. The adjusted mean estimates, adjusted mean differences, and 95% confidence intervals were presented. The adjusted mean differences were in terms of combination therapy minus monotherapy.

Primary Efficacy Outcomes

The primary outcome measure of interest at Year 2 was combination therapy versus each monotherapy for change from baseline of IPSS. Although IPSS improvement categories were secondary endpoints, they were presented in the primary efficacy section to provide a more comprehensive overview of improvement in symptom as measured by IPSS.

At Month 24, statistically significant ($p<0.01$) greater reduction from baseline in IPSS was observed with combination therapy compared with either dutasteride or tamsulosin monotherapy.

For LOCF analysis, the mean change from baseline for IPPS was -6.2, -4.9 and -4.3 with combination therapy, dutasteride monotherapy and tamsulosin monotherapy, respectively. This represents an adjusted mean difference between combination and dutasteride of -1.3 points (95%CI -1.69, -0.86. $p<0.001$). The adjusted mean difference between combination therapy and tamsulosin was -1.8 points (95% CI -2.23, -1.40. $p<0.001$). This is summarised in Table 2, along with values for at visit analysis. Regarding the superiority of combination therapy versus dutasteride alone, the adjusted mean difference of -1.3 does not meet the pre-defined superiority margin of 1.5 points for LOCF analysis, although the data for at visit analysis does reach this difference. In both LOCF and at visit analysis, the pre-defined superiority measure of 1.0 point for combination therapy over tamsulosin monotherapy was reached in both analyses.

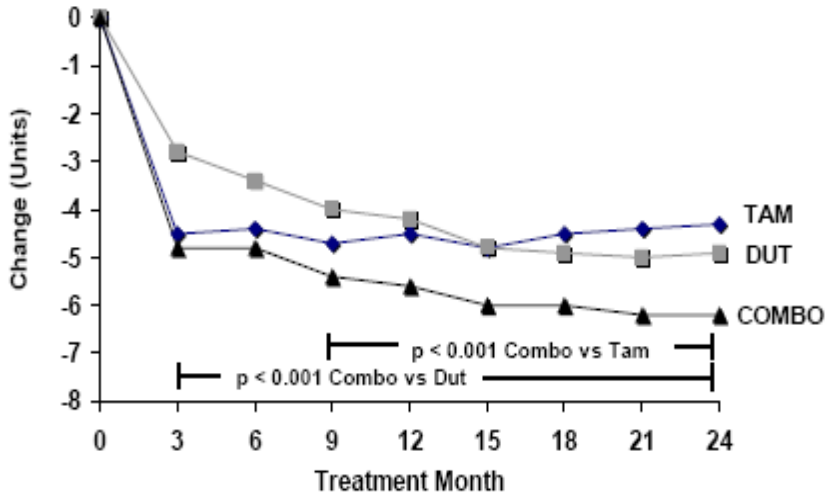
Table 2: IPSS Change from Baseline at Month 24 (ITT population) – ARI40005

Change from Baseline Analysis	Combination N=1610	Dutasteride N=1623	Tamsulosin N=1611
LOCF, n	1575	1592	1582
Adjusted mean (units)	-6.2	-4.9	-4.3
Adj mean difference[a]	---	-1.3	-1.8
[95% CI]	---	[-1.69, -0.86]	[-2.23, -1.40]
p-value vs. combo[b]	---	<0.001	<0.001
At Visit, n	1258	1287	1237
Adjusted mean (units)	-6.8	-5.3	-5.0
Adj mean difference[a]	---	-1.5	-1.9
[95% CI]	---	[-1.93, -1.08]	[-2.28, -1.43]
p-value vs. combo[b]	---	<0.001	<0.001

a. Combination minus each monotherapy
b. Based on t-test from general linear model (Change from baseline IPSS = treatment + cluster + baseline IPSS)

IPSS scores at each post-baseline assessment from Month 3 to Month 24 were consistently lower in the combination group compared to each monotherapy group. The reductions in IPSS were statistically significant for combination versus dutasteride from Month 3 onwards, and improved continually until Month 24. The reductions in IPSS for combination therapy versus tamsulosin were statistically significant from Month 9. This is demonstrated in Figure 1.

Figure 1: Mean change from baseline in IPSS (LOCF) – ARI40005

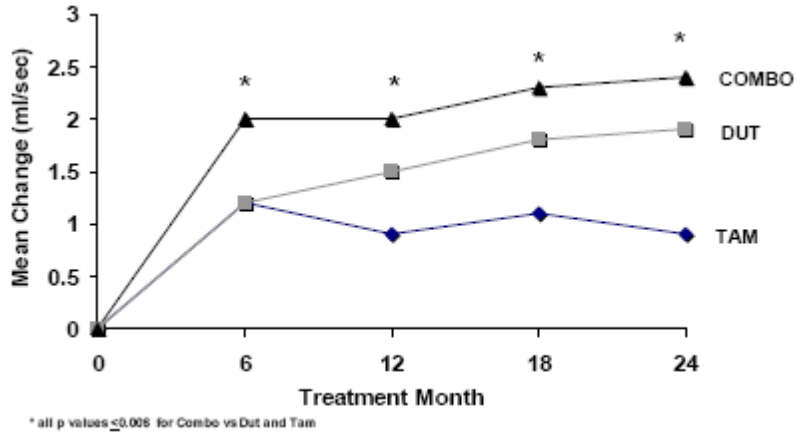


At Month 24, a statistically significantly greater proportion of subjects treated with combination therapy had IPSS improvement of≥2 units, ≥3 units, and ≥25% from baseline compared to either monotherapy. Compared to dutasteride monotherapy, the proportion of patients with IPSS improvements of≥2 units, ≥3 units, or an improvement of ≥25% from baseline was statistically significantly higher on combination therapy at Month 3, and was sustained to Month 24. Compared to tamsulosin monotherapy, the proportion of patients with IPSS improvements of≥2 units, ≥3 units, or an improvement of ≥25% from baseline was statistically significantly higher on combination therapy at Month 9, and was sustained to Month 24.

Secondary Efficacy Outcomes

Changes (increases) in peak urinary flow rate (Q_{max}) from baseline were consistently higher on combination therapy compared to either monotherapy at each 6 month assessment, and this was continued over the 24 Month period (Figure 2). At Month 24, the adjusted mean change from baseline in Q_{max} was 2.4 mL/sec for combination therapy, compared to 1.9 mL/sec for dutasteride monotherapy, and 0.9 mL/sec for tamsulosin. These increases in Q_{max} were statistically significant between combination therapy and both monotherapies at each assessment point from Month 6 to Month 24.

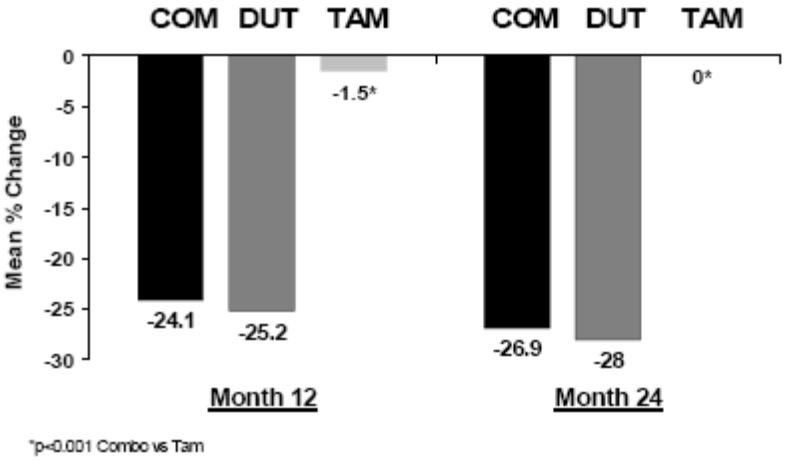
Figure 2: Change from Baseline in Q_{max} (LOCF) – ARI40005



The proportion of patients with improvements in Q_{max} of 30% or ≥3 mL/sec compared to baseline was statistically significantly higher on combination therapy than on tamsulosin alone at each 6 Month assessment point up until 24 months. A statistically significant difference at 24 months between combination therapy and dutasteride alone with regard to these endpoints could not be demonstrated due to *a priori* defined multiplicity guidelines.

With regard to prostate volume (PV) the observed mean PV at Months 12 and 24 showed similar reduction from baseline for both the combination group and the dutasteride monotherapy group. However, tamsulosin monotherapy showed no reduction in PV from baseline to Month 24 and both combination therapy and dutasteride monotherapy showed statistically significantly greater reduction in PV compared with tamsulosin monotherapy. These results are depicted in Figure 3.

Figure 3: Adjusted mean percentage change from baseline in prostate volume (LOCF, ITT population) – ARI 40005



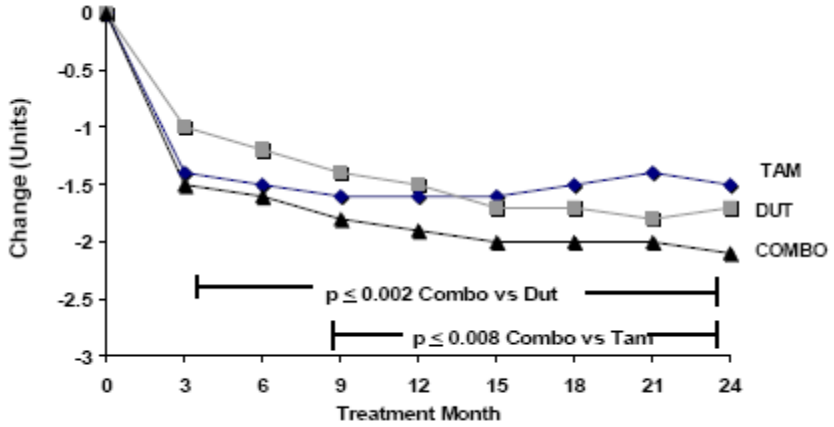
Health Outcomes

The health outcome measures at the Year 2 analysis were change from baseline in BII, BHS (QOL Q8 of IPSS) and Patient Perception of Study Medication (PPSM).

Baseline BII values were similar across all treatment groups. BII scores at each 3 month assessment period were consistently lower in the combination group compared to either monotherapy (Figure 4). The adjusted mean changes (reductions) in BII were statistically significantly greater on combination therapy compared to either monotherapy after 24

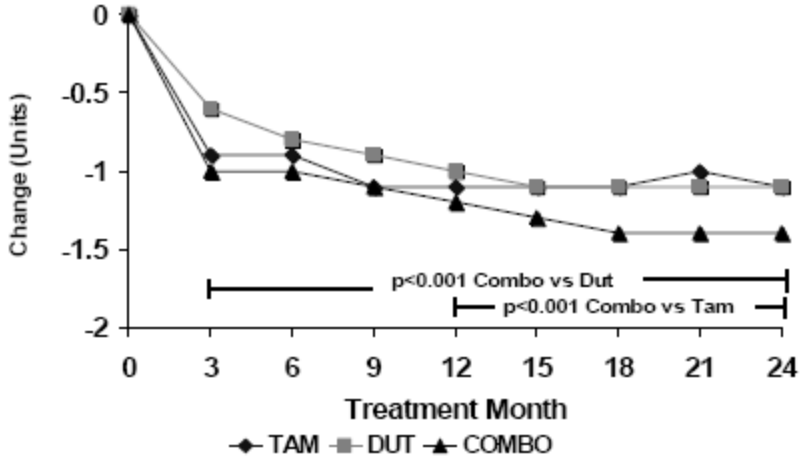
months, the adjusted mean improvement from baseline was -2.1 points, -1.7 and -1.5 in the combination group, dutasteride monotherapy and tamsulosin monotherapy groups, respectively. Statistically significant differences between combination therapy and dutasteride monotherapy were observed at all 3 month intervals from Month 3 onwards. Statistically significant differences between combination therapy and tamsulosin monotherapy were reached from Month 9 onwards.

Figure 4: Adjusted mean change from baseline in BII (LOCF) – ARI40005



Baseline BHS values were similar across all treatment groups. Reductions from baseline in BHS were consistently numerically lower with combination therapy compared to either monotherapy and continued over the 24 month period (Figure 5). At Month 24, the reduction in BHS from baseline with combination therapy was statistically significantly greater than with either monotherapy, with adjusted mean change being -1.4 points with combination therapy compared to -1.1 points in both monotherapy groups. Statistically significant differences were observed between combination therapy and dutasteride from Month 3 onwards. Statistically significant differences were observed between combination therapy and tamsulosin from Month 12 onwards.

Figure 5: Adjusted mean change from baseline in BHS (LOCF) – ARI40005



The PPSM is a tool that was developed by the sponsor specifically for this study to quantify patient perception and satisfaction with the effect of the study treatment. PPSM expectations at screening were similar across all treatment groups. The proportion of patients who expressed any satisfaction, or felt that they had shown an improvement in their symptoms at Month 24 was statistically significantly higher in the combination group compared with either monotherapy, except for change in pain prior to urinating. However, there is no reference made in the submission to any external validation of this scoring system, so the

evaluator advised caution in the interpretation of any results or conclusions drawn from this information.

Non-Pivotal Trials - Study ARI40002

This study was a short-term pilot, multicentre, double-blind, parallel group, randomised study to investigate the effect on urinary symptoms of discontinuing tamsulosin, following 24 weeks of combination treatment with 500 µg dutasteride and 400 µg tamsulosin daily in subjects with BPH. The two treatment groups were to receive either 36 weeks of combination therapy with dutasteride 500 µg daily and tamsulosin 400 µg daily (TD36 group), or 24 weeks of combination therapy followed by 12 weeks of dutasteride 500 µg daily monotherapy (TD24+D12 group). The study was conducted in accordance with GCP guidelines and all applicable declarations, and the study period was between February 2000 and September 2001.

Inclusion criteria were male≥45 years of age, with a diagnosis of BPH according to history and clinical examination (including digital rectal examination, DRE), with IPSS≥12, enlarged PV (>30 cm^3) as determined by DRE. Exclusion criteria included any history or evidence of prostate cancer, PSA <1.5 ng/mL or >10.0 ng/mL, a history of urethral instrumentation within 7 days of screening or episode of AUR within 3 months of screening, use of medications which may interact with either study medication, or any significant medical comorbidities.

The study commenced with a 4 week single-blind placebo run in period prior to randomisation to one of the study groups. The last 12 weeks of the study where the two treatment groups were taking different medications was performed in a double-blind manner. Once randomised, patients were to self administer active study medication for 36 weeks and then a further week of placebo. Patients were assessed as outpatients at screening, baseline, and then at 4, 12, 24, 30, 36 and 37 weeks post baseline. Use of other BPH treatments was forbidden during the study, as was use of medications thought to have an interaction with tamsulosin. Treatment compliance was assessed using capsule counts.

A total of 421 patients were enrolled and entered the placebo run-in phase of the study, of which 94 discontinued prior to randomisation. The main reason for discontinuing was a PSA <1.5 or >10.0 ng/mL (66/421 patients). Other reasons, each reported by ≤2% of the patients were AEs, withdrawal of consent, lost to follow up and major protocol variation. The remaining 327 patients were randomised and comprise the ITT population for analysis. Major protocol violations were reported for 23/327 (7%) subjects overall [11/164 in TD36 group (7%); 12/163 in TD24 and D12 group (7%)], which resulted in their exclusion from the per protocol (PP) population. Main violations reported were concurrent use of drugs with anti-androgenic properties or anabolic steroids (5 patients in each group) and use of alpha-agonists within 48 hours prior to any visit (5 patients in each group). The treatment blinding was not broken for any patients. The compliance with study medication was calculated at each visit by counting the number of capsules returned. Mean study drug compliance for dutasteride and tamsulosin or matched placebos from baseline to end of active treatment was 98%. Baseline demographic data for the two groups were. Current medical conditions were reported by the majority of patients at screening (82%), with similar numbers in each treatment group (80% in TD 36 group, 83% in TD 24+D12 group).

Efficacy endpoints and statistical considerations

The primary objective was to assess any difference at 30 weeks post baseline, in the proportion of patients experiencing an improvement or no change in their urinary symptoms (as perceived by the patients themselves), following discontinuation or continuation of

tamsulosin for the two groups. This was assessed according to response to the question: *"Over the past 2 weeks, on average have you felt better, worse, or the same, with respect to your urinary symptoms, than at your last visit?"* It should be noted that this question had not been externally validated as an indication of treatment success or satisfaction. These data were analysed using a Mantel-Haenszel test controlling for country. The hypothesis being tested was that there is no association between a patient's response to the primary efficacy question and their randomised treatment group. The lower 97.5% confidence limit was used to conclude if dutasteride-only treatment was non-inferior or clinically as good as combination therapy. If the lower 97.5% confidence limit was less negative than -0.20, then non-inferiority could be claimed.

Secondary endpoints included:

(i) mean change in IPSS for patients within each treatment group from 24 weeks post baseline to 30 and 36 weeks post baseline,
(ii) mean change in IPSS for all patients between baseline and 4, 12, and 24 weeks post baseline, (iii) proportion of all subjects in each treatment group experiencing an improvement or no change in their symptoms at 36 weeks post baseline,
(iv) proportion of patients in each treatment group who expressed a preference for the regimen received within the first 24 weeks when questioned at week 30 as shown in response to the question: *"did you prefer the medication you were taking up to your last visit more that the medication you are now taking?"*
(v) mean change in IPSS-QOL score in each treatment group between 24 and 36 weeks post baseline, and
(vi) mean change in QOL question score for all patients between baseline, and 4, 12 and 24 weeks post baseline.

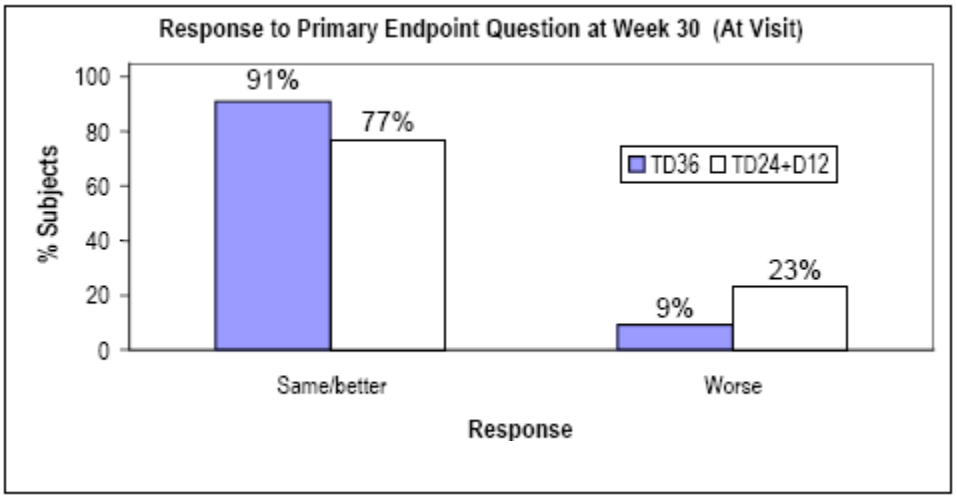
Although the study was a pilot study, it was calculated that 200 subjects were required to enable the study to show that following combination therapy for 24 weeks, single treatment with dutasteride was clinically as good as combination relative to the primary endpoint. This was based on the CIs of 95% and power of 80%. To allow for drop out of 25%, a target sample size of 250 patients was chosen. The intention to treat (ITT) population was considered the primary efficacy and safety population, and consisted of all patients randomised to treatment after the 4 week placebo run-in period. For a non-inferiority study, the PP study population usually provides a better indication.

Primary Efficacy Outcomes

After 24 weeks of combination therapy, a similar number in each treatment group felt the same or better at Week 24 compared to the previous visit (TD 36: 89%, TD24+D12: 87%) which suggests that the patients were well balanced with regard to response to combination therapy across both groups.

At Week 30, 91% (139/154) patients who continued combination therapy after 24 weeks (TD 36 group), felt the same or better regarding urinary symptoms than at the previous visit. In the group who discontinued tamsulosin after Week 24 (TD24+D12 group), 71% (115/151) felt the same or better than at the previous visit. This is displayed in Figure 6. These data were analysed using a Mantel-Haenszel test controlling for country, and the difference in proportion was -0.11 (p=0.001; 95%CI: -0.18, -0.04), demonstrating non-inferiority of dutasteride-only treatment compared to the combination therapy.

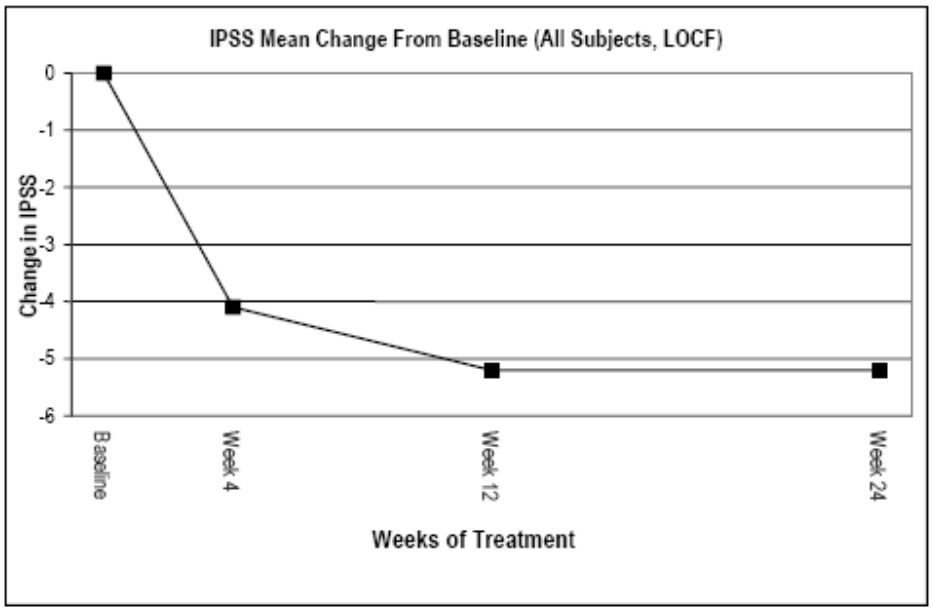
Figure 6: Response to primary end-point question at week 30 – ARI40002



Secondary Efficacy Outcomes

With regards to change in IPSS from baseline with time, continuous, consistent improvements in IPSS were observed from baseline to Week 24 in both groups (Figure 7). At baseline, the mean IPSS score was 16.4 in the TD36 group and 16.5 in the TD24+D12 group, and at Week 24, the mean IPSS value was 11.2 in both groups. After Week 24, when treatment changed in the TD24+D12 group to receiving dutasteride monotherapy, the IPSS mean scores were slightly higher in this group compared to the group that continued combination therapy.

Figure 7: Mean change in IPSS from Baseline – ITT population, LOCF – ARI40002



At Week 30, in the TD24+D12 group who had ceased tamsulosin 6 weeks earlier, there was an adjusted mean change in IPSS from Week 24 of +1.2 points (that is, worsening of

symptoms), compared to the TD36 group who showed continued improvement with an adjusted mean change in IPSS from Week 24 of -0.5 points. The adjusted mean difference between the groups was 1.6 points which was statistically significant (p<0.001; 95% CI: 0,8, 2.5) At Week 36, there was an improvement in IPSS in both groups from Week 30. The overall adjusted mean change in IPSS from Week 24 was -0.9 in the TD 36 group and 0.0 in the TD24+D12 group.

Mean change in the IPSS-QoL question from baseline was carried out at Weeks 4, 12, 24, 30 and 36 using LOCF approach. The score for this question consistently improved from baseline in all subjects during the 24 week combination phase of the treatment. At Week 30, the adjusted mean change from Week 24 in the TD36 group was -0.1 compared to 0.1 in the TD24+D12 group. At Week 36, the adjusted mean change from Week 24 was -0.1 in both groups.

Regarding treatment preference, patients were asked at Week 24 and Week 30 if they had any preference for the treatment received up to the last visit compared to that taken in the most recent period. At Week 24, 79% of subjects in both treatment groups did not prefer the medication they had taken up to Week 12 to their current treatment, demonstrating that both treatment groups were well balanced before changing treatments. At Week 30, 71% of patients in the dutasteride-only group did not prefer the medication they had taken up to Week 24 (combination). Similarly, 81% of patients receiving combination treatment after Week 24 did not prefer the medication they had taken up to Week 24.

Non-Pivotal Trials - Study ARI40013

This study was an open label multicentre Phase IIIb study to evaluate the safety and efficacy of dutasteride with or without tamsulosin in the treatment of a large cohort of patients with symptomatic BPH under routine clinical conditions. Patients were assigned to a treatment regimen for at least 36 weeks based on their baseline IPSS-QOL score. If the IPSS-QOL was <4 points they were to receive monotherapy with dutasteride 500 µg once daily (od) [monotherapy group, MT]. If the IPSS-QOL was ≥4 points they were to receive combination therapy with dutasteride 500 µg od plus tamsulosin 400 µg od for 24 weeks, followed by dutasteride monotherapy for the remaining 12 weeks [combination therapy group, CT]. The study was conducted in accordance with all GCP guidelines and the study was conducted between March 2002 and march 2003.

Inclusion criteria were age >50 years, diagnosis of BPH based on history and physical examination (including DRE), IPSS of >7 at screening, a PSA between 1.5 ng/mL and 10.0 ng/mL, PVR of <200 mL. Exclusion criteria included history or evidence of prostate carcinoma, urethral instrumentation within 14 days of screening, previous treatment with 5-ARI, and other significant comorbidity. Prohibited concomitant medication included other alpha blockers, medications that may interact with alpha blockers (for example, cimetidine, warfarin) and drugs with antiandrogenic properties.

A total of 2403 subjects were initially screened, and of these, 2385 patients were considered eligible for participation in the study. Of these 2385 patients, 811 were assigned to receive dutasteride monotherapy (MT), and 1574 were assigned to the dutasteride/ tamsulosin combination therapy group (CT). These numbers met the expected ratio of 1:2 (MT:CT) according to baseline severity. A total of 713 patients in the MT group and 1291 patients in the CT group completed the study. Demographics of patients included were similar between the treatments. As expected by the treatment assignment criterion, patients assigned to receive combination therapy had higher baseline values for efficacy variables such as IPSS-QOL, IPSS, and BII compared with patients assigned to receive monotherapy.

Efficacy endpoints and statistical considerations

The primary efficacy outcomes were changes from baseline in the IPSS and BII after 36 weeks of treatment. Secondary outcome measures included changes from baseline in IPSS and BII over the entire study period, number of patients requiring surgery or experiencing AUR during the treatment; changes in prostate volume (PV) and post-void residual volume (PVR) were analysed.

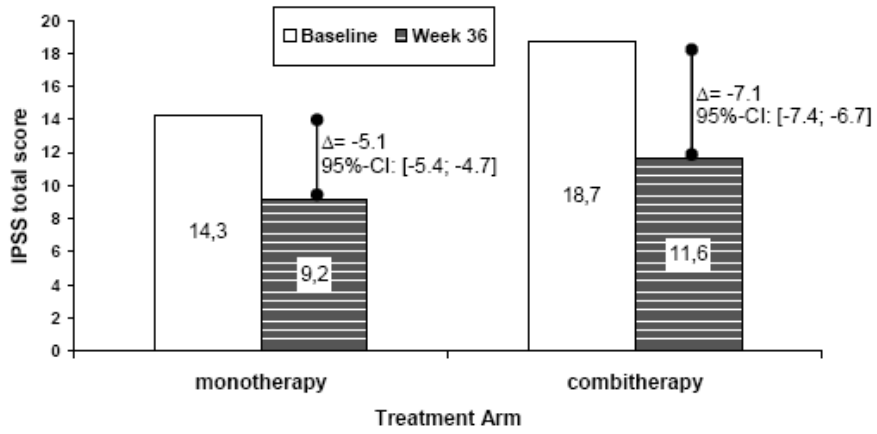
The planned sample size was 3000, although no statistical sample size calculation was performed as there was no statistical hypothesis generated. The sample size of 3000 was chosen as it was considered to potentially identify hypothetical rare adverse events (occurring with an incidence of 0.1%) with a probability of 90%. The ITT population was to consist of all patients assigned to one of the treatment groups who received at least one dose of the study medication. For this population, the LOCF method was used to account for any missing values for IPSS and BII for the primary efficacy endpoint. Other analysis populations were defined, but for the purposes of this evaluation, the ITT population was the focus.

The primary statistical analysis referred to pre and post comparisons of IPSS and BII within the two treatment groups by calculating confidence intervals of the respective estimates. Inferential statistical analyses for treatment comparisons were not performed. The pre-planned individual treatment duration was 36 weeks, but an extension of the treatment for a further 12-36 weeks was allowed in case of a pending market authorisation of dutasteride at the time of Visit 5 (Week 36). This made the maximum individual treatment duration 72 weeks.

Primary Efficacy Outcomes

At Week 36, both the treatment groups showed statistically significant reductions in the primary efficacy variables, with negative 95% CI values that did not cross zero. In the monotherapy group, the mean total IPSS had changed by -5.1 [95%CI:-5.4, -4.7] and the mean BII had changed by -2.3 [95%CI: -2.5, -2.1]. In the combination group the mean total IPSS had changed by -7.1 [95%CI:-7.4, -6.7] and the mean BII had changed by -2.3 [95%CI: -3.6, -3.3]. These changes are displayed graphically in Figure 8.

Figure 8: Mean changes in IPSS total scores by treatment groups from baseline to Week 36 (ITT, LOCF) – ARI40013

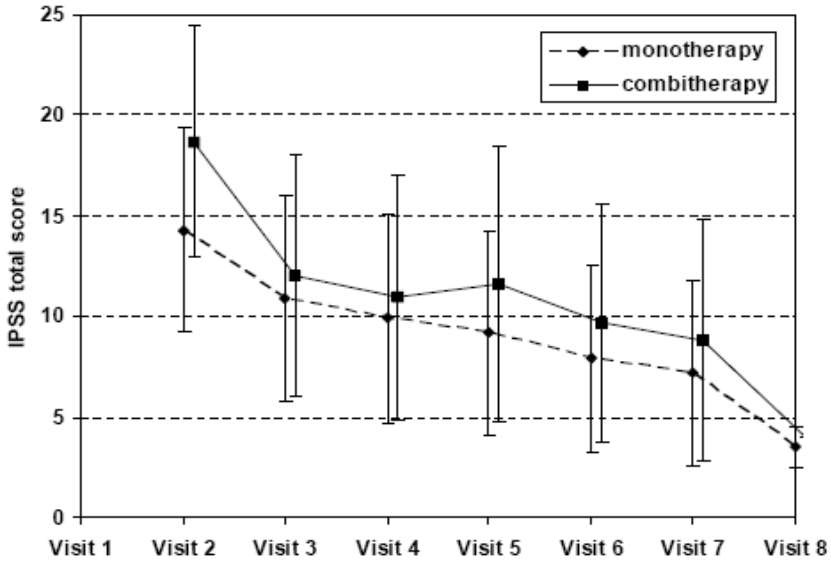


Descriptively, the mean reduction was stronger in the CT group compared to the MT group, but it was stated in the submission, and agreed by the evaluator, that this is most likely explained by the patients in the CT group starting with higher baseline values, indicating worse symptoms. Therefore the evaluator recommended that no conclusions on differences in efficacy between the two treatments should be drawn from this data.

Secondary Efficacy Outcomes

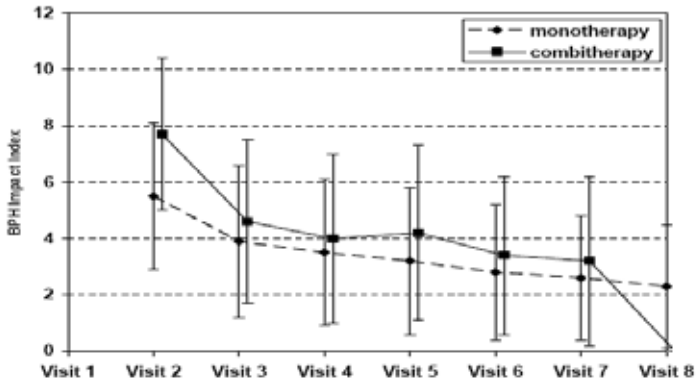
Changes in IPSS and BII over time were initially defined as secondary outcome measures, although in the submission they were analysed with the primary outcome measure. The change in total IPSS and BII values with time are displayed graphically in Figures 9 and 10. It can be noted that in the CT group, there was a slight increase in the BII and IPSS from Week 24 to Week 36, which corresponds to the withdrawal of tamsulosin from their treatment regimen.

Figure 9: Course of IPSS total score with LOCF up to Visit 5 (Week 36) – ARI40013



Note: Data given as arithmetic mean and standard deviation.
Note: The number of observations decreased considerably from Visit 5 onwards:
Monotherapy: Visits 2-5: N=808; Visit 6: N=351; Visit 7: N=45, Visit 8: N=4
Combitherapy: Visit 2: N=1,564; Visits 3-5: N=1,565; Visit 6: N=614; Visit 7: N=80, Visit 8: N=2

Figure 10: Course of BII with LOCF up to Visit 5 (Week 36) – ARI40013



Note: Data given as arithmetic mean and standard deviation.
Note: The number of observations decreased considerably from Visit 5 onwards:
Monotherapy: Visit 2: N=793; Visit 3: N=803; Visits 4-5: N=805; Visit 6: N=346;
Visit 7: N=43, Visit 8: N=4
Combitherapy: Visit 2: N=1,516; Visit 3: N=1,549; Visit 4: N=1,551; Visit 5: N=1,553;
Visit 6: N=608; Visit 7: N=76; Visit 8: N=2

The evaluator recommended caution in interpreting any data from these figures beyond Visit 5 (Week 36) because this is a voluntary extension, and as mentioned in the notes accompanying the figures, the numbers analysed reduces dramatically. There is no discussion in the submission as to reasons for certain patients deciding to extend treatment. In fact at Visit 8, the final plot on these figures, the numbers involved are 2 patients in the CT group and 4 in the MT group. The evaluator recommended disregarding any data presented after Visit 5 (Week 36).

There was also a reduction in the other pre-defined secondary efficacy variables of IPSS-QoL, PV and PVR in both treatment groups. These reductions were comparable in the two groups. The mean PV changed from baseline to study end by 15.1 mL (±13.9) (mean percentage change -25.4%) in the MT group and by -15.8 mL (±16.6) (mean percentage change -25.5%) in the CT group. The PVR changed by -21.3 ±47.9 mL in the MT group and by -21.7 mL (±54.8) in the CT group. The 95% confidence intervals for the changes in mean in both PV and PVR indicated statistically significant changes from baseline in both treatment groups. No comparison is offered between the treatment groups, which seems appropriate to the evaluator as the two treatment groups were not matched for disease severity at baseline.

The overall rate of patients experiencing AUR during the study was 0.5% in the MT group (4 patients) and 1.7% in the CT group (26 patients). It was difficult to draw any meaningful conclusions from these data due to the fact that treatment groups were defined by severity of symptoms, and the increased number of patients experiencing AUR in the CT group again likely reflects that this was the group that had more significant disease at baseline. Prostate surgery was documented for one subject in each treatment group.

Efficacy Conclusions

After 2 years of treatment in the pivotal study ARI40005, combination therapy with dutasteride and tamsulosin was statistically significantly superior to either monotherapy with regard to symptom improvement (as evidenced by reduction in IPSS) and improvement in urinary flow rate (Q_{max}) and proportion of subjects with clinically relevant $\geq$2 units, 3 units and 75% improvement in IPSS as well as >30% and >3mL improvement in Q_{max}.

However, it should be noted that in study ARI40005, the adjusted mean difference in IPSS between combination therapy and dutasteride monotherapy of -1.3 did not reach the pre-defined anticipated superiority of -1.5 when using LOCF analysis.

Combination therapy with dutasteride and tamsulosin was significantly superior to tamsulosin monotherapy at reducing prostate volume, and was comparable to dutasteride monotherapy (Study ARI40005).

Data regarding health outcome measures for study ARI40005 also demonstrated that combination therapy with dutasteride and tamsulosin was statistically significantly superior to either monotherapy on improvement in health outcomes as measured by previously validated scores using BII and BHS scores.

Data from the short-term pilot study ARI40002 provided supportive evidence of efficacy of combination therapy with dutasteride and tamsulosin in treating symptoms of BPH over a short period of 24-36 weeks.

In study ARI40002, 77% of patients felt the same or better in the 6 weeks following ceasing tamsulosin than they did at Week 24, compared to 91% of patients who continued on combination therapy. Despite a p-value of 0.001, the CIs did not exceed the pre-defined equivalence criteria set to demonstrate non-inferiority.

Study ARI40002 also demonstrated that once tamsulosin was stopped after 24 weeks, patients had an increase in their symptom score that was statistically significantly higher than patients who continued combination therapy.

Data from study ARI40013 demonstrates efficacy of combination therapy in treating patients over a short period of 36 weeks with a combination of dutasteride and tamsulosin. However, in view of the difference in baseline disease severity between the two treatment groups, the open-label design, and absence of any statistical comparison, no conclusions from this study

can be drawn regarding any increase in benefit of combination therapy compared to monotherapy.

Safety

The adverse effect (AE) profles for both dutasteride and tamsulosin are well documented. The most reported AEs for dutasteride are primarily related to sexual function (impotence, altered libido, ejaculation disorders) and gynaecomastia. These events, together with incidence of prostate cancer, are defined as AEs of special interest in clinical trials involving dutasteride. The most common AEs described for tamsulosin are headache, dizziness, rhinitis, infection, abnormal ejaculation and asthenia. Other important AEs which are reported less frequently include orthostatic hypotension and syncope.

The target population for these drugs is ageing men with BPH, and comorbidities are prevalent in this population, which may complicate the interpretation of safety data. Common conditions include hypertension, ischaemic heart disease, diabetes, COPD, cancer and cerebrovascular disease.

Data in this submission to support the safety of co-administration of dutasteride and tamsulosin are provided in the pre-defined 2-year analysis of data from the pivotal study ARI40005, and the supporting studies ARI40002 and ARI40013. There was no integration of data across these studies because of differences in design and treatment schedules.

All three studies included treatment-emergent adverse events, laboratory data and vital signs. A drug-related AE was an event considered by an investigator to have a reasonable possibility of being related to the study medications.

Additionally, study ARI40005 included measures of total serum PSA and post-void residual volume. Cardiovascular events were analysed as events of special interest in study ARI40005 to address any possibility of long-term reduction of DHT leading to a relative hypogonadal state and increased risk of cardiovascular events.

Pivotal Study - Study ARI40005

Drug Exposure

In total 4844 patients were randomised to receive one of the study treatment regimens, with 1610 being randomised to receive combination therapy with dutasteride and tamsulosin, 1623 receiving dutasteride alone and 1611 receiving tamsulosin alone. Overall mean exposure to investigational product was similar across the treatment groups with >80% of patients in each treatment group being treated for >720 days.

Overview of Adverse Events

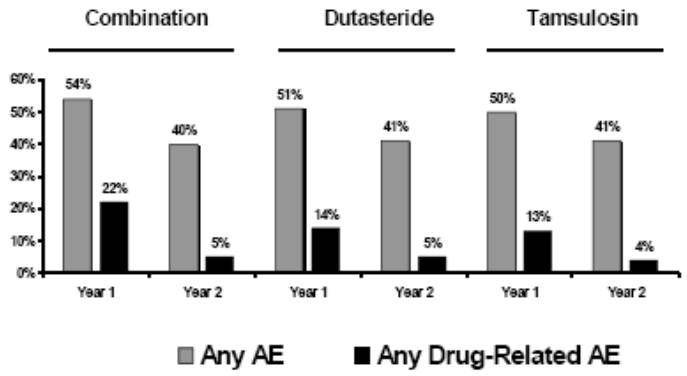
At the pre-defined 2 year analysis point, the overall incidence of AEs and serious AEs (SAEs), including deaths, was similar across the three treatment groups at 63-65% (Table 3). The incidence of drug-related AEs was statistically significantly higher in the combination group (24%) compared to each monotherapy group (18% in the dutasteride group and 16% in the tamsulosin group). The overall incidence of AEs and drug related AEs was higher in all groups in Year 1 compared with Year 2, and this is illustrated in Figure 11.

Table 3: Number (%) of Patients with AEs by Type (ITT population) – ARI 40005

AE type	Combination N=1610	Dutasteride N=1623		Tamsulosin N=1611	
	n (%)	n (%)	p-value	n (%)	p-value
Any AE	1048 (65)	1039 (64)	0.53	1011 (63)	0.17
Any drug-related AE	391 (24)	291 (18)	<0.001	259 (16)	<0.001
Any SAE	188 (12)	196 (12)	0.74	207 (13)	0.33
Deaths	20 (1)	19 (1)	-	21 (1)	-
Any AE withdrawal from study	164 (10)	127 (8)	0.020	148 (9)	0.34
Any AE withdrawal from study drug	159 (10)	123 (8)	0.021	143 (9)	0.33

Treatment-emergent defined as AEs with onset on or after randomisation (or missing onset of treatment date).
1. Combination versus each monotherapy were compared using Fisher's exact test.

Figure 11: Overall incidence of AEs and Drug-related AEs in Year 1 and Year 2 (ITT population) – ARI40005



The most frequently reported adverse effects by MedDRA Preferred Term (PT) across the three treatment groups were erectile dysfunction (4-8%), hypertension (5-6%) and nasopharyngitis (5-6%).[18] The most common AEs are summarised in Table 4. The incidence of erectile dysfunction was significantly higher in the combination group (8%) than in the tamsulosin group (4%)($p<0.001$). The incidence of retrograde ejaculation, ejaculation failure and decreased semen volume was also higher on combination therapy than with either monotherapy. The incidence of other AEs was similar across the treatment groups. The incidence of adverse events by MedDRA System Organ Class (SOC) was similar across all three treatment groups, although more patients in the combination group had reproductive and breast disorders compared to each monotherapy group.

[18] MedDRA = Medical Dictionary for Regulatory Activities

Table 4: Number (%) of Patients with Common AEs (>3% in any group) by PT (ITT population) - ARI 40005

Preferred Term	Combination N=1610 n (%)	Dutasteride N=1623 n (%)	Tamsulosin N=1611 n (%)
Any AE	1048 (65)	1039 (64)	1011 (63)
Erectile dysfunction	132 (8)	118 (7)	72 (4)
Hypertension	81 (5)	92 (6)	90 (6)
Nasopharyngitis	80 (5)	91 (6)	102 (6)
Retrograde ejaculation	70 (4)	10 (<1)	18 (1)
Back pain	68 (4)	61 (4)	73 (5)
Libido decreased	60 (4)	52 (3)	28 (2)
Influenza	50 (3)	50 (3)	63 (4)
Dizziness	50 (3)	39 (2)	51 (3)
Upper respiratory tract infection	45 (3)	35 (2)	35 (2)
Arthralgia	45 (3)	36 (2)	47 (3)
Ejaculation failure	41 (3)	10 (<1)	14 (<1)
Headache	25 (2)	49 (3)	38 (2)

AEs with onset on or after randomisation (or missing onset of treatment date).

Serious Adverse Events, Deaths and Discontinuations due to Adverse Events

At the 2-year data cut-off point, there had been a total of 61 deaths, the majority of which were due to cardiac disorders (24 patients) or neoplasms (14 patients). One death occurred prior to randomisation and was not included in subsequent analysis. The most frequent fatal AE across all treatment groups was myocardial infarction. There was only one death, from a myocardial infarction in the dutasteride monotherapy group, which was considered by the investigator to have a reasonable possibility of being related to the treatment medication.

The overall incidence of SAEs was similar across the treatment groups, with the most frequently reported SAEs being prostate cancer and myocardial infarction. The incidence of myocardial infarction was similar across the three groups. Regarding prostate cancer, the incidence was lower in the dutasteride monotherapy group compared with the other two groups which were comparable. The incidence of SAEs was higher in patients≥65 years compared to younger patients, and more patients in this older group reported prostate cancer. The incidence of SAEs considered related to the study medication was similar across the treatment groups, and most of these drug related SAEs were disorders of cardiac, nervous or vascular system.

The overall incidence of AEs leading to premature withdrawal from the study was 10% in the combination group, compared to 8% in the dutasteride group and 9% in the tamsulosin group. The most frequently reported AEs leading to withdrawal were erectile dysfunction, prostate cancer and reduced libido. More patients on combination therapy withdrew due to AEs related to sexual function compared to each monotherapy group. More patients withdrew due to AEs during the first year of treatment compared to the second year across all treatment groups.

Withdrawals considered to be related to the study medications were higher in the combination group compared with each monotherapy group. The most frequently reported drug-related AE leading to withdrawal was erectile dysfunction, with similar incidence across the treatment groups.

Adverse Events of Special Interest

The following were defined as adverse events of special interest: altered libido, impotence, ejaculation disorders, prostate cancer and breast disorders. The incidence of impotence, altered libido and breast disorders were similar in both the combination and dutasteride only group, and slightly higher than in the tamsulosin group (Table 5). Ejaculation disorders were more common in the combination group than either monotherapy group. The incidence of prostate cancer was numerically lower in the dutasteride group compared with the combination and tamsulosin group. Few AEs of special interest were severe or led to premature withdrawal from the study.

Table 5: Incidence of Adverse Events of Special Interest (ITT population) - ARI40005

Composite AE Category	Number (%) Subjects					
	Combination N=1610		Dutasteride N=1623		Tamsulosin N=1611	
	Total	AE WD[a]	Total	AE WD[a]	Total	AE WD[a]
Ejaculation disorder	159 (10)	19 (1)	32 (2)	2 (<1)	49 (3)	9 (1)
Impotence[b]	132 (8)	21 (1)	118 (7)	13 (1)	73 (5)	13 (1)
Altered (decreased) libido	100 (6)	17 (1)	83 (5)	11 (1)	51 (3)	5 (<1)
Breast disorders	44 (3)	10 (1)	49 (3)	3 (<1)	21 (1)	3 (<1)
Breast tenderness	34 (2)	8 (1)	31 (2)	3 (<1)	12 (1)	1 (<1)
Breast enlargement[c]	23 (1)	7 (<1)	29 (2)	2 (<1)	13 (1)	2 (<1)
Prostate cancer	21 (1)	17 (1)	11 (1)	7 (<1)	26 (2)	21 (1)

a. AE led to withdrawal
b. Category includes erectile dysfunction
c. Category includes gynecomastia

Most of the reports of altered libido, impotence and ejaculation disorders occurred in the first six months of treatment in each group, and diminished over time with the study. The mean onset time for impotence and ejaculation disorder was notably earlier in the combination group compared with either monotherapy. Onset of breast disorders was evenly distributed over time. The incidence of prostate cancer was low, and reported more frequently in all treatment groups during Year 2 compared to Year 1.

Combination therapy was associated with a significantly higher risk of ejaculation disorders compared with either monotherapy (Table 6). Relative to tamsulosin monotherapy, combination therapy was also associated with significantly higher risk of altered libido, impotence and breast disorders.

Table 6: Relative Risk Estimates for Adverse Events of Special Interest (ITT population) - ARI40005

Composite AE Term	Relative risk estimate[1] [95% CI]	
	Combination vs Dutasteride	Combination vs Tamsulosin
Altered (decreased) libido	1.23 (0.92, 1.65)	2.06 (1.46, 2.89) ***
Impotence	1.14 (0.89, 1.47)	1.87 (1.40, 2.48)***
Ejaculation disorders	5.25 (3.59, 7.68)***	3.47 (2.51, 4.79)***
Prostate cancer	1.95 (0.94, 4.05)	0.82 (0.46, 1.46)
Breast disorders	0.91 (0.61, 1.37)	2.15 (1.28, 3.61)***
Breast enlargement	0.81 (0.47, 1.39)	1.80 (0.91, 3.55)
Breast tenderness	1.12 (0.69, 1.81)	2.91 (1.51, 5.62)***

AEs with onset on or after randomisation (or missing onset of treatment date).
*** Statistically significant; p-value versus combination based on log rank test
1. Relative risk (hazard ratio) based on Cox proportional hazards model

Cardiovascular AEs of special interest were defined as those included in the following categories: acute coronary syndrome, ischaemic coronary artery disorders/ atherosclerosis, ischaemic cerebrovascular events, cardiac failure, arrhythmias, and peripheral vascular disease. The incidence of cardiovascular AEs of special interest was similar across all three treatment groups, with the most frequently reported being myocardial infarction and coronary artery disease. Combination therapy was not associated with a significantly greater risk of cardiovascular AEs relative to either monotherapy. Although the relative risk of cardiac failure appears higher, the CIs cross zero and are relatively wide, reflecting the small numbers of patients with cardiac failure in each group.

Adverse Events in Special Groups

AE profiles in elderly patients (≥65 years of age) were generally similar to those in the younger patients in the study. Younger men reported a higher incidence of AEs related to sexual function across all treatment groups, which may reflect that a higher number of younger patients were sexually active.

Of the study population, 12% were non-White. There was a higher incidence of AEs in non-White patients in all three treatment groups (75-76%) compared with White patients (61-64%). In the combination group, most individual AEs were reported with a higher incidence by non-Whites than Whites.

Fifty percent of the study population reported concurrent cardiovascular conditions, and 21% reported concurrent endocrine disorders. There was no apparent difference in incidence or type of AEs in any treatment group noted between patients with and without these conditions.

The overall incidence of AEs in each treatment group was higher in patients using concomitant medications (cardiovascular drugs, endocrine and metabolic drugs, NSAIDs, phosphodiesterase type V inhibitors, or quinolones) compared with those not using one of these medications. This was considered by the sponsor to be expected due to the increased risk of AEs associated with the underlying conditions and medications used to treat them and the evaluator agreed with this interpretation.

Laboratory Abnormalities, Vital Signs and Clinical Findings

The mean values for all haematology and clinical chemistry laboratory parameters were similar across the treatment groups at baseline, and Months 12 and 24. During this period, transitions in laboratory tests from baseline were similar across the treatment groups, with no consistent pattern being noted when comparing abnormalities. The proportion of patients with any parameter outside the pre-specified threshold was low and similar across the treatment groups (2% of patients). The majority of patients with threshold laboratory values had associated AEs, for example, diabetes and anaemia.

Baseline PSA and the corresponding baseline values for subjects with total PSA measurements at Months 12 and 24 were similar across the treatment groups. After Months 12 and 24 the mean PSA was consistently lower in the combination and dutasteride monotherapy group, compared to a small rise in the tamsulosin monotherapy group. The adjusted mean changes (reductions) from baseline in total PSA were significantly greater on combination therapy when compared to tamsulosin monotherapy at Months 12 and 24, whereas there was no statistical difference between combination and dutasteride monotherapy over time.

Assessment of gynaecomastia and digital rectal examinations were conducted at baseline and at 6-month intervals. At baseline, 8% of patients in each treatment group had evidence of gynaecomastia. The incidence of post-baseline gynaecomastia was 8% in both the

combination and dutasteride groups and in the tamsulosin group, it was 6%. A statistically significant higher proportion of patients in the combination group developed nipple tenderness compared to the tamsulosin group. The proportion of patients with an abnormal prostate on DRE clinically at baseline (2-3%) and at each 6-month interval up until Month 24 (1-2%) was low and similar across the treatment groups. There was no statistically significant difference between the combination and monotherapy groups in the proportion of patients who developed an abnormal prostate post baseline.

There were no clinically relevant trends noted in vital signs during the study. There was a similar proportion of patients with any baseline or post-baseline value outside the normal threshold across the treatment groups. The most frequently reported post-baseline threshold parameter was raised systolic blood pressure, and the incidence was similar across the treatment groups (14% in the combination group, 15% in each of the monotherapies).

Median changes in post void residual volume were significantly greater with combination therapy
(-8.0 mL) compared to tamsulosin monotherapy (-1.0 mL) ($p<0.001$). The reduction was also greater than with dutasteride alone (-4.0 mL), but statistical significance was not reached.

Supporting Studies - Study ARI40002

Drug Exposure and Overview of Adverse Events

A total of 421 patients were enrolled and entered the placebo run-in phase of this study, of which 94 discontinued prior to randomisation. The remaining 327 patients were randomised to receive either tamsulosin and dutasteride combination therapy for 36 weeks (TD36), or tamsulosin and dutasteride combination therapy for 24 weeks followed by dutasteride only for 12 weeks (TD24+D12). This comprised the ITT population for analysis.

During the first 24-week treatment period, the mean extent of exposure to study drug was similar between the treatment groups. The minimum exposure was 3 days, with this patient withdrawing prematurely due to an AE. During the final 12 weeks of the study, the median exposure was 84 days in both groups.

Overview of Adverse Events

During the first 24 week treatment phase, a total of 150 patients (46%) experienced 316 AEs, with a similar percentage in each treatment group experiencing an AE (TD36: 79 patients [48%], 159 events, TD24+D12: 71 patients [44%], 157 events). There were no clear differences between the treatment groups in the proportion of patients with an AE, or for specific AEs reported. Other than sexual function AEs (ejaculation disorders, impotence, altered libido), the only other AE reported in ≥5% of patients was malaise and fatigue (Table 7). During the final 12 weeks of the treatment phase of the study, 32 patients (20%) who were maintained on combination therapy experienced 49 AEs, whereas in the group who received dutasteride only, 42 patients (26%) experienced 63 AEs. There were no clear differences between the groups.

Table 7: Summary of Common Adverse Events (>5% of patients) occurring in ITT population.

Summary of Treatment-Emergent Adverse Events in ≥5% of Subjects in Either Treatment Group
(Intent-to-Treat Population in Protocol ARI40002)

	TD36 Group (N=164)		TD24+D12 Group (N=163)	
	No.[a]	%	No.[a]	%
Week 0-24				
Any Adverse Event	79	48%	71	44%
Any Drug-related Adverse Event	45	27%	36	22%
Adverse Events in ≥5% subjects:				
Ejaculation disorder	12	7%	12	7%
Altered (decreased) libido	7	4%	10	6%
Impotence	8	5%	4	2%
Malaise & fatigue	10	6%	3	2%
Week 24-36				
Any Adverse Event	32	20%	42	26%
Any Drug-related Adverse Event	11	7%	5	3%
Week 36-37				
Any Adverse Event	11	7%	9	6%
Week 37-52				
Any Adverse Event	13	8%	12	7%

[a]Represents the number of subjects reporting one or more adverse events

In total there were 156 AEs reported by 96 patients (29%) that were considered by the investigators to be drug-related (that is, having a reasonable possibility of being caused by the study medication). The incidence of drug-related AEs was similar between the treatment groups (Table 8). Events related to sexual function and malaise and fatigue were the most commonly reported drug related AEs.

Table 8: Summary of Common (>5% patients) Drug-related Adverse Events (ITT population)

Summary of Drug-Related Adverse Events with Onset After Randomisation up to Week 37 in ≥5% of Subjects in Either Treatment Group
(Intent-to-Treat Population in Protocol ARI40002

	TD36 Group (N=164)		TD24+D12 Group (N=163)	
	No.[a]	%	No.[a]	%
Any Drug-related Adverse Event	54	33%	42	26%
Adverse Events in ≥5% subjects:				
Ejaculation disorder	14	9%	13	8%
Altered (decreased) libido	9	5%	10	6%
Impotence	9	5%	6	4%
Malaise & fatigue	8	5%	2	1%

[a]Represents the number of subjects reporting one or more adverse events

Serious Adverse Events, Deaths and Discontinuations due to Adverse Events

During the treatment phase of the study there were no deaths. However, during the follow-up period from Week 37 to Week 52 one patient died. He developed acute pulmonary oedema and cardiorespiratory arrest 27 days after his last dose of study medication. Review of the death narrative suggested that this death may not be related to the study medication due to his pre-existing cardiovascular disease and diabetes.

During the treatment phase of the study, 10 patients reported 13 SAEs. Of these, 7 were in the TD36 group and 3 were in the TD24+D12 group. The incidence of all SAEs was ≤1% and

consisted mainly of cardiovascular events (for example, angina, arterial stenosis and arteriospasms) and gastrointestinal disorders (including herniae and obstruction). Only one SAE was considered by the investigators to have a reasonable possibility of being related to the study medication. A patient in the TD36 group developed chest pain and was found to have a pulmonary embolism. A further 7 AEs were reported during the follow up phase of the study, including the fatal AE described above. Four of these SAEs were experienced by 3 patients in the TD 36 group, and 3 experienced by 2 patients in the TD24+D12 group. None of these SAEs were considered by the investigators as being related to the study drug.

After randomisation, during the active treatment phase, there were a total of 21 AEs in 14 patients (TD36: 7patients/ 12 events, 4%; TD24+D12: 7 patients/ 9 events, 4%) which led to premature discontinuation of study medication. Of those patients who withdrew prematurely, 9 experienced 12 events which were considered by the investigators as having a reasonable possibility of being related to the study drug. With the exception of malaise and fatigue (which occurred in 2% in TD36 and <1% in TD24+D12), all other AEs leading to withdrawal occurred with frequency <1%.

Adverse Events of Special Interest

The AEs of special interest in the study included altered libido, impotence, disorders of sexual function, ejaculation disorders and gynaecomastia. The incidence of these AEs was comparable between the treatment groups and is summarised in Table 9. In the TD36 group, one subject was withdrawn for each of the events altered libido and impotence, and in the TD24+D12 group, one patient was withdrawn due to ejaculation disorder.

Table 9: Treatment Emergent AEs of Special Interest

Treatment-Emergent Adverse Events of Special Interest
(Intent-to-Treat Population in Protocol ARI40002)

	All Adverse Events				Drug-Related Adverse Events			
	TD36 Group (N=164)		TD24+D12 Group (N=163)		TD36 Group (N=164)		TD24+D12 Group (N=163)	
	No.[a]	%	No.[a]	%	No.[a]	%	No.[a]	%
Altered (decreased) libido	9	5%	11	7%	9	5%	10	6%
Impotence	9	5%	6	4%	9	5%	6	4%
Ejaculation disorders	14	9%	14	9%	14	9%	13	8%
Sexual function disorders	0	-	1	<1%	0	-	1	<1%
Gynaecomastia	1	<1%	0	-	1	<1%	0	-

[a] Represents the number of subjects reporting one or more adverse events.

Altered libido was reported by 9 (5%) patients in the TD36 group and by 11 (7%) in the TD24+D12 group. In all cases except for one in the TD24+D12 group, this was considered by the investigators to be related to the study medication. Median time to onset for altered libido was 29 days in the TD36 group and 46 days in the TD24+D12 group. At the time of the study report, altered libido had been noted to have resolved in 1/9 of patients in the TD36 group and in 2/11 patients in the TD24+D12 group.

Impotence was reported by 9 (5%) patients in the TD36 group and 6 (4%) in the TD24+D12 group, and in all except the one case that withdrew in the TD36 group was reported as mild. The investigators considered all cases of impotence to be related to the study medication. Of these events, one case in the TD36 group resolved whilst still on the study medication, and two cases (one from each group) resolved off therapy.

Ejaculation disorders were reported by 14 (9%) patients in the TD36 group and 14 (9%) in the TD24+D12 group. All reports were of mild-moderate intensity, and all except one case in the TD24+D12 group were considered by the investigators as being related to the study medication.

One patient in the TD24+D12 group reported a non-specific sexual function disorder of moderate intensity, which was considered by the investigators to be related to the study drug. The patient continued the study, and the disorder resolved off treatment.

One patient in the TD36 group reported gynaecomastia of mild intensity, which was considered by the investigators to be related to the study medication. Time to onset was 31 days, and at the time of the study report, this had remained unresolved.

There were two patients who reported one episode of AUR in the TD24+D12 group, which occurred during the treatment phase. One patient in each group required prostate surgery during the study period.

Laboratory Abnormalities, Vital Signs and Clinical Findings

The incidence of post-baseline laboratory values outside threshold was <1% for each analyte tested in both groups with the exception of alkaline phosphatise >1.5 the upper limit of normal (ULN) which occurred in 2 patients (1%). There was no statistical difference noted between the two groups.

The mean baseline PSA was 4.33 ng/mL (±2.17) in the TD36 group and 4.33 ng/mL (±2.21) in the TD24+D12 group. At week 36, in the TD 36 group, the mean PSA had decreased to 2.52 ng/mL (±1.78) with an adjusted mean change of -1.8 ng/mL. In the TD24+D12 group the mean PSA at Week 36 had decreased to 2.55 ng/mL (±1.93), an adjusted mean change of -1.8 ng/mL.

Vital signs were comparable at baseline between the groups. During the treatment period there were 20% of patients in the TD36 group that had a measurement outside threshold, compared to 14% in the TD24+D12 group, with no statistically significant differences between the groups. Of patients that exceeded the upper systolic blood pressure threshold (<165 mmHg), 18% were in the TD36 group and 12% in the TD24+D12 group. There was no statistical difference, and generally these were single events with no obvious trends.

There was no significant change evident between the groups regarding evidence of gynaecomastia or changes in findings on DRE.

Supporting Studies - Study ARI40013

Drug Exposure and Overview of Adverse Events

A total of 2403 patients were screened, with 2385 patients being exposed at least once to the study medication. There were 1574 patients exposed to at least one dose of combination therapy with dutasteride 500 µg and tamsulosin 400 µg (CT group) and there were 811 patients allocated to the dutasteride monotherapy group (MT). Duration of exposure to study medication was between 36 and 72 weeks.

Overview of Adverse Events

Adverse events occurring prior to first exposure to study medication were reported in 26 of the 2403 patients, 3 of which were not subsequently randomised. There were no pre-treatment SAEs reported. No statistical analysis of AE occurrence between the two groups is made, which the evaluator agreed was appropriate, given the non-matched nature of the treatment groups with regard to baseline disease characteristics.

A summary of the overall AEs occurring after the first dose of study medication is presented in Table 10. The incidence of AEs, SAEs and drug-related AEs was similar in both treatment groups, whereas the number of deaths was higher in the CT group. In the MT group, 303 patients (37.4%) reported any AE, compared to 613 patients (39.0%) in the CT group. The most commonly reported AEs (approximately 10% in each treatment group) were in the *Reproductive System and Breast Disorders* SOC, and within this group the most frequently reported AEs by preferred terms were erectile dysfunction (4.4%), prostatitis (1.3%), retrograde ejaculation (1.3%), sexual dysfunction (0.8%) and gynaecomastia (0.6%) (Table 11). It was also noted that AEs in the class *Renal and Urinary Disorders* occurred more frequently in the CT group (108 patients, 6.9%) compared to the MT group (33 patients, 4.1%). This may well be due to the fact that patient allocated to the CT group had more severe disease at baseline (as evidenced by higher IPSS scores), and were therefore at higher risk of developing urinary AEs.

Table 10: Summary of Overall Treatment Emergent Adverse Events (TEAEs) (ITT population) – ARI40013

	MT group N=811 n (%)	CT group N=1,574 n (%)	Total N=2,385 n (%)
Subjects with any TEAEs	303 (37.4%)	613 (39.0%)	916 (38.4%)
Subjects with non-fatal serious TEAEs	40 (4.9%)	78 (5.0%)	118 (5.0%)
Subjects with fatal serious TEAEs	1 (0.1%)	9 (0.6%)	10 (0.4%)
Subjects with serious TEAEs[a]	41 (5.1%)	87 (5.5%)	128 (5.4%)
Subjects with drug-related TEAEs	122 (15.0%)	279 (17.7%)	401 (16.8%)
Subjects with drug-related serious TEAEs	2 (0.3%)	4 (0.3%)	6 (0.25%)
Subjects with dutasteride-related serious TEAEs[b]	2 (0.3%)	3 (0.2%)	5 (0.2%)
Subjects with premature withdrawal due to AEs	59 (7.3%)	173 (11.0%)	232 (9.7%)

a No source, but the incidence of serious TEAEs could be calculated as the sum of subjects with non-fatal and fatal events, since no subjects with fatal TEAEs had previously experienced a non-fatal serious TEAE (ie, no overlapping events, cf. subject listings).
b Related to dutasteride alone or to both dutasteride and tamsulosin.
Note: No death was regarded as drug-related.
Note: "Drug-related" generally means a suspected relationship to dutasteride and/or tamsulosin (investigator's assessment).

Table 11: Overview of Most Common Specified TEAEs within SOCs *Reproductive System and Breast Disorders* and *Renal and Urinary Disorders* by PT (ITT population) – ARI40013

	MT group N=811 n (%)	CT group N=1,574 n (%)	Total N=2,385 n (%)
Reproductive system and breast disorders			
erectile dysfunction	38 (4.7%)	68 (4.3%)	106 (4.4%)
prostatitis	7 (0.9%)	24 (1.5%)	31 (1.3%)
retrograde ejaculation	4 (0.5%)	27 (1.7%)	31 (1.3%)
sexual dysfunction	6 (0.7%)	12 (0.8%)	18 (0.8%)
gynaecomastia	6 (0.7%)	8 (0.5%)	14 (0.6%)
Renal and urinary disorders			
dysuria	6 (0.7%)	40 (2.5%)	46 (1.9%)
urinary retention	5 (0.6%)	29 (1.8%)	34 (1.4%)
pollakiuria	3 (0.4%)	12 (0.8%)	15 (0.6%)
nocturia	3 (0.4%)	12 (0.8%)	15 (0.6%)
urge incontinence	2 (0.3%)	10 (0.6%)	12 (0.5%)

Note: Multiple answers per subject were possible.

Drug-related AEs were defined as those considered by the investigators to have a possible relationship to the study medication. There was a similar overall incidence between the treatment groups, with 122 patients (15.0%) in the MT group and 279 patients (17.7%) in the CT group experiencing AEs considered to be drug related. The most commonly reported drug-related AEs were related to sexual function and vegetative signs (for example, headache, fatigue, diarrhoea, hyperhidrosis, vertigo and nausea) and are summarised in Table 12.

Table 12: Drug-related AEs with an Incidence of 0.5% or more in Total Population (ITT population) – ARI40013

	MT group N=811 n (%)	CT group N=1,574 n (%)	Total N=2,385 n (%)
Erectile dysfunction	31 (3.8%)	59 (3.8%)	90 (3.8%)
Retrograde ejaculation	4 (0.5%)	25 (1.6%)	29 (1.2%)
Headache	8 (1.0%)	18 (1.1%)	26 (1.1%)
Loss of libido	7 (0.9%)	19 (1.2%)	26 (1.1%)
Vertigo	2 (0.3%)	24 (1.5%)	26 (1.1%)
Fatigue	8 (1.0%)	13 (0.8%)	21 (0.9%)
Sexual dysfunction	4 (0.5%)	11 (0.7%)	15 (0.6%)
Gynecomastia	6 (0.7%)	8 (0.5%)	14 (0.6%)
Libido decreased	5 (0.6%)	9 (0.6%)	14 (0.6%)
Nausea	2 (0.3%)	11 (0.7%)	13 (0.6%)
Diarrhoea	4 (0.5%)	7 (0.4%)	11 (0.5%)
Hyperhidrosis	1 (0.1%)	10 (0.6%)	11 (0.5%)

Note: Multiple answers per subject were possible.

Serious Adverse Events, Deaths and Discontinuations due to Adverse Events

There were 13 deaths during the treatment and follow up stages of the study, one in the MT group and 12 in the CT group. Of these, 10 occurred during the active treatment phase (one in the MT group, 9 in the CT group). None of these deaths were considered by the investigators as being possibly related to the study medication.

There were 118 patients (40 patients [4.9%] in the MT group and 78 patients [5.0%] in the CT group) who experienced SAEs. The overall rate of SAEs was similar between the two treatment groups**.** There were 8 patients that experienced AEs that were considered by the investigators as being possibly related to the study medication. Five of these were in the CT group (palpitations, atrial fibrillation, hyperbilirubinaemia, syncope and myocardial infarction) and three of them were in the MT group (raised blood pressure, peritoneal neoplasm, and gynaecomastia). Overall the analysis of the SAEs did not reveal any findings that would imply a re-assessment of the known risk-benefit profile of dutasteride.

There were 173 patients (11.0%) in the CT group and 59 patients (7.3%) in the MT group that withdrew from the study prematurely because of AEs. The AEs that most commonly led to withdrawal were dysuria and AUR, which occurred more frequently in the CT group compared to the MT group. The observed difference between the treatment groups in patients withdrawing in the CT group compared to the MT group, especially with regard to renal and urinary disorders, is potentially best explained by the increased severity of the disease at baseline in this group.

Adverse Events of Special Interest

There were no pre-defined AEs of special interest. There was an ad hoc analysis comparing AEs of special interest such as erectile dysfunction, altered libido, ejaculation disorders, breast disorders, BPH, AUR, prostate resection and prostate, pancreas or breast cancer between MT- and CT-treatment groups. It was found that these tended to occur earlier in the treatment period. Numerical differences between the treatment groups with a higher frequency of the ad hoc AE observed in the CT group were seen with UAR (1.7% versus

0.5%), BPH symptoms (5.0% versus 2.7%), ejaculation disorders (2.9% versus 1.2%) and prostate cancer (0.4% versus 0.0%). There were no reports of breast or pancreatic cancer.

Laboratory Abnormalities, Vital Signs and Clinical Findings

Laboratory values were recorded at baseline for all patients, but were only recorded at the end if there were any clinically significant abnormal values or changes from baseline. Consequently, post-baseline documentation of laboratory values was reported as being scarce. Generally analysis of laboratory values did not indicate any clinically relevant or unexpected risk associated with the study medication.

There were no noteworthy changes in heart rate or blood pressure during the study period

Safety Conclusions

A total of 3511 patients were treated with combination therapy with dutasteride 500 µg once daily and tamsulosin 400 µg once daily across the three studies evaluated. Combination therapy was well tolerated, for up to two years in the pivotal study ARI40005.

In the pivotal study ARI40005, the overall incidence of adverse effects was similar in the combination therapy and monotherapy groups.

The incidence and type of adverse events occurring whilst on combination therapy in all three studies were consistent with the already known safety profiles of dutasteride and tamsulosin.

The most commonly reported AEs considered to be drug-related were related to sexual function, especially ejaculation disorders, which occurred more commonly with combination therapy compared to either monotherapy.

Incidence of SAEs was similar across the treatment groups and the most frequently reported were cardiovascular disorders.

There was no significant adverse trend in vital signs, clinical findings or laboratory values in any of the studies.

Post-marketing Experience

The sponsor examined four primary sources for post-marketing information related to the combined use of dutasteride and tamsulosin. They examined the public literature, their own GSK world-wide safety database OCEANS (Operating Companies Event Accession and Notification System), and two publicly available external post-marketing safety databases, FDA Adverse Event Reporting System (AERS) and the World Health Organization (WHO) Vigibase.

Published literature was searched using Medline and the following search terms: Avodart, Duagen, or dutasteride with Flomax, Omnic or tamsulosin. The cut off date for the search was May 2007. There were three publications reporting safety data specific to the co-administration of dutasteride and tamsulosin in men with BPH. Two of these describe the results of the SMART-1 trial which was presented for evaluation as ARI40002, the safety findings of which are described in this report above. The third publication reported the results of a randomised 6-month study comparing tamsulosin 400 µg combined with dutasteride 500 µg once daily (n=52) versus tamsulosin 400 µg combined with finasteride 5 mg once daily (n=52) in men with symptomatic BPH.[19] Incidence of sexual function disorder was similar in both treatment groups (six patients in the tamsulosin/ finasteride group and five patients in

[19] Mohanty NK, Singh UP, Sharma NK, Arora Rp, Amitabh V. A comparative study of fixed dose of Tamsulosin with finasteride vs Tamsulosin with dutasteride in the management of benign prostatic hyperplasia. Indian J Urol 2006; 22: 130-134.

the tamsulosin/ dutasteride group) and that there were no significant changes from baseline with regard to laboratory values in either group.

As of May 2007, GSK OCEANS had received 361 spontaneous reports (total of 780 AEs) mentioning dutasteride as a suspect or concomitant drug and tamsulosin as a suspect or concomitant drug. The most commonly reported AEs were drug ineffective (47 events), gynaecomastia (20), dysuria (20), pollakiuria (15), nocturia (14), erectile dysfunction (14), and breast tenderness (14).

The FDA AERS contained 279 reports mentioning both dutasteride and tamsulosin, and Vigibase contained 141 reports mentioning both dutasteride and tamsulosin. Disproportionality analysis using these databases revealed no adverse events unique to the combination of dutasteride with tamsulosin; the events reported with high frequency when dutasteride and tamsulosin were co-reported are consistent with the known safety profile or pharmacological activity of either dutasteride, tamsulosin, or the clinical effects of the underlying BPH.

Clinical Summary and Conclusions

Avodart is a preparation containing dutasteride 500 µg which has previously been approved by the TGA in November 2002 for the indication "treatment of patients with symptomatic benign prostatic hyperplasia with an enlarged prostate". This further application has been submitted to request approval for an extension of the current indication to include co-administration with an alpha blocker to assist in the treatment of BPH.

Data from all three studies evaluated in this report support the efficacy of combination therapy with dutasteride 500 µg and tamsulosin 400 µg once daily in the improvement of symptoms in patients with BPH. Data from the pivotal study ARI40005 demonstrated that combination therapy with dutasteride and tamsulosin was significantly better at improving symptoms, as evidenced by change in IPSS, than either drug used as monotherapy. Also urinary flow rates were demonstrated to be significantly improved with combination therapy compared to either monotherapy. Reduction in prostate volume was similar when treated with either combination therapy or dutasteride alone, with both being superior to monotherapy with tamsulosin.

The safety profile of co-administration was favourable, with the nature and frequency of AEs reported in all three studies being consistent with the safety profiles of either monotherapy. The most frequently reported drug-related AEs were related to sexual function (impotence, altered libido, ejaculation disorders), and ejaculation disorders were more commonly reported with combination therapy.

The proposed wording of the new indication is:

Avodart, as monotherapy or in combination with an alpha blocker, is indicated for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate.

The sponsors have conducted studies using only one alpha blocker, tamsulosin but the wording of the proposed indication implies that dutasteride could be used with any alpha blocker. In fact, the sponsor's letter of introduction to one part of the submission states the following:-'This type II variation is to amend the Avodart SmPC (Summary of Product Characteristics) to include wording on the combined use of dutasteride and the alpha blocker tamsulosin in order to deliver the respective benefits.' However, the proposed indication does not specify that dutasteride can only be used in combination with tamsulosin.

The other commonly used alpha blockers for treatment of BPH include the long-acting alpha blockers, terazosin (1 to 5 mg daily) and doxazosin (1 to 8 mg daily), both of which require dose-titration. The selective α_{1a} blockers such as tamsulosin and alfuzosin are associated with fewer systemic side effects obviating the need for dose titration. The sponsors have demonstrated efficacy and safety of combination therapy of dutasteride only with tamsulosin. Safety and efficacy of dutasteride in combination with other α_1 blockers such as terazosin, doxazosin or alfuzosin was not evaluated.

Therefore the proposed indication cannot be approved due to the fact that the sponsor has shown efficacy and safety of dutasteride in combination with tamsulosin only and not other alpha blockers.

It is acknowledged however that there is sufficient evidence of clinical efficacy, with statistically and clinically significant improvement in symptoms and a favourable safety profile following combination therapy of dutasteride with tamsulosin for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate. Hence, the application could be approved subject to incorporation of appropriate changes to the proposed indication.

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Medicines Safety Monitoring (OMSM). The ongoing safety concerns were identified by the sponsor as follows:

Important identified risks:

- Sexual adverse events (altered [decreased] libido, impotence, ejaculation disorders) and breast disorders (enlargement and tenderness)
- Allergic reactions, including rash, pruritus, urticaria, localised oedema, and angioedema

Important potential risks:

- Male breast cancer
- Cardiovascular Events
- High-grade prostate cancer
- Interference with formation of external male genitalia in the foetus

Important missing information:

- Men with severe hepatic impairment
- Men with unstable medical conditions

In principle there was no objection to the sponsor implementing the proposed application of routine pharmacovigilance activities for all the specified ongoing safety concerns and the application of additional pharmacovigilance activities for 'Male breast cancer', 'Cardiovascular events', 'High-grade prostate cancer' and 'Interference with formation of external male genitalia in the foetus'.[20]

[20] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;

The sponsor provided an assurance that updates will be provided in Periodic Safety Update Reports (PSURs), unless a significant safety issue emerges requiring more immediate notification to regulatory authorities. In addition completion and analysis of the ongoing 2-year, observational Study ARI103094 for follow-up of prostate cancer cases reported during the 4-year Study ARI40006 is scheduled for 2012. This was considered acceptable.

Nevertheless the OMSM requested that the sponsor provide to the TGA a copy of the targeted follow-up questionnaire specific to breast cancer and a copy of the targeted follow-up questionnaire used to request additional information on spontaneous reports of prostate cancer.

Routine risk minimisation activities will include warnings or notification of undesirable effects in the Australian PI for all the specified ongoing safety concerns, except for 'Men with unstable medical conditions', as there is no evidence from controlled clinical trials of additional safety concerns in men taking dutasteride who developed these conditions during the trial.[21] This was considered generally acceptable.

Recommendations were also made with respect to the proposed Australian PI but these are beyond the scope of this AusPAR.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

Nonclinical studies using a combination of dutasteride and an alpha blocker were not submitted. The sponsor's *Nonclinical Overview* and supportive documentation were focused on co-prescription of dutasteride and tamsulosin only (and not on any other currently registered alpha blockers).

The nonclinical evaluator was of the opinion that the sponsor had provided an acceptable justification for the absence of non-clinical combination studies by reference to the TGA-approved EU guideline and consideration of extensive clinical experience with co-administration of the products.[13] Also both dutasteride and tamsulosin had been previously evaluated individually in nonclinical development programs and the potential for adverse pharmacodynamic, pharmacokinetic or toxicological interactions appeared to be low.

The nonclinical evaluator concluded that the proposed indication for use of dutasteride with an alpha blocker was too broad as the submitted dossier was focused on the specific co-administration of dutasteride with tamsulosin. Therefore there were no objections, on nonclinical grounds, to the co-prescription of dutasteride (Avodart) and tamsulosin for the treatment of BPH. However, the use of dutasteride with other alpha-1-adrenergic blockers was not supported by the data package.

- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

[21] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Clinical

The clinical data comprised the following studies:

- one clinical pharmacology study, ARIA1011
- 3 Phase III clinical efficacy and safety studies of the co-administration of dutasteride and tamsulosin – Study ARI40005 was a pre-determined interim 2-year analysis of a 4-year pivotal study; Studies ARI40002 and ARI40013 were supporting studies.

Tamsulosin was selected as the alpha blocker of choice for co-administration because there is no need for dose titration, it has a more favourable safety profile compared with other alpha blockers and there are no known PK/PD interactions between dutasteride and tamsulosin. Combination therapy with other alpha blockers such as alfuzosin, prazosin and doxazosin was not evaluated.

The clinical evaluator recommended approval for an extension of indications to include combination therapy of dutasteride and tamsulosin for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate but recommended rejection of the wider extension to include combination therapy of dutasteride with all alpha blockers. The principal reason for the latter rejection was that the data in the submitted dossier demonstrated the efficacy and safety of only the combination of dutasteride with tamsulosin. The safety and efficacy of dutasteride in combination with other α_1 blockers such as terazosin, doxasin or alfuzosin were not evaluated.

Pharmacology

The pharmacology of dutasteride was evaluated in a Phase I alpha blocker – dutasteride interaction study (ARIA 1011), completed in January 1999. This randomized, open-label, single-sequence, 56-day crossover study in 48 healthy volunteers assessed the PD/PK interactions between dutasteride and either of the alpha blockers, tamsulosin or terazosin. There were the following findings:

- Similar DHT suppression was observed with dutasteride alone compared with the combination treatments with either alpha blocker. Similar trough concentrations of dutasteride were observed during combination treatment with either alpha blocker.
- Dutasteride 500 µg had no effect on the steady state pharmacokinetics of tamsulosin 400 µg or terazosin titrated to 10 mg. In addition, similar DHT suppression was observed with dutasteride alone compared to the combination treatment with either alpha blocker. Similar trough concentrations of dutasteride were observed during combination treatment with both alpha blockers.

ARIA 1011, the study in healthy volunteers discussed under the previous point, showed that dutasteride does not affect the pharmacokinetics of tamsulosin. However, the effects of tamsulosin on the pharmacokinetics of dutasteride were not evaluated in this study[22]. In addition to the data from ARIA 1011, the metabolic pathways for dutasteride and tamsulosin as well as the exposure levels for dutasteride were examined for any evidence that would support a clinically significant interaction between these two compounds.

Dutasteride is metabolized by the CYP3A4/5 isoenzymes. Available literature supplied by the sponsor and the approved PI for tamsulosin indicate that tamsulosin does not inhibit CYP3A4, 2C9 or 2D6, making a drug interaction with dutasteride unlikely. *In vitro* studies

[22] In previously evaluated studies, ARIA1001 & ARIA2001, higher levels of exposure to dutasteride than from the approved dosage regimens were investigated for periods of up to 6 months and found not to be associated with significant safety concerns.

with human liver microsomes show that CYP3A4 and CYP2D6 are the predominant enzymes responsible for tamsulosin metabolism. There are no time-dependent changes in the pharmacokinetics of tamsulosin with multiple dosing, making it unlikely that tamsulosin induces any of the isoenzymes responsible for its metabolism. From the studies included in the dossier for initial registration, dutasteride has been demonstrated to have a wide safety margin.

Efficacy

Pivotal Study ARI40005 (CombAT – Combination with Alpha blocker Therapy)

ARII40005 was the Phase III study designed to demonstrate the superiority of combination therapy of dutasteride 500 µg and tamsulosin 400 µg over dutasteride 500 µg or tamsulosin 400 µg alone. It was a multicentre, randomized, double-blind, parallel-group study of the improvement of symptoms and clinical outcome in men with moderate to severe symptomatic BPH and it consisted of a 4-week single-blind placebo run-in period, a 4-year double-blind treatment period and a 16-week safety follow-up period.

The primary efficacy endpoint at Year 2 was change from baseline in the International Prostate Symptom Score (IPSS) and the primary comparisons of interest for this parameter were the combination therapy versus each monotherapy. For IPSS, the hypothesised superiority of combination therapy over dutasteride monotherapy was 1.5 units and for tamsulosin monotherapy was 1.0 unit. Comparable efficacy gains versus placebo have been demonstrated for finasteride, tamsulosin and alfuzosin.

Key Year 2 secondary endpoints included change from baseline in prostate volume (PV), peak urinary flow rate (Q_{max}), BPH Impact Index (BII), BPH-related health status (question 8 of the IPSS, also known as IPSS-QOL) as well as the proportions of subjects with IPSS improvement from baseline of≥ 2 units, ≥ 3 units and ≥ 25% and the proportions of subjects with Q_{max} improvements from baseline of≥ 30% and ≥ 3 mL/sec.

Primary efficacy results: At 24 months, a statistically significantly greater reduction (improvement) from baseline in IPSS was achieved with combination therapy compared with either dutasteride or tamsulosin monotherapy. The hypothesised superiority margin of 1.5 units of combination therapy over dutasteride monotherapy was met in the At Visit analysis (but not in the LOCF analysis) and that of 1.0 unit over tamsulosin was satisfied in both At Visit & LOCF analyses. These results are shown in Table 2.

Reductions from baseline in IPSS were consistently numerically greater with combination therapy compared with either monotherapy and were continued over 24 months. These differences were statistically significant between combination therapy and dutasteride beginning at Month 3 and between combination therapy and tamsulosin beginning at Month 9. These results are shown in Table 13. This Table displays the plateauing of the differences between the results for the combination and dutasteride monotherapy groups and the gradual widening of the differences between the results of the combination and tamsulosin monotherapy groups. These trends reflect the differences in physiological action and time to onset of action of dutasteride and tamsulosin.

Table 13: Change from Baseline in IPSS (LOCF and At Visit), ITT population - ARI40005

Time Point	Adjusted mean change from baseline (SE)					
LOCF	N	Combination	N	Dutasteride	N	Tamsulosin
Month 3	1564	-4.8 (0.14)	1582	-2.8 (0.14)	1573	-4.5 (0.14)
Month 9	1575	-5.4 (0.14)	1592	-4.0 (0.14)	1582	-4.7 (0.14)
Month 12	1575	-5.6 (0.15)	1592	-4.2 (0.15)	1582	-4.5 (0.15)
Month 24	1575	-6.2 (0.15)	1592	-4.9 (0.15)	1582	-4.3 (0.15)
At Visit						
Month 3	1541	-4.8 (0.14)	1570	-2.8 (0.14)	1562	-4.5 (0.14)
Month 6	1471	-5.0 (0.14)	1509	-3.5 (0.14)	1507	-4.5 (0.14)
Month 12	1389	-6.0 (0.15)	1426	-4.5 (0.15)	1429	-4.7 (0.15)
Month 24	1258	-6.8 (0.15)	1287	-5.3 (0.15)	1237	-5.0 (0.16)

	Adjusted mean difference of combination from monotherapy (SE) [95% CI]			
LOCF	Dutasteride	P-value [1]	Tamsulosin	P-value [1]
Month 3	-2.0 (0.192) [-2.33,-1.57]	<0.001	-0.26 (0.192) [-0.63, 0.12]	0.18
Month 9	-1.4 (0.199) [-1.79, -1.01]	<0.001	-0.74 (0.199) [-1.13, -0.35]	<0.001
Month 12	-1.4 (0.202) [-1.80,-1.01]	<0.001	-1.1 (0.203) [-1.53,-0.73]	<0.001
Month 24	-1.3 (0.212) [-1.69,-0.86]	<0.001	-1.8 (0.212) [-2.23,-1.40]	<0.001
At Visit				
Month 3	-2.0 (0.191) [-2.37,-1.62]	<0.001	-0.31 (0.191) [-0.68, 0.07]	0.11
Month 6	-1.5 (0.195) [-1.89, -1.12]	<0.001	-0.51 (0.195) [-0.90, -0.13]	0.009
Month 12	-1.5 (0.205) [-1.92,-1.11]	<0.001	-1.3 (0.205) [-1.68,-0.88]	<0.001
Month 24	-1.5 (0.215) [-1.93,-1.08]	<0.001	-1.9 (0.217) [-2.28,-1.43]	<0.001

1. p-values based on t-tests from the general linear model

Selected key secondary endpoints: Changes (increases) in peak urinary flow rate, Q_{max}, from baseline were consistently higher on combination therapy compared with either monotherapy at each 6 month assessment up to 24 months. These results are seen in Table 14.

Table 14: Change from Baseline in Q_{max} (LOCF) – ARI40005

Time Point	Adjusted mean change from baseline (SE)					
	N	Combination	N	Dutasteride	N	Tamsulosin
Month 6	1388	2.0 (0.12)	1406	1.2 (0.12)	1445	1.2 (0.11)
Month 12	1477	2.0 (0.12)	1483	1.5 (0.12)	1510	0.9 (0.12)
Month 18	1487	2.3 (0.12)	1496	1.8 (0.12)	1517	1.1 (0.12)
Month 24	1492	2.4 (0.12)	1502	1.9 (0.12)	1519	0.9 (0.12)

	Adjusted mean difference of combination from monotherapy (SE) [95% CI]			
	Dutasteride	P-value [1]	Tamsulosin	P-value [1]
Month 6	0.75 (0.162) [0.43, 1.06]	<0.001	0.78 (0.161) [0.46, 1.09]	<0.001
Month 12	0.50 (0.164) [0.17, 0.82]	0.002	1.12 (0.163) [0.80, 1.44]	<0.001
Month 18	0.47 (0.172) [0.14, 0.81]	0.006	1.23 (0.171) [0.90, 1.57]	<0.001
Month 24	0.51 (0.172) [0.17, 0.84]	0.003	1.52 (0.172) [1.19, 1.86]	<0.001

1. P-values based on t-tests from the general linear model

At Month 24, a statistically significantly greater proportion of subjects treated with combination therapy had IPSS improvements of≥ 2 units, ≥ 3 units and ≥ 25% from baseline compared with either monotherapy. Compared with dutasteride monotherapy, these improvements were sustained from Month 3, while compared with tamsulosin monotherapy, these improvements were sustained from Month 9. These results are shown in Table 15.

Table 15: IPSS Changes from Baseline – Improvement Categories Tested for Significance (LOCF) - ARI40005

Time point Improvement category	Combination N=1610 n (%)	Dutasteride N=1623 n (%)	p-value [1]	Tamsulosin N=1611 n (%)	p-value [1]
Month 3	N=1564	N=1582		N=1573	
≥2 units	1132 (72)	935 (59)	<0.001	1109 (71)	0.24
≥3 units	1015 (65)	824 (52)	<0.001	1000 (64)	0.42
≥25%	888 (57)	654 (41)	<0.001	851 (54)	0.12
Month 6	N=1572	N=1591		N=1581	
≥2 units	1139 (72)	997 (63)	<0.001	1102 (70)	0.082
≥3 units	1040 (66)	884 (56)	<0.001	988 (62)	0.029
≥25%	914 (58)	746 (47)	<0.001	868 (55)	0.060
Month 9	N=1575	N=1592		N=1582	
≥2 units	1170 (74)	1053 (66)	<0.001	1104 (70)	0.004
≥3 units	1082 (69)	958 (60)	<0.001	1006 (64)	0.002
≥25%	979 (62)	835 (52)	<0.001	912 (58)	0.009
Month 24	N=1575	N=1592		N=1582	
≥2 units	1207 (77)	1121 (70)	<0.001	1078 (68)	<0.001
≥3 units	1128 (72)	1027 (65)	<0.001	980 (62)	<0.001
≥25%	1054 (67)	934 (59)	<0.001	876 (55)	<0.001

1. P-value based on a Mantel-Haenszel test controlling for cluster

Consistent changes in all the other secondary endpoints were observed in favour of the combination therapy compared with either of the monotherapies.

Non-pivotal trials - Study ARI40002

This was a short-term, pilot, multi-centre, double-blind, parallel group randomised study to investigate the effect on urinary symptoms of discontinuing tamsulosin, following 24 weeks of combination treatment with 500 µg dutasteride and 400 µg tamsulosin daily in subjects with BPH. Patients were randomised in a 1:1 ratio to receive either 36 weeks of combination therapy with dutasteride 500 µg daily and tamsulosin 400 µg daily (TD36 group) or 24 weeks of combination therapy followed by 12 weeks of dutasteride 500 µg daily monotherapy (TD24 + D12 group). The last 12 weeks were performed in a double-blind manner.

The primary objective was to assess any difference at 30 weeks post baseline, in the proportions of patients experiencing an improvement or no change in their urinary symptoms following discontinuation or continuation of tamsulosin. The study was designed as a non-inferiority study such that if the lower bound of the 97.5% CI for the difference in proportions was less negative than -0.20, then non-inferiority could be claimed.

At Week 30, 91% (139/154) patients who continued combination therapy after 24 weeks (TD36 group), felt the same or better regarding urinary symptoms than at the previous visit. In the group who discontinued tamsulosin after Week 24 (TD24 + D12 group), 77% (115/151) felt the same or better than at the previous visit. The point estimate for the difference in these proportions was -0.11 with a corresponding CI of [-0.18, -0.04]. As the lower bound, -0.18, was less negative than -0.20, non-inferiority between the two treatments was demonstrated.

Study ARI40002 also demonstrated that once tamsulosin was stopped after 24 weeks patients, over the following 6 weeks, had an increase in their symptom score that was statistically significantly higher than that for the patients who continued on combination therapy.

Non-pivotal trials - Study ARI40013

This was an open-label, multicentre, Phase IIIb study to evaluate the safety and efficacy of dutasteride with or without tamsulosin in the treatment of a large cohort of patients with symptomatic BPH under routine clinical conditions. If the baseline IPSS-QOL score was < 4 points they were to receive monotherapy with dutasteride 500 µg once daily [monotherapy group, MT]. If the baseline IPSS-QOL score was 4 points or more, they were to receive combination therapy with dutasteride 500 µg once daily plus tamsulosin 400 µg once daily for 24 weeks, followed by dutasteride monotherapy for the remaining 12 weeks [combination therapy group, CT]. Of the 2385 patients considered eligible for participation, 811 were assigned to the MT group and 1574 to the CT group, these numbers being in accord with the expected ratio of 1:2 (MT:CT), according to baseline severity.

The primary efficacy outcomes of interest were the changes in IPSS and BII from baseline to Week 36 of the study. At Week 36, both the treatment groups showed reductions in the primary efficacy variables. In the monotherapy group, the mean total IPSS had changed by -5.1, 95% CI [-5.4, -4.7] and the mean BII by -2.3, 95% CI [-2.5, -2.1]. In the combination group, the corresponding changes were, for the IPSS, -7.1, 95% CI [-7.4, -6.7] and for the BII score, -2.3, 95% CI [-3.6, -3.3].

As acknowledged in the submission and noted by the evaluator, the larger mean reduction in IPSS in the CT group compared with that in the MT group, was most likely explained by the patients in the CT group having started from higher baseline values, indicative of worse symptoms. On the basis of the latter and also because of the open-label design and the absence of any formal, pre-defined statistical comparison, the evaluator recommended that no conclusions could be drawn from this study relating to an increased benefit of combination therapy compared to monotherapy. While the Delegate agreed with this, it is reassuring that the results of this study are consistent with those of the pivotal study. The evidence adduced from this study is therefore supportive.

Safety

As noted by the clinical evaluator:

- A total of 3511 patients were treated with combination therapy with dutasteride 500 µg once daily and tamsulosin 400 µg once daily across the three studies, ARI40005, ARI40002 and ARI40013. Combination therapy was well tolerated, for up to two years in the pivotal study, ARI40005.
- In the pivotal study ARI40005, the overall incidence of adverse effects was similar in the combination therapy and monotherapy groups.
- The incidences and types of adverse events occurring whilst on combination therapy in all three studies were consistent with the already known safety profiles of dutasteride and tamsulosin.
- The most commonly reported adverse events considered to be drug-related were related to sexual function, especially ejaculation disorders, which occurred more commonly with combination therapy compared to either monotherapy.
- The incidence of SAEs was similar across the treatment groups and the most frequently reported were cardiovascular disorders. In the pivotal study, cardiovascular AEs of special interest were defined as those in the following categories: acute coronary syndrome, ischaemic coronary artery disorders/atherosclerosis, ischaemic cerebrovascular events, cardiac failure, arrhythmias and peripheral vascular disease. The incidence of cardiovascular AEs of special interest was similar across all three treatment groups, with the most frequently reported being myocardial infarction and coronary artery disease. Combination therapy was not associated with a significantly greater risk of cardiovascular AEs relative to either monotherapy.
- It was noted that the relative risk of cardiac failure appeared higher, with a 4.54-fold higher risk in the combination group relative to the dutasteride monotherapy group and a 2.29-fold higher risk in the combination group relative to the tamsulosin monotherapy group. While the associated confidence intervals do include unity and are relatively wide, reflective of the small numbers of events involved, they do stand out somewhat in relation to the relative risk estimates for the other cardiovascular AEs of special interest.
- There were no significant adverse trends in vital signs, clinical findings or laboratory values in any of the studies.

With respect to post-marketing experience for the combined use of dutasteride and tamsulosin, the sponsor submitted data gleaned from four primary sources. As noted by the evaluator, various analyses, including disproportionality analyses did not reveal any adverse events unique to the combination of dutasteride and tamsulosin. The high frequency adverse events reported with the concomitant use of dutasteride and tamsulosin were consistent with the known safety profile or pharmacological activity of either of the two drugs or the clinical effects of the underlying BPH.

Other Data/Issues

In August 2009, the sponsor submitted another category 1 application, PM-2009-02487-3-3, to update the Clinical Trials and Precautions sections of the PI for Avodart (dutasteride) with particular information about cardiac failure from the 4-year results of two studies, the first being the pivotal study for this submission, ARI40005 and the second being a study named

REDUCE, a 4-year comparison of placebo and dutasteride in men at risk of developing prostate cancer. In these two 4-year clinical studies, the incidence of cardiac failure was higher among subjects taking the combination of dutasteride and an alpha blocker, primarily tamsulosin, than it was among subjects not taking the combination. This submission is currently being evaluated by the TGA.

With regard to the issue of cardiac failure, in section 5.2, Pharmacodynamic properties, of the EU Summary of Product Characteristics (SmPC), there is the following entry under the heading Cardiac failure: "*In this 4 year BPH study* (i.e. the CombAT study – Delegate) *the incidence of the composite term cardiac failure in the combination group (14/1610, 0.9%) was higher than in either monotherapy group: Avodart, (4/1623, 0.2%) and tamsulosin, (10/1611, 0.6%)*". Reference to this finding about cardiac failure is repeated in the second paragraph of section 4.4, Special warnings and precautions for use. The reporting is qualified by the fact that no causal relationship between Avodart (alone or in combination with an alpha blocker) and cardiac failure has been established.

Response by the sponsor to the TGA Clinical & Non-clinical evaluation reports

The sponsor responded with a summary of clinical data to support the extension of indication to include combination with an alpha blocker, rather than just the specific combination with tamsulosin. The clinical data are summarised below.

Firstly, given their different modes of action, alpha blockers offer rapid symptomatic relief without targeting the underlying disease process while 5 ARIs such as dutasteride and finasteride provide mid- and long-term symptom relief.

Dutasteride has been shown not to inhibit the *in vitro* metabolism of model substrates of any of the major cytochrome P450 isoenzymes. As noted by the sponsor, these data suggest that dutasteride will not have a significant effect on the pharmacokinetics of any of the alpha blockers currently used to treat BPH.

The sponsor submitted copies of guidelines from the American Urological Association, the European Association of Urology and the Canadian Urological Association which state that the four alpha blockers alfuzosin, doxazosin, tamsulosin and terazosin all have similar clinical efficacy in treating LUTS. The same guidelines did acknowledge some small differences in side effect profiles. The sponsor also reviewed the published literature to support the contention that these four alpha blockers have similar efficacy in terms of improving symptoms.

The safety and tolerability of dutasteride in combination with an alpha blocker has been studied in CombAT with tamsulosin and also in a small study (n = 24) of two weeks duration in healthy men in which no PK or PD interaction was observed between dutasteride and tamsulosin or terazosin (ARIA 1011).

In the GSK sponsored study ARI40001 (*a multicentre, randomised, double-blind, double-dummy, parallel-group study to compare the efficacy of dutasteride 500 µg once daily versus finasteride 5 mg once daily for 12 months in the treatment of subjects with BPH, followed by an optional 24 months open label phase*), dutasteride has been shown to have a similar safety and tolerability profile as the type 2 5ARI finasteride.

The sponsor then gave a summary of 3 short-term (6-12 months) and one long-term (> 4 years) finasteride and alpha blocker combination trials which have been reported in the literature. The combinations examined were those of finasteride and slow-release alfuzosin, finasteride and terazosin and finasteride and doxazosin. Each combination was shown to be as well tolerated as each of the component alpha blocker monotherapies for example. The

sponsor then argued that, because of the two similar safety profiles of dutasteride and finasteride, then similar safety profiles may be expected of these same combinations with dutasteride substituted for finasteride.

Risk Management Plan

A Risk Management Plan (RMP) evaluation report, prepared by OMSM, was sent to the sponsor on 04 June 2010. A RMP had been submitted by the sponsor in support of this application and the ongoing safety concerns were identified by the sponsor as follows:

Important identified risks:

- sexual adverse events (altered [decreased] libido, impotence, ejaculation disorders) and breast disorders (enlargement and tenderness)
- allergic reactions, including rash, pruritus, urticaria, localised oedema and angioedema

Important potential risks:

- male breast cancer
- cardiovascular events
- high-grade prostate cancer
- interference with formation of external male genitalia in the foetus

Important missing information:

- men with severe hepatic impairment
- men with unstable medical conditions

The OMSM evaluator was of the opinion that, in principle, there was no objection to the sponsor implementing the proposed routine pharmacovigilance activities for all the specified ongoing safety concerns and the additional pharmacovigilance activities for 'male breast cancer', 'cardiovascular events', 'high-grade prostate cancer' and 'interference with formation of external male genitalia in the foetus'. The sponsor provided assurances concerning the provision of PSURs and the follow-up of all prostate cancer cases reported in the final (4-year) study report of ARI40006. The sponsor was asked to provide copies of the targeted follow-up questionnaires with regard to breast and prostate cancer. The sponsor's proposed risk minimisation activities were considered acceptable.

The Delegate strongly endorsed all of the recommendations made in the RMP evaluation report, particularly those to do with breast and prostate cancer.

Risk-Benefit Analysis

Data from the pivotal study, ARI40005, demonstrated that combination therapy with dutasteride 500 µg once daily and tamsulosin 400 µg once daily, was significantly better at improving symptoms, compared with either monotherapy, as shown by the statistically significant reduction from baseline in IPSS at the 24-month endpoint. Consistent changes in all the secondary endpoints, for example, peak urinary flow rate and the proportions of subjects exhibiting changes in IPSS$\geq 2, \geq 3$ & $\geq 25\%$ from baseline, were observed in favour of the combination therapy compared with either of the monotherapies.

The evidence provided by the supportive studies, while not as robust as that provided by the pivotal studies was internally consistent for each study and also consistent with the results of the pivotal study. The limitations of each of the supportive studies have already been pointed out by the clinical evaluator. ARI40002 was only a short-term, pilot study in a small group of 327 patients who were randomised. ARI40013, with 2385 subjects, did not achieve its planned sample size of 3000. The latter figure was chosen because it is the minimum number required to identify, with a probability of 90%, adverse events occurring with an incidence of at least 0.1%. There were no pre-defined hypotheses with respect to efficacy outcomes. Furthermore, the study was open-label and the two groups, those started on combination therapy and those on monotherapy, were not balanced with regard to baseline disease characteristics, deliberately so by the study design. Therefore it is not really possible to

compare the efficacy outcomes between the two groups in ARI40013. Indeed all one can say from the latter study is that the efficacy results moved were in the same direction as those from the pivotal study. The Delegate expressed interested as to what the sponsor hoped to demonstrate, efficacy-wise, in this study.

As noted by the clinical evaluator, the safety profile of co-administration was favourable, with the nature and frequency of AEs reported in all three studies being consistent with the safety profiles of either monotherapy. Both dutasteride and tamsulosin are currently approved drugs for the treatment of BPH. No significant new safety concerns with co-administering the two drugs were identified. Some sexual (erectile dysfunction, loss of libido and disorders of ejaculation) and breast (nipple pain) adverse events were numerically higher in the combination drug group. However, these events were uncommon, not life-threatening and can be satisfactorily addressed in the product information. The Delegate noted that there has been some updating of the EU SmPC regarding the increased incidence of cardiac failure in subjects on the combination of dutasteride and tamsulosin but with the qualification that no causal relationship between Avodart (alone or in combination with an alpha blocker) and cardiac failure has been established. There has, as yet, been no such updating of the US PI. There is currently under evaluation by the TGA a submission, PM-2009-02487-3-3, for an updating of the Australian-approved PI with regard to the issue of cardiac failure, similar to that in the EU SmPC.

It is important to note, as did the clinical evaluator, that all studies evaluated employed only the one alpha blocker, tamsulosin, in combination with dutasteride. The indication proposed by the sponsor refers to the use of Avodart in combination with an alpha blocker, without any qualification of the latter term. This indication, if approved, would permit the combination of dutasteride with any alpha blocker in the treatment of BPH. There is an immediate inconsistency with the proposed instructions under Dosage and Administration where the term "*alpha blocker*" is not used but rather the more narrowly defined term, "*alpha-1 adrenergic blocker*". As noted by the clinical evaluator, in the sponsor's very own introduction, there was a statement that the application to amend the EU SPC was "*to include wording on the combined use of dutasteride and the alpha blocker tamsulosin in order to deliver the respective benefits*".

According to the approved PI for tamsulosin, pharmacological studies have established that tamsulosin is a selective, potent and competitive α_1-adrenoceptor antagonist and that it has a greater affinity for the α_{1A}-receptor subtype, predominantly present in the human prostate. α_1-adrenoceptor antagonists generally can reduce blood pressure by lowering peripheral resistance. However, no reduction in blood pressure of any clinical significance was observed during studies with tamsulosin. Tamsulosin is indicated "*for the relief of lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH)*". The recommended dosage is one tablet, 400 µg daily. There is no dose titration.

According to the approved PI for alfuzosin, it is a selective antagonist of post-synaptic α_1-adrenoceptors. *In vitro* pharmacology studies have documented the antagonist properties of alfuzosin for the α_1-receptors located in the trigone of the urinary bladder, urethra and prostate. *In vivo* animal studies have shown that alfuzosin decreases urethral pressures and therefore resistance to the urine flow during micturition. Pharmacodynamic studies of uroselectivity with alfuzosin have not been conducted in patients with prostatic hypertrophy. α_1-adrenergic blocking agents reduce standing blood pressure and increase heart rate and these effects are maximal after the first intake and at peak plasma concentrations. In clinical studies with alfuzosin, adverse effects related to these effects were infrequent. Alfuzosin is indicated for "*treatment of the functional symptoms of benign prostatic hyperplasia*". The

recommended dose is one 10 mg tablet daily. As for tamsulosin, there is no need for dose titration. The efficacy of alfuzosin 10 mg daily in BPH was assessed in a 12-week double-blind, placebo-controlled study with a statistically significant reduction in IPSS (143 patients on alfuzosin versus 154 on placebo). The use of alfuzosin in the adjuvant therapy of catheterisation after an acute episode of acute urinary retention related to BPH and its use in the prevention of relapse of AUR have been evaluated in two 6-month placebo-controlled studies. In one of the latter, there was a statistically significant reduction in the risk of need for surgery in the alfuzosin group compared with the placebo up to 3 months.

According to the approved PI for doxazosin, it exerts its vasodilator effect via selective and competitive blockade of post junctional α_1- adrenoceptors. Studies in normal human subjects have shown that doxazosin competitively antagonized the pressor effects of phenylephrine (an α_1-agonist) and the systolic pressor effect of noradrenaline. Doxazosin and prazosin have similar abilities to antagonise phenylephrine. The antihypertensive effect of doxazosin results from a reduction in systemic vascular resistance. It has been shown to inhibit the contractions of prostatic tissue and has improved urodynamics and symptoms in patients with BPH. It is indicated firstly "*for the treatment of mild to moderate hypertension*" and secondly "*for the relief of manifestations of mild to moderate benign prostatic hyperplasia*". The first general comment under Dosage and Administration for doxazosin is that dosage must be individualized. In the management of benign prostatic hyperplasia, the initial dose is 1 mg (half a 2 mg tablet) once daily. Depending on the individual patient's urodynamics and BPH symptomatology, dosage may then be increased to 2 mg and thereafter to 4 mg and up to the maximum recommended dose of 8 mg. The recommended titration interval is 1-2 weeks. The usual recommended dose is 2-4 mg once daily. The efficacy of doxazosin in BPH has been evaluated in 3 randomised, double-blind, parallel, placebo-controlled clinical trials and an open uncontrolled trial (803 on doxazosin, 235 on placebo). The onset of efficacy was seen within 2-3 weeks and was maintained for treatment periods of up to 7 months. In Version 5 (2008 edition) of the Cardiovascular Therapeutic Guidelines, it was stated that doxazosin was tested in a large controlled trial of anti-hypertensive therapies and that the doxazosin arm of this trial was stopped early because of an excessive rate of heart failure.

According to the approved PI for terazosin, the vasodilatory hypotensive action of terazosin appears to be produced mainly by blockade of alpha-1-adrenoceptors. Studies suggest that alpha-1-adrenoceptor blockade is also useful in improving the urodynamics in patients with chronic bladder outlet obstruction, such as in BPH. In *in vitro* experiments, terazosin has been shown to antagonise phenylephrine-induced contractions in human prostatic tissue. In clinical trials terazosin has been shown to improve the urodynamics and symptomatology in patients with BPH. It is indicated firstly "*for the relief of the manifestations of mild to moderate BPH. Treatment should be stopped if patients have not responded after three months of therapy*" and secondly "*in the treatment of hypertension*". As with doxazosin, the dose of terazosin should be adjusted according to the patient's individual response. One mg at bedtime is the starting dose for all patients and this dose should not be exceeded. This initial dosing regimen should be strictly observed to minimize the potential for severe hypotensive effects. With regard to dosage in BPH specifically, the dose may be slowly increased to achieve the desired response in BPH patients. Beginning the initial dosage of 1 mg daily, there is then a slow dose titration over 4 weeks to the usual recommended dose range of 5 to 10 mg administered once a day. Efficacy has been demonstrated in clinical studies of up to 18 months but data on longer term use is not yet available.

According to the approved PI for prazosin, it causes a decrease in total peripheral resistance. Animal studies suggest that the vasodilator effect of prazosin is related to blockade of post-

synaptic alpha-adrenoceptors. Clinically, the antihypertensive effect is believed to be a direct result of peripheral vasodilation. There is evidence of statistically significant improvement in urinary flow following prazosin therapy in patients with BPH. Prazosin has four indications, the first being "*the treatment of hypertension of varied aetiology and all grades of severity*", the second "*the treatment of severe refractory congestive heart failure*", the third "*the treatment of Raynaud's Phenomenon and Raynaud's disease*" and the fourth "*as an adjunct in the symptomatic treatment of urinary obstruction caused by BPH in patients awaiting prostatic surgery*". Under Dosage and Administration, the first general comment is there is evidence that patient toleration is best when therapy is initiated with a low starting dose. With respect to the specific indication involving BPH, the recommended starting dose is 500 µg twice daily, given for a period of 3 to 7 days and then adjusted according to clinical response. The maintenance dosage is 2 mg twice daily. The use of doses over 4 mg daily has not been studied and cannot be recommended at present. Doses up to 4 mg daily have produced amelioration of symptoms for periods of up to 4 weeks but currently longer term data are not available. Postural hypotension may occur.

Of the alpha blockers, only tamsulosin and alfuzosin do not require dose titration. Doxazosin, terazosin and prazosin all require careful initial dose titration because of the risk of postural hypotension. Tamsulosin and alfuzosin are indicated for the relief of symptoms in BPH, the latter without qualification. Doxazosin and terazosin are indicated only for mild to moderate BPH and prazosin has a somewhat restricted indication as an adjunct in the symptomatic treatment of urinary obstruction caused by BPH in patients awaiting prostatic surgery. None of the alpha blockers besides tamsulosin has been studied out to 2 years and certainly not in combination with dutasteride for this length of time. The sponsor has submitted a response to the clinical evaluation report in which it argues that the four alpha blockers, tamsulosin, alfuzosin, terazosin and doxazosin have similar efficacy and safety profiles. However, this is in the form of various urology association guidelines and *post hoc* comparisons. There are no actual head-to-head clinical studies of efficacy and safety comparing any of these four alpha blockers. Thus the evidence adduced for this purpose is low level in nature. Furthermore, prazosin, an alpha blocker approved for use in BPH, has been omitted completely from the discussion in the response and yet it would be, by default, covered by the proposed indication. Indirect comparisons with finasteride in combination are not appropriate as finasteride is not approved for use in combination with any alpha blockers. However, the most important reason for restricting approval for the specific combination of dutasteride and tamsulosin is that there is no other combination of dutasteride and an alpha blocker which has been studied for such a length of time in a clinical outcome study. Furthermore, the study is ongoing and is to remain double-blinded for the full study length of 4 years. Thus overall, the Delegate was of the view that the extension of indications is only supported by robust clinical evidence for the combination of dutasteride and tamsulosin.

The Delegate proposed to reject the submission in so far as it refers to combination with an alpha blocker (meaning all alpha blockers) but approve the submission for an extension of indications restricted to combination with tamsulosin.

The Delegate proposed to impose the following specific condition of registration, namely that the sponsor is required to submit as evaluable data within the context of a category 1 submission, the final study report of the completed 4-year clinical trial, ARI40005 (CombAT – Combination with Alpha blocker Therapy). Adherence to the RMP will also be a specific condition of registration.

The Delegate also asked the following question of the Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC):

Does the ACPM agree with the Delegate that there is only sufficient evidence to permit an extension of indication to include co-administration of dutasteride with tamsulosin or is it of the opinion that the evidence may be generalized to permit combination with all or some alpha blockers?

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended approval of the submission to extend the indication for Avodart to include:

For use as monotherapy for the management of symptomatic benign prostatic hyperplasia (BPH) or as combination therapy with an alpha blocker which is approved for use in BPH and which has been dose titrated in accordance with the relevant recommendations in the production information for that alpha blocker.

Changes to the Product Information (PI) and Consumer Medicines Information (CMI) which should be made prior to approval include:

- clear and detailed rules in the relevant sections of the PI section about the requirement of stabilisation of cardiovascular function when initiating combination therapy or adding either dutasteride or an alpha blocker to the regimen. Detail should include reference to the clinical impact of the selectivity profiles of different alpha blockers, the risk of instability, including hypotension and congestive heart failure, and the need for careful titration in the context of:
- Starting dutasteride with an alpha blocker
- Adding dutasteride to an existing alpha blocker regimen

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Avodart containing dutasteride 500 µg, indicated for:

Use as monotherapy for the management of symptomatic benign prostatic hyperplasia (BPH) or as combination therapy with an alpha blocker which is approved for use in BPH and which has been dose titrated in accordance with the relevant recommendations in the product information for that alpha blocker.

Approval was subject to the following specific condition of registration:

- The Risk Management Plan Version 02 dated 1 December 2009, as agreed with the Office of Product Review, must be implemented.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
www.tga.gov.au