CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-319

MEDICAL REVIEW

NDA 21319

Date submitted: December 21, 2000
Date received: December 21, 2000
Draft review completed: September 24, 2001
Review completed: October 11, 2001

Medical Officer Review

Sponsor: GlaxoSmithKline
Five Moore Drive
Research Triangle Park, North Carolina 27709

Drug: Generic: **Dutasteride**
Trade: Pending

Route of administration: Oral

Dosage form: Soft-gelatin capsule

Strength: 0.5 mg

Proposed indication: Treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate gland

Related IND's: [redacted]

George S. Benson, MD
Medical Officer _____

Mark S. Hirsch, MD
Urology Team Leader _____

Executive Summary:

I. Recommendations

In the opinion of this reviewer, from a clinical perspective, dutasteride 0.5 mg soft-gelatin capsules taken once/day should be approved for the indication of "treatment of benign prostatic hyperplasia (BPH) in men with an enlarged prostate gland." Several clinical pharmacology questions concerning the drug remain unanswered and these questions should be addressed in Phase 4 commitments. These questions primarily concern the fact that 55% of the administered dose has not been accounted for and the metabolic pathways have not been adequately determined. Labeling changes have been proposed to caution use of the drug in patients with hepatic impairment and those taking concomitant CYP3A4 inhibitors.

II. Summary of Clinical Findings

A. Brief overview of the clinical program

Dutasteride is a Type 1 and Type 2 5 alpha-reductase inhibitor. 5 alpha–reductase is the enzyme responsible for converting testosterone (T) to dihydrotestosterone (DHT) and DHT is thought to be the primary androgen responsible for prostatic growth. Type I 5 alpha reductase is the dominant form of the enzyme in liver and skin and Type II is the dominant form in the prostate. Men who have congenital Type II 5 alpha-reductase deficiency have small prostate glands throughout life and do not develop benign prostatic hyperplasia (BPH). Although Type I 5 alpha-reductase is also present in the prostate gland, its role in this tissue is not clear. There are no known congenital deficiencies of the Type I enzyme.

Proscar (finasteride), a Type II 5 alpha-reductase inhibitor, is the only currently marketed 5 alpha-reductase inhibitor (at a dose of 5 mg/day) for the treatment of BPH. The proposed dose of dutasteride given as a soft-gelatin capsule is 0.5 mg/day.

In support of NDA 21319, the sponsor submitted 3 pivotal Phase 3 trials. **ARIA3001** and **ARIA3002** were conducted entirely in the United States and **ARIB3003** was conducted in 19 countries. The design of all 3 studies was virtually identical; the only significant difference was in the timing of the first post-baseline prostate volume assessment. All three trials are 4 year studies. The first 2 years consist of randomized, double-blind, placebo-controlled, parallel group studies followed by a 2 year open-label extension. The first year of the trials was designed to evaluate the efficacy and safety of dutasteride in the treatment of BPH. The second year portion of the trials was designed to determine the effect of dutasteride on the incidence of acute urinary retention and the need for prostate surgery. **This NDA submission contains only data from Year 1 of the pivotal studies dealing with the treatment of BPH.** The sponsor plans to provide the results from Year 2 of the double-blind treatment phase and from the open-label phase (Years 3 and 4) in subsequent submissions.

In the 3 pivotal studies, 4324 patients were randomized (2158 patients to the placebo group and 2166 to dutasteride). Three thousand five hundred twenty-two (3522) patients (1750 placebo and 1772 dutasteride) completed the 12 month treatment period.

B. Efficacy

The primary efficacy endpoint in all Phase 3 trials was the change from baseline at 12 months in the American Urologic Association Symptom Index (AUASI). This validated questionnaire is currently used as a primary endpoint for all drug trials of the treatment of BPH. Statistically significant improvement was seen by month 3 ($p<0.032$) and through month 12 ($p<0.001$) in ARIA3002, by month 6 ($p<0.038$) and through month 12 ($p<0.001$) in ARIB3003, and by month 12 in ARIA3001 ($p<0.001$) (Table 1).

Table 1. AUASI Change from Baseline

	ARIA3001		ARIA3002		ARIB3003	
	Placebo	Dutasteride	Placebo	Dutasteride	Placebo	Dutasteride
Month 1	N=706	N=703	N=664	N=677	N=723	N=737
Mean	-1.4	-1.3	-1.2	-1.2	-1.4	-1.5
Mean difference		0.1		0.0		-0.1
p-value		0.81		0.98		0.78
Month 3	N=709	N=705	N=670	N=663	N=738	N=750
Mean	-2.1	-2.3	-1.8	-2.4	-2.8	-2.7
Mean difference		-0.2		-0.6		0.0
p-value		0.39		**0.032**		0.90
Month 6	N=709	N=705	N=671	N=664	N=741	N=750
Mean	-2.4	-2.9	-1.9	-2.7	-2.8	-3.4
Mean difference		-0.5		-0.8		-0.6
p-value		0.12		**0.008**		**0.038**
Month 12	N=709	N=705	N=671	N=664	N=742	N=750
Mean	-2.0	-3.0	-1.3	-2.8	-2.9	-4.1
Mean difference		-1.1		-1.5		-1.2
p-value		**<0.001**		**<0.001**		**<0.001**

In general correspondence dated September 7, 2001, the sponsor noted that a review of the one year data indicated that there were "data changes between data provided in the Year 1 NDA and the subsequent Year 1 portion of the cumulative 0-2 year data for the sNDA." These data changes resulted in one change in the statistical analysis. The p-value for the 6 month analysis of the AUASI in Trial ARIB3003 changed from 0.038 to 0.053.

The mean decrease from baseline in AUASI scores across the 3 studies pooled was –3.3 units for dutasteride and –2.1 units for placebo at Month 12; the mean AUASI difference between the 2 treatment groups was –1.2. Each study was powered based on achieving a

mean difference (dutasteride versus placebo) of –1.5 units in AUASI. Although this mean difference was not achieved at Month 12 in ARIA3001 or ARIB3003, the 95% confidence interval around the difference included –1.5 in both trials.

The 2 major secondary endpoints were prostate volume and maximum urinary flow rate (Q_{max}).

Prostate volume: Beginning at the earliest time point measured in each study (Month 1 in ARIA3001, Month 3 in ARIA3002, and Month 6 in ARIB3003), significant decreases ($p<0.001$) in mean percent change from baseline prostate volume were seen when comparing patients treated with dutasteride 0.5 mg versus those who received placebo. The mean percent decrease in prostate volume across the 3 studies pooled was –24.6% for dutasteride versus –3.4% for placebo at Month 12; the mean difference compared with placebo was –21.2%.

Q_{max}: Significant improvement in Q_{max} from baseline was seen at Month 1 in ARIB3003 ($p=0.002$) and by Month 3 in ARIA3001 ($p=0.017$) and ARIA3002 ($p=0.006$) and continuing through Month 12 in all three pivotal studies. The mean increase in Q_{max} across the three studies pooled was 1.6 cc/sec for dutasteride and 0.7 cc/sec for placebo at Month 12; the mean difference was 0.9 cc/sec.

The changes in AUASI are clinically and statistically meaningful. The changes in Q_{max} are modest but highly statistically significant at 12 months in all three studies. There is minimal data directly comparing dutasteride to the approved 5 alpha-reductase inhibitor (finasteride). The improvements in AUASI, Qmax, and prostate volume appear, however, to be similar to finasteride.

C. Safety

Safety data is drawn from a total of 5305 patients enrolled in 19 completed studies conducted in the United States and 18 other countries. The 5305 patients included 240 in 7 single-dose volunteer studies, 110 in 5 repeat-dose volunteer studies, 4324 in the 3 pivotal studies, and 631 in 4 supporting efficacy studies. In the 3 pivotal studies, 2166 patients took dutasteride for a total of 1866 patient years of drug exposure. In addition, 2 year safety data is provided for 445 patients who completed the 2 year double-blind phase of ARIA3002. The patient population in the clinical trials reflects the probable marketing exposure.

Reported significant adverse events are primarily those related to known side effects of 5 alpha-reductase inhibitors. Adverse events of special interest in patients taking 5 alpha-reductase inhibitors (3 pivotal studies combined) are shown in Table 2.

Table 2. Adverse Events of Special Interest in Patients Taking 5 alpha-Reductase Inhibitors

	Placebo (N=2158)	Dutasteride (N=2166)
Decreased libido	49 (2%)	88 (4%)
Impotence	76 (4%)	141 (7%)
Ejaculation disorder	18 (<1%)	53 (2%)
Sexual function disorder	2 (<1%)	7 (<1%)
Gynecomastia	11 (<1%)	32 (1%)
Prostate cancer	12 (<1%)	11 (<1%)

One patient in the open label portion of ARIA3002 developed infiltrating ductal carcinoma of the breast 340 days after initiating open-label treatment. He had received placebo for 2 years during the double-blind phase of the study. This reviewer believes that a causal relationship can not be made to dutasteride in this single case.

Six other concerns exist regarding potential adverse events in patients taking 5 alpha-reductase inhibitors:

1) Exposure of a pregnant woman to dutasteride could result in inadequate development of the genitalia of a male fetus. Exposure could result from ingesting capsules, contact with broken gelcaps and subsequent absorption through the skin, or through contact with semen from a male taking dutasteride. This issue is adequately addressed in the Warnings section of the label. With respect to exposure of a female partner to dutasteride in seminal fluid, the sponsor believes that the maximum exposure to a woman via semen would be a daily dose of drug that was 186-fold less on a mg/kg basis than the dose that had no effect on male primate embryo fetal development. In the pivotal trials patients were prohibited from engaging in unprotected intercourse with women of childbearing age. The maximum concentration of dutasteride found in semen was 14 ng/mL. Assuming total absorption of 70 ng in 5 cc of seminal fluid, the serum level in the partner was estimated by the Division's pharmacologist to be approximately 0.0175 ng/mL. This concentration in this "worst case scenario" is below the no effect and low effect concentrations of 0.05 and 0.07 ng/mL observed for the effect on adrenal and other organ weights in the monkey and the 2.0 ng/mL low effect level for external genitalia changes in mice. The recommendation for prohibiting unprotected intercourse with women of childbearing age has been discontinued by the sponsor and is not included in the label. This reviewer agrees with the pharmacology/toxicology reviewer and believes that the administration of dutasteride does not require condom use when engaging in sexual intercourse with a woman of childbearing potential.
2) No pregnancies in female partners of dutasteride treated patients occurred in the pivotal studies. Six pregnancies (1 placebo and 5 dutasteride) occurred in other studies. In the five partners of dutasteride patients, 3 healthy boys and 2 healthy girls were delivered.
3) Serum PSA levels decreased by approximately 50% after 6 months of dutasteride therapy. Reduction in PSA in patients taking 5 alpha-reductase inhibitors and its impact on prostate cancer detection is well recognized and this issue is adequately addressed in the label.

4) Since 5 alpha-reductase inhibitors block the conversion of T to DHT, serum T levels do increase. The increase in serum T is approximately 20% and this reviewer does not believe that this increase is clinically significant.
5) Semen quality is adversely affected by 5 alpha-reductase inhibitors.
In Trial ARIA1009, although the number of patients studied was low, no clinically significant adverse effect on sperm concentration, sperm motility, or sperm morphology was demonstrated. Mean ejaculate volume decreased and corresponding total sperm per ejaculate decreased by 25%, but still remained within the normal range.
Two dutasteride treated patients did experience decreases in their sperm count to less than 10% of baseline at the end of 52 weeks of drug exposure. Both patients showed recovery at the 26 week follow-up visit.
6) The sponsor initially recommended that blood donations should not be made for approximately 6 months after discontinuing treatment to avoid the possibility of inadvertent exposure to pregnant women. The sponsor now believes that exposure from blood donation to be inconsequential, as the amount of drug in a unit of blood is similar to the daily dose administered in the primate fetal development study on a ng/kg basis. In this primate study, pregnant females received this dose daily for 80 days with no effect on male fetal genital development. Therefore this recommendation is not included in the proposed labeling. Based on serum concentration, however, the concentration of dutasteride in a recipient immediately following blood transfusion can be calculated to be approximately 5.0 ng/mL. This concentration is higher than the 2.0 ng/mL level which is associated with abnormalities of the external genitalia in mice. Because of the presumed long half-life of the drug following transfusion, this reviewer agrees with the pharmacology/toxicology reviewer and believes that blood donations should not be made for approximately 6 months following discontinuation of the drug and this recommendation has been included in the proposed label. In addition, the Office of Blood Applications, CBER, has been notified of this issue.

A consultation was obtained from the CardioRenal Division regarding the QT interval study ARI10019. This draft study report of preliminary results was submitted with the 120 Day Safety Update. The CardioRenal consultant concluded that: "This study showed no effect of dutasteride 0.5 mg or 5 mg on the uncorrected QT interval. (Since the ventricular rate was unaffected by the drug, no correction factor is necessary.) The range of serum concentration of dutasteride during the study was from approximately 20 ng/ml to approximately 900 ng/ml. This finding, however, does not rule out an effect of dutasteride on repolarization at higher concentrations." In this context, this reviewer does not find any realistic risk of QT prolongation with dutasteride.

The incidence of other common adverse events (ENT infections and musculoskeletal pain) was equal to or less than the incidence in patients taking placebo. No significant cardiovascular, hepatic, hematologic, or renal toxicity was identified. (One 68-year-old man with jaundice, increased liver function tests, and dilation of the bile duct was reported via IND Safety Report on August 6, 2001. This man had been taking dutasteride for approximately 36 months when he presented with a bilirubin of 3.1 mg/dL, alkaline

phosphatase of 627 U/L, and SGPT of 978 U/L. Abdominal ultrasound and CT showed biliary ductal dilation without an obvious cause. A biliary stent was placed and liver biopsies performed. He was then lost to follow-up and the investigator has been unable to obtain further information. Liver biopsy results are pending at the time of the safety submission. In the opinion of this reviewer, this episode is probably not drug related.)

Although data directly comparing the safety of dutasteride and finasteride was not submitted in this application, the adverse events seen across clinical trials studying these 2 drugs appear similar in type and in incidence.

D. Dosing

The 0.5 mg dose of dutasteride was selected based on results from ARIA1003 and ARIA2001. Dutasteride 0.5 mg was the lowest maximally effective dose of dutasteride with regard to DHT suppression (ARIA1003 and ARIA2001) and decreases in prostate volume (ARIA2001). The 0.5 mg dose also appeared to have the best balance between efficacy and safety in the population studied and was chosen as the dose for the phase 3 trials. The 0.01 mg dose appears to be the clinical no effect level based on comparability with placebo results for DHT suppression and prostate volume reduction.

E. Special Populations

Gender differences: Dutasteride is indicated for the treatment of BPH. The drug is contraindicated in women and children.

Racial differences: The effect of race of pharmacokinetics has not been studied. The number of non-Caucasian patients in the clinical trials is too small to draw meaningful conclusions.

Issues with elderly: The pharmacokinetics and pharmacodynamics were evaluated in 36 healthy men between the ages of 24 and 87 years following administration of a single 5 mg dose of dutasteride. Exposure to dutasteride, represented by AUC and Cmax, was not statistically different between age groups. No differences in drug effect, as measured by DHT reduction, were observed between age groups. The half-life, however, appears to be prolonged with increased age. According to the sponsor, preliminary evidence from population PK sampling in the Phase 3 trials revealed no significant differences in exposure between older and younger men.

Of 2166 men treated with dutasteride in the 3 pivotal studies, 60% were age 65 and over and 15% were age 75 and over. No overall differences in safety or efficacy were observed between these patients and younger patients. The sponsor advises that no dose adjustment is needed in the elderly and this reviewer agrees.

Renal impairment: The effect of renal impairment on dutasteride pharmacokinetics has not been studied. Since virtually no dutasteride is excreted unchanged in the urine, the sponsor advises no dose adjustment for renal impairment and this reviewer agrees.

Hepatic impairment: The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied. Dutasteride is extensively metabolized in the human. Thus, hepatic insufficiency is likely to increase exposure to dutasteride. However, safety data from 60 patients exposed to ten times the recommended dose for 6 months did not reveal any significant adverse events. The sponsor suggests a precaution for the use of dutasteride in this population and this reviewer agrees.

Pediatric issues: A pediatric waiver was applied for and granted.

Pregnancy use information: Dutasteride is contraindicated in women. Warnings concerning effects of the drug on pregnancy are discussed above.

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Clinical Review **Page**

Clinical Review

1) Introduction, Background

A. Drug Action and State of Armamentarium for Drug Therapy of the Symptoms of BPH

Dutasteride (trade name pending) is a Type 1 and Type 2 5 alpha-reductase inhibitor. The proposed indication is the "treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate gland." The recommended dose is 0.5 mg orally daily.

BPH is a common condition in aging men. Historically, symptomatic BPH has been treated primarily by surgery consisting either of transurethral or open surgical prostatectomy. Several "minimally invasive" techniques including microwave therapy and laser vaporization have been introduced. The frequency of surgery for BPH has markedly decreased in recent years primarily because of the development of pharmacologic therapy.

Two major approaches to drug development have led to approval of 2 major classes of drugs for treating the symptoms of BPH. The first drugs to be approved for this indication were alpha-adrenergic receptor blocking agents. These drugs are thought to improve symptoms of BPH by blocking alpha-adrenergic receptor mediated smooth muscle contraction in the prostatic stroma (and probably bladder neck) and thereby decreasing the magnitude of bladder outlet obstruction. The alpha-adrenergic blocking drugs terazosin, doxazosin, and tamsulosin are approved for this indication.

The second approach to the drug therapy of BPH consists of 5 alpha-reductase inhibition. Dihydrotestosterone (DHT) is thought to be the primary androgen responsible for facilitating hyperplastic growth of the prostate. DHT is produced from testosterone by the action of the enzyme 5 alpha-reductase. Treatment with a 5 alpha-reductase inhibitor is thought to decrease the size of the prostate and thereby decrease the degree of prostatic obstruction. The 5 alpha-reductase (Type 2) inhibitor finasteride is currently approved for the treatment of symptomatic BPH in men with an enlarged prostate gland. Dutasteride is also a 5 alpha-reductase inhibitor. This drug inhibits both Type 1 and Type 2 5 alpha-reductase. Type 1 is the predominant isozyme form in the skin and liver while type 2 predominates in the prostate. The Type 1 enzyme has also been found in the prostate, but the clinical relevance of this isozyme in BPH is not known.

B. Milestones in Drug Development:

[redacted] (dutasteride for the treatment of benign prostatic hyperplasia) was originally filed on April 4, 1995. An End-of-Phase 2 meeting was held on August 7, 1997. The Clinical pre-NDA meeting was held on December 5, 2000.

C. Foreign marketing history:

Dutasteride has not been marketed outside of the United States. No Marketing Authorization Applications have been submitted.

D. Important Issues with Pharmacologically Related Agents:

The only pharmacologically related drug (5 alpha-reductase inhibitor) approved for the treatment of BPH is finasteride (Proscar). Because 5 alpha-reductase inhibitors may cause abnormalities of the external genitalia of a male fetus, these drugs are contraindicated in women who are or who may potentially become pregnant. In addition, women should not handle crushed or broken drug tablets when they are pregnant or may become pregnant because of the possibility of absorption of drug and the subsequent potential risk to a male fetus. 5 alpha-reductase inhibitors decrease serum PSA levels by approximately 50% and this fact should be recognized when screening or diagnosing men for prostate cancer. Adverse events associated with 5 alpha-reductase inhibitors include impotence, decreased libido, decreased volume of ejaculate, ejaculation disorder, breast enlargement, and breast tenderness.

II. Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, and Statistics

There are no unresolved chemistry, microbiology, or statistical issues. The pharmacology/toxicology reviewer has recommended: 1) labeling changes regarding the fact that blood donation should be prohibited until dutasteride has been discontinued for a period of 6 months and 2) labeling changes regarding the margins of safety found in the carcinogenicity and reproductive toxicity studies of dutasteride and its metabolites. These changes have been made in the proposed label.

III. Human Pharmacokinetics and Pharmacodynamics

Several significant clinical pharmacology issues remain unresolved. Approximately 55% of the administered dutasteride dose is not accounted for. Metabolic pathways have not been adequately determined for this drug whose elimination half-life is approximately 5 weeks. The identification of the isoenzymes responsible for the metabolism of dutasteride is unknown. The available data from *in vitro* studies show that CYP3A4 is responsible for approximately 4% of the metabolism of this drug. No other isozymes were identified as being responsible for the metabolism of dutasteride. Based on *in vivo* data, however, dutasteride is extensively metabolized to approximately 11 metabolites (4 major and 6 minor). The structural identity and pharmacological activity of some of the metabolites is unknown.

No information is available concerning the pharmacokinetics of the drug in renal or hepatic impaired patients. It has been noted that virtually no parent drug is excreted unchanged in the urine.

Information regarding drug-drug interactions is limited. Dutasteride does not inhibit the in vitro metabolism of model substrates for cytochrome P450 isoenzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 in vitro. Following oral dosing for 6 months to rats and dogs, dutasteride did not induce hepatic cytochrome P450 isoenzymes CYP1A, CYP2B, and CYP3A. Human studies have shown no pharmacokinetic or pharmacodynamic interactions between dutasteride and tamsulosin (ARIA1011), terazosin (ARIA1011), warfarin (ARI10016), digoxin (ARI10017), and cholestyramine (ARIA1010). Otherwise, no drug-drug interaction studies based upon metabolic pathways have been conducted.

IV. Description of Clinical Data and Sources

The following materials were reviewed: 1) Overview section, integrated summary of safety, and the integrated summary of efficacy from the NDA 2) Three 12 month pivotal studies (ARIA3001, ARIA3002, and ARIB3003) 3) Trial ARIA1009 –"An investigation of the Pharmacokinetics of GI198745 and the Effects of GI198745 on Semen Characteristics When Administered Daily for 12 Months to Healthy Male Subjects" 4) Two year safety data for ARIA 3002 5) Trial ARIB3004 – "A six-month, randomized, double-blind, placebo-controlled, parallel group study to evaluate the effects of repeat dose oral GI198745 on detrusor pressure and urinary flow in patients with lower urinary tract symptoms suggestive of bladder outlet obstruction, with optional six-month open-label extension" 6) Trial ARI10010 – "A Double-Blind, Placebo-Controlled, Randomized, Parallel Group Study to Investigate the Changes in the Corrected QT Interval Following Repeat Oral Doses of GI198745 in Healthy Male Volunteers: Preliminary Data as of March 7, 2001, for the 120-Day Safety Update for NDA 21-319; Dutasteride Soft Gelatin Capsules"

V. Clinical Review Methods

The 3 pivotal 12 month trials were reviewed in detail and these reviews are attached as appendices A, B, and C. Trial ARIA1009 (the effect of dutasteride on semen parameters) was reviewed in detail and is attached as Appendix D. Appendix E contains a review of the 120 Day Safety Update, ARI10010 (the QT study), and year 2 safety data for ARIA3002. Appendix F contains a review of Trial ARIB3004 (the urodynamic study). DSI audits of 3 sites were reviewed. The data appeared to be acceptable from 2 of the 3 sites. At the third site (enrolling patients in ARIA3002), the prostate volume data "appeared inaccurate" because of equipment calibration problems. Seventy-six patients were enrolled at this site and measurement errors were identified in 8 of the 12 patients reviewed during the inspection. The prostate volume changes were consistent across the 3 pivotal studies. The likelihood of erroneous prostate volume (a secondary endpoint) data from this one site significantly impacting the results prostate volume changes in this NDA is low.

Adequate documentation was submitted to comply with financial disclosure. The sponsor performed adequate "due diligence" to obtain documentation from non-compliant investigators. The rate of return for Trials ARIA3001 and ARIA3002 was less than 80%,

but these studies were large, multi-center studies, with no one center enrolling more than 7% of the patients in the study (the studies were underway at the time that the Financial Disclosure Rule took effect). It is unlikely that these studies were biased. The disclosure of financial interests from five investigators is also unlikely to bias the outcome of the studies because none of these investigators enrolled a significant number of patients at their sites.

VI. Integrated Review of Efficacy

A. Introduction: The sponsor has demonstrated in 3 adequate, well-controlled studies that dutasteride significantly improves the AUASI and Qmax in patients with BPH. These 2 endpoints are currently accepted for Phase 3 studies evaluating drug therapy for BPH. The proposed indication is "for the treatment of symptomatic benign prostatic hyperplasia in men with an enlarged prostate gland."

B. Approach to Review of Drug Efficacy
The efficacy data base consists of 3 pivotal and 4 supporting studies (Table 1).

Table 1. Summary of Patients in Pivotal and Supporting Efficacy Studies

Trial	PBO	0.01 mg	0.05 mg	0.1 mg	0.5 mg	2.5 mg	5.0 mg
ARIA[1] 3001	720				720		
ARIA[1] 3002	685				677		
ARIB[1] 3003	753				769		
ARIB[2] 3004	58				56		
ARIB[3] 2002	19						24
ARIA[4] 1003	6			8	8	16	9
ARIA[5] 2001	59	58	53		57	57	60
Total	2300	58	53	8	2287	73	93

1 = pivotal study
2 = phase 3 urodynamic study
3 = phase 2 pilot study to determine intraprostatic DHT levels
4 = phase 1 study in patients with BPH
5 = phase 2 dose ranging study

The 3 pivotal trials ARIA3001, ARIA3002, and ARIB3003 were reviewed in detail (see appendices A, B, and C). The urodynamic results of Trial ARIB3004 and the dose ranging study ARIA2001 were reviewed.

C. Review of Clinical Trials

The 3 pivotal trials (ARIA3001, ARIA3002, and ARIB3003) were randomized, double-blind, placebo-controlled, 2-year parallel group studies of the efficacy and safety of dutasteride 0.5 mg in the treatment of BPH (year 1) and disease management (year 2) followed by a 2 year open-label extension. Results from Year 2 of the double-blind treatment phase, and from the open-label treatment phase (Years 3 and 4), will be reported in two subsequent submissions.

Two of the three multicenter trials (ARIA3001 and ARIA3002) were conducted entirely in the United States and the third (ARIB3003) was conducted in 19 countries (including the United States). The design of all three studies was virtually identical; the only difference between ARIA3001 and ARIA3002 was a difference in the timing of the first post-baseline prostate volume assessment (at month 1 in ARIA3001 and at month 3 in ARIA3002). The first post-baseline prostate volume assessment was at Month 6 in ARIB3003. In addition, in ARIB3003 blood samples were obtained for determination of dutasteride serum concentrations and serum luteinizing hormone (LH) levels were assessed.

Key study entry criteria for all 3 trials included: 1) men > 50 years of age with a diagnosis of BPH (according to medical history and physical examination, including digital rectal examination 2) AUASI greater than or equal to 12 3) Q_{max} of less than or equal to 15 cc/sec with a minimum voided volume of 125 cc 4) prostate volume of >30 cc as determined by transrectal ultrasound. Patients were excluded if they had a post void residual urine volume of >250 cc or a serum PSA level of <1.5 ng/mL or > 10.0 ng/mL. These eligibility criteria are considered appropriate.

All patients enrolled in the Phase 3 studies initially entered into a 4-week, single-blind, placebo run-in. Patients were then randomized to dutasteride 0.5 mg or placebo. A total of 4324 patients were randomized (2158 to placebo and 2166 to dutasteride). A total of 3522 patients completed 12 months of treatment (1750 or 81% placebo and 1772 or 82% dutasteride). This design is considered appropriate.

The primary efficacy endpoint in all Phase 3 trials was the change from baseline at 12 months in the American Urologic Association Symptom Index (AUASI). The primary endpoint (AUASI) was assessed at baseline and at Months 1, 3, 6, and 12). This validated questionnaire is currently used as a primary endpoint for all drug trials of the treatment of BPH. Statistically significant improvement was seen by month 3 ($p<0.032$) and through month 12 ($p<0.001$) in ARIA3002), by month 6 ($p<0.038$) and through month 12 ($p<0.001$) in ARIB3003, and by month 12 in ARIA3001 ($p<0.001$) (Table 1).

Table 1. AUASI Change from Baseline

	ARIA3001		ARIA3002		ARIB3003	
	Placebo	Dutasteride	Placebo	Dutasteride	Placebo	Dutasteride
Month 1	N=706	N=703	N=664	N=677	N=723	N=737
Mean	-1.4	-1.3	-1.2	-1.2	-1.4	-1.5
Mean difference		0.1		0.0		-0.1
p-value		0.81		0.98		0.78
Month 3	N=709	N=705	N=670	N=663	N=738	N=750
Mean	-2.1	-2.3	-1.8	-2.4	-2.8	-2.7
Mean difference		-0.2		-0.6		0.0
p-value		0.39		**0.032**		0.90
Month 6	N=709	N=705	N=671	N=664	N=741	N=750
Mean	-2.4	-2.9	-1.9	-2.7	-2.8	-3.4
Mean difference		-0.5		-0.8		-0.6
p-value		0.12		**0.008**		**0.038**
Month 12	N=709	N=705	N=671	N=664	N=742	N=750
Mean	-2.0	-3.0	-1.3	-2.8	-2.9	-4.1
Mean difference		-1.1		-1.5		-1.2
p-value		**<0.001**		**<0.001**		**<0.001**

In general correspondence dated September 7, 2001, the sponsor noted that a review of the one year data indicated that there were "data changes between data provided in the Year 1 NDA and the subsequent Year 1 portion of the cumulative 0-2 year data for the sNDA." These data changes resulted in one change in the statistical analysis. The p-value for the 6 month analysis of the AUASI in Trial ARIB3003 changed from 0.038 to 0.053. This change has no significant impact on overall efficacy conclusions.

The mean decrease from baseline in AUASI scores across the 3 studies pooled was –3.3 units for dutasteride and –2.1 units for placebo at Month 12; the mean AUASI difference between the 2 treatment groups was –1.2. Each study was powered based on achieving a mean difference (dutasteride versus placebo) of –1.5 units in AUASI. Although this mean difference was not achieved at Month 12 in ARIA3001 or ARIB3003, the 95% confidence interval around the difference included –1.5 in both trials. This drug-related improvement in AUA-SI, though modest. is considered to have some clinical importance.

Main secondary endpoints (changes from baseline in prostate volume and Qmax)

Prostate volume:

Beginning at the earliest time point measured in each study (Month 1 in ARIA3001, Month 3 in ARIA3002, and Month 6 in ARIB3003), significant decreases ($p<0.001$) in

mean percent change from baseline prostate volume were noted when comparing patients treated with dutasteride versus placebo (Table 2).

Table 2. Prostate Volume Percent Change from Baseline

	ARIA3001		ARIA3002		ARIB3003	
	Placebo	Dutasteride	Placebo	Dutasteride	Placebo	Dutasteride
Month 1	(N=704)	(N=702)	NA	NA	NA	NA
Mean	-2.9%	-8.5%				
Mean difference		-5.6%				
p-value		<0.001				
Month 3	NA	NA	(N=645)	(N=630)	NA	NA
Mean			-1.9%	-15.9%		
Mean difference				-14.1%		
p-value				<0.001		
Month 6	(N=706)	(N=705)	(N=654)	(N=641)	(N=672)	(N=674)
Mean	-3.5%	-20.1%	-2.3%	-19.7%	-7.8%	-24.7%
Mean difference		-16.6%		-17.4%		-16.9%
p-value		<0.001		<0.001		<0.001
Month 12	(N=706)	(N=705)	(N=655)	(N=641)	(N=682)	(N=682)
Mean	-2.0%	-23.2%	-2.0%	-22.9%	-6.0%	-27.6%
Mean difference		-21.2%		-20.9%		-21.5%
p-value		<0.001		<0.001		<0.001

The mean percent decrease in prostate volume across the 3 studies pooled was –24.6% for dutasteride and –3.4% for placebo at Month 12; the mean difference was –21.2%. This drug-related effect on prostatic volume may translate into improvement in long-term disease management.

Q_{max}:

Significant change from baseline in Q_{max} was seen by Month 1 in ARIB3003 (p=0.002), by Month 3 in ARIA3001 (p=0.017) and ARIA3002 (p=0.006), and continued through Month 12 in all three pivotal studies (Table 3).

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Table 3. Qmax (cc/sec) Change from Baseline

	ARIA3001 Placebo	ARIA3001 Dutasteride	ARIA3002 Placebo	ARIA3002 Dutasteride	ARIB3003 Placebo	ARIB3003 Dutasteride
Month 1	(N=676)	(N=686)	(N=647)	(N=629)	(N=6903)	(N=710)
Mean	0.5	0.7	0.6	0.8	0.5	1.0
Mean difference		0.2		0.1		0.5
p-value		0.31		0.47		**0.002**
Month 3	(N=702)	(N=703)	(N=664)	(N=651)	(N=724)	(N=742)
Mean	0.6	1.1	0.7	1.2	0.6	1.6
Mean difference		0.5		0.5		1.0
p-value		**0.017**		**0.006**		**<0.001**
Month 6	(N=703)	(N=706)	(N=667)	(N=653)	(N=730)	(N=743)
Mean	0.7	1.1	0.8	1.2	0.8	1.5
Mean difference		0.4		0.5		0.9
p-value		**0.041**		**0.025**		**<0.001**
Month 12	(N=703)	(N=706)	(N=669)	(N=653)	(N=732)	(N=744)
Mean	0.7	1.3	0.8	1.7	0.6	1.7
Mean difference		0.7		0.8		1.1
p-value		**<0.001**		**<0.001**		**<0.001**

The mean Q_{max} across the three studies pooled was 1.6 cc/scc for dutasteride and 0.7 cc/sec for placebo at Month 12; the mean difference was 0.9 cc/sec.

Other secondary endpoints:

Change in dihydrotestosterone (DHT) from baseline: At Month 12, the mean percent decrease in DHT ranged from 93.1% to 93.6% for dutasteride treated patients in the three pivotal studies (Table 4). Mean serum DHT levels either did not change or increased in placebo treated subjects.

Table 4. DHT Percent Change from Baseline

	ARIA3001 Placebo	ARIA3001 Dutasteride	ARIA3002 Placebo	ARIA3002 Dutasteride	ARIB3004 Placebo	ARIB3004 Dutasteride
Month 12	(N=655)	(N=647)	(N=590)	(N=562)	(N=591)	(N=609)
Mean	1.7%	-93.6%	4.5%	-93.5%	-0.5%	-93.1%
Mean difference		-95.3%		-98.0%		-92.6%
p-value		<0.001		<0.001		<0.001

Change in testosterone (T) from baseline: At Month 12, dutasteride-treated patients exhibited significant increases ($p<0.001$) in mean change from baseline testosterone concentrations as compared to placebo-treated patients (Table 5).

Table 5. Testosterone Percent Change from Baseline

	ARIA3001		ARIA3002		ARIB3003	
	Placebo	Dutasteride	Placebo	Dutasteride	Placebo	Dutasteride
Month 12	(N=653)	(N=644)	(N=588)	(N=560)	(N=594)	(N=609)
Mean	-2.0%	16.5%	2.1%	21.9%	0.0%	16.2%
Mean difference		18.5%		19.8%		16.2%
p-value		<0.001		<0.001		<0.001

For dutasteride treated patients the mean testosterone serum concentrations at Month 12 were within limits of normal range. An examination of individual T values is included under the "Safety" section.

Health Outcome results: Change from baseline in the BPH Impact Index (BII) was examined at Months 1, 3, 6, and 12. At Month 12, statistically significant improvement ($p<0.001$) was seen in all 3 pivotal studies. In these trials, a minimum perceptible difference (a difference for the results to be considered clinically meaningful) was defined as a mean decrease of 0.5 point on the BII relative to baseline. The difference from baseline in ARIA3001 was 0.51, in ARIB3003 was 0.46, and in ARIA3002 was 0.42.

Sub-group analysis based on prostate size: In patients with baseline prostate volumes >40 cc, mean AUASI was significantly lower in the in the dutasteride group than in the placebo group at Month 12 in all 3 pivotal trials ($p<0.001$). In the subgroup of patients with prostate volumes <40 cc, statistical significance versus placebo was not achieved for change from baseline AUASI (primary endpoint) at any time point measured in the 3 pivotal trials. This information is appropriately described in the product label.

Supporting efficacy studies: ARIB3004 was a 6 month, multicenter, double-blind, placebo-controlled, parallel group study in men with symptoms suggestive of bladder outlet obstruction. Patients were randomized to either placebo or dutasteride 0.5 mg. The primary objective of this urodynamic study was to compare the effect of dutasteride therapy on detrusor pressure at maximum urinary flow. This parameter is accepted as a surrogate objective measurement for the clinical manifestations of bladder outlet obstruction. No statistically significant difference was seen between dutasteride and placebo in detrusor pressure at maximum urinary flow (this parameter actually increased rather than decreased in both patient groups). A positive trend towards improvement in AUASI, Q_{max}, and prostate volume was noted in the dutasteride compared to the placebo group.

D. Efficacy conclusions:

All three pivotal trials showed statistically significant changes in the primary endpoint (AUASI) and the main secondary endpoints (Qmax and prostate volume) over baseline

when compared to placebo at 12 months. The AUASI decrease is clinically meaningful and the Q_{max} improvement is modest. Patients with a baseline prostate volume >40 cc showed statistical improvement in AUASI while those patients with a baseline prostate volume < 40cc did not. Although data directly comparing dutasteride and finasteride were not submitted in this application, the efficacy of these 2 drugs when compared across trials appears similar. In the opinion of this reviewer, from an efficacy standpoint, dutasteride should be approved.

VII. Integrated Review of Safety

A. Conclusions

The risks associated with dutasteride 0.5 mg for the treatment of symptoms of BPH identified in the clinical trials are acceptable. The incidence of sexual dysfunction and gynecomastia is increased over placebo. Although comparative data was not submitted in this application, adverse events appear to be similar to the only other currently marketed 5 alpha-reductase inhibitor for BPH (finasteride, Proscar).

Several clinical pharmacology questions concerning the drug remain unanswered and these questions should be answered in Phase 4 commitments. These questions primarily concern the fact that 55% of the administered dose has not been accounted for and the metabolic pathways have not been adequately determined. Labeling changes concerning the use of the drug in patients with hepatic impairment and the concomitant use of CYP3A4 inhibitors have been proposed to the sponsor.

Since 5 alpha-reductase inhibitors decrease circulating DHT, exposure of a pregnant woman to high concentration of the drug could result in inadequate development of the genitalia of a male fetus. Exposure could result from ingesting capsules, contact with broken gelcaps and subsequent absorption through the skin, or through contact with semen from a male taking dutasteride. Because of the potential risks, dutasteride should not be used in females, and women of childbearing age should not handle broken gel capsules. Pharmacokinetic data from Phase 2 studies show that the half-life of 0.5 mg/day dutasteride is approximately 3 to 5 weeks. Since total body elimination may take 4 months or more, patients in the dutasteride trials were informed that they should avoid unprotected intercourse with women of childbearing age for at least 4 months after discontinuation of therapy. The sponsor now believes that the potential maximum exposure to a woman via semen would be a daily dose that was 186-fold less than the dose that had no effect on male primate embryo fetal development. The maximum concentration of dutasteride found in semen was 14 ng/mL. Assuming total absorption of 70 ng in 5 cc of seminal fluid, the serum level in the partner was estimated to be approximately 0.0175 ng/mL by the Division's pharmacologist. This concentration in this "worst case scenario" is below the no effect and low effect concentrations of 0.05 and 0.07 ng/mL observed for the effect on adrenal weight in the monkey and the 2.0 ng/mL low effect level for external genitalia changes in mice. The recommendation for prohibiting unprotected intercourse with women of childbearing age has been discontinued by the sponsor and is not included in the label. This reviewer agrees with

the pharmacology/toxicology reviewer and believes that the administration of dutasteride does not require condom use when engaging in sexual intercourse with a woman of childbearing potential.

The sponsor initially recommended that blood donations should not be made for approximately 6 months after discontinuing treatment to avoid the possibility of inadvertent exposure of pregnant women to dutasteride. The sponsor now believes that exposure from blood donation to be inconsequential, as the amount of drug in a unit of blood is similar to the daily dose administered in the primate fetal development study on a ng/kg basis. In this primate study, pregnant females received this dose daily for 80 days with no effect on male fetal genital development. Therefore, this recommendation was not included in the proposed labeling. Based on serum concentration, however, the concentration of dutasteride in a recipient immediately following blood transfusion can be calculated to be approximately 5.0 ng/mL. This concentration is higher than the 2.0 ng/mL level which is associated with abnormalities of the external genitalia in mice. Because of the presumed long half-life of the drug following transfusion, this reviewer agrees with the pharmacology/toxicology reviewer and believes that blood donations should not be made for approximately 6 months following discontinuation of the drug and this recommendation has been included in the proposed label. In addition, the Office of Blood Applications, CBER, has been notified of this issue.

B. Extent of Exposure

Data presented in the Integrated Summary of Safety is drawn from a total of 5305 patients enrolled in 19 completed studies conducted in the United States and 18 other countries. The 5305 patients included 240 in 7 single-dose volunteer studies, 110 in 5 repeat-dose volunteer studies, 4324 in the 3 pivotal efficacy studies, and 631 in 4 supporting efficacy studies. In the 3 pivotal studies, 2166 patients took dutasteride for a total of 1866 subject years of drug exposure.

C. Methods of Safety Review:

The Integrated Summary of Safety, the pivotal trials (ARIA3001, ARIA3002, and ARIB3003), Trial ARIA1009 (effect of dutasteride on semen analysis), and the 120 day safety update were reviewed for safety in detail (see Appendices A, B, C, D, and E). Trial ARI10019 (a trial to evaluate the QT interval entitled "A Double-Blind, Placebo Controlled, Randomized, Parallel Group Study to Investigate the Changes in the Corrected QT Interval Following Repeat Oral Doses of GI198745 In Healthy Male Volunteers: Preliminary Data as of 7 March 2001 for the 120-Day Safety Update for NDA 21-319; Dutasteride Soft Gelatin Capsules") was reviewed in consultation with the CardioRenal Division. Two year safety data for Trial ARIA3002 which was submitted with the 120 Day Safety Update was reviewed.

D. Summary of Safety Findings

D.1. Three Pivotal Studies

In the 3 pivotal studies combined, 4324 patients were randomized. Demographic characteristics of the patients are shown in Table 6.

Table 6. Demographic Characteristics of Patients Enrolled in the Three Pivotal Studies

	Placebo (N=2158)	Dutasteride (N=2166)
Age (years)		
Mean	66.1	66.5
Minimum-maximum	47-91	50-94
Race n (%)		
Caucasian	1986 (92%)	1974 (91%)
Black	79 (4%)	82 (4%)
Hispanic	60 (3%)	68 (3%)
Asian/Oriental	20 (<1%)	28 (1%)
Other	13 (<1%)	14 (<1%)

A summary of adverse events reported by >5% of patients in either treatment group in the 3 pivotal trials combined is shown in Table 7.

Table 7. Summary of Most Common Treatment-Emergent Adverse Events (3 Pivotal Studies)

	Placebo (N=2158)	Dutasteride (N=2166)
Any adverse event	1363 (63%)	1386 (64%)
Most common adverse events		
ENT infections	119 (6%)	137 (6%)
Musculoskeletal pain	150 (7%)	112 (5%)
Viral ENT infections	106 (5%)	95 (4%)
Impotence	76 (4%)	141 (7%)

The incidence of adverse events of special interest in patients taking 5 alpha-reductase inhibitors are shown in Table 8.

Table 8. Adverse Events of Special Interest in Patients Taking 5 alpha-Reductase Inhibitors

	Placebo (N=2158)	Dutasteride (N=2166)
Decreased libido	49 (2%)	88 (4%)
Impotence	76 (4%)	141 (7%)
Ejaculation disorder	18 (<1%)	53 (2%)
Sexual function disorder	2 (<1%)	7 (<1%)
Gynecomastia	11 (<1%)	32 (1%)
Prostate cancer	12 (<1%)	11 (<1%)

Two percent of patients treated with dutasteride withdrew due to a drug-related reproductive system adverse event. <1% of patients in each treatment group withdrew due to any specific reproductive system adverse event. The median time of onset for impotence was 154 days in the placebo group and 75 days for the dutasteride group. Deaths: Eight (<1%) patients in the placebo group and 12 (<1%) patients in the dutasteride experienced fatal serious adverse events; none of the fatal adverse events was considered to be related to study drug by the investigator. The causes of death in the placebo group were cardiac arrest, disseminated intravascular coagulation, bladder cancer, rectal cancer, lung cancer, lung metastasis. cerebrovascular event, and acute myocardial infarct. The causes of death in the dutasteride group were myocardial infarction, bladder cancer, worsening COPD, angiosarcoma, cardiac arrest, cerebrovascular accident, coronary artery disease, cerebrovascular accident, myelogenous leukemia, lung cancer, death from natural causes, and myocardial infarction. The sponsor believes that there is no difference in the incidence of overall deaths or deaths due to cardiovascular events between the drug and placebo groups. This reviewer agrees.

Serious adverse events: Serious adverse events were reported by 171 (8%) in the placebo group and by 197 (9%) in the dutasteride group. Almost all serious adverse events were considered by the investigator to not be related to study drug. Four serious adverse events in four patients were considered by the investigator to be related to study drug. Three of these events were in placebo treated patients. The dutasteride patient experienced a severe "allergic" rash approximately one year after starting study medication. This patient was hospitalized and all concomitant medication was stopped. The event resolved 11 days after onset. Fifty-two (2%) of the placebo patients and 45 (2%) of the dutasteride patients withdrew from the trials due to serious adverse events.

Pregnancy: No pregnancy was reported by any female partner of a patient enrolled in any of the 3 pivotal trials.

Abnormal laboratory study frequency: Among patients with a normal baseline and at least one post-baseline laboratory value, approximately one-third of the patients in the placebo (32%) and dutasteride (33%) treatment groups had at least one abnormal post-baseline laboratory value. More patients in the dutasteride group than in the placebo group had normal to abnormal changes in alkaline phosphatase (3% and 1% respectively) and ALT (5% and 3% respectively). Less than 1% of these elevations met the "clinically significant" threshold values. These differences are not considered indicative of a meaningful drug-related effect on the liver.

Changes in prostate specific antigen (PSA): Dutasteride reduced total serum PSA by approximately 40% following 3 months of treatment and approximately 50% following 6 months of treatment (Table 9).

Table 9. Percent Change from Baseline PSA

	Placebo (N=2158)	Dutasteride (N=2166)
Month 1 Mean	(N=2041) 2.7%	(N=2040) -8.7%
Month 3 Mean	(N=2119) 2.2%	(N=2124) -32.2%
Month 6 Mean	(N=2124) 5.7%	(N=2129) -39.1%
Month 6 Mean Median	(N=2127) 9.2% 2.4%	(N=2130) -42.6% -51.2%

Reviewer's comment: A new baseline PSA concentration should be established after 3 to 6 months of treatment and this new value should be used to assess potentially cancer-related changes in PSA. To interpret an isolated PSA value in a man treated with dutasteride for 6 months or more, the PSA value should be doubled for comparison with normal values in untreated men. The label appropriately describes this issue.

Prostate cancer: Twelve patients in the placebo group and 11 in the dutasteride group were diagnosed with prostate cancer during the study.

Serum testosterone (T): Since 5 alpha-reductase inhibitors block the conversion of testosterone to DHT, elevation of serum T may occur. Fourteen patients (3 placebo and 11 dutasteride) had serum T values which were normal at baseline but exceeded the top normal value of 10,000 pcg/mL at some point during the first year of the study. All but one of these 14 patients had a screening T level of >5,000 pcg/mL. The maximum T level recorded was 13,500 pcg/mL. The sponsor believes that even in these "outliers" that maximum total testosterone levels were not unsafe. This reviewer agrees.

E.2. Safety information included in other trials and supportive trials

Effect of dutasteride on the QT interval (ARI10010) (see Cardiorenal consultation for detailed review:

This protocol was a double-blind, placebo-controlled, randomized, parallel group study to investigate the changes in the corrected QT interval following repeated oral doses of dutasteride in healthy male volunteers. There were 3 treatment arms consisting of oral daily dose of placebo, oral daily doses of 0.5 mg dutasteride (with a one day loading dose of 25 mg), and oral daily doses of 5 mg dutasteride (with a 7 day loading dose of 40 mg). In the 5 mg dutasteride group, mean serum dutasteride concentration was approximately 900 ng/ml. Ninety-seven healthy men with a screening QTc interval of <450 msec were randomized. Twelve-lead ECG's were recorded for 12 hours after dosing on Days –1, 1,

and 28 at predose and at 1, 2, 3, 4, 6, 8, 10, and 12 hours post-dose. ECG's were also obtained at days 7, 14, and 21 after start of dosing. Compared to placebo, neither dose of dutasteride had an effect on ventricular rate. The primary study endpoint was mean QT. QT corrected for heart rate (Bazett's and Fridericia's) was also calculated. Mean QT changes from baseline were similar for all 3 treatment groups at all time points. Compared to placebo, neither dose of dutasteride had an effect on the QT interval.

The CardioRenal consultant concluded that: "This study showed no effect of dutasteride 0.5 mg or 5 mg on the uncorrected QT interval. (Since the ventricular rate was unaffected by the drug, no correction factor is necessary.) The range of serum concentration was from approximately 20 ng/ml to approximately 900 ng/ml. This finding, however, does not rule out an effect of dutasteride on repolarization at higher concentrations." Thus, there does not appear to be an effect of dutasteride on the QT interval.

Effect of dutasteride on spermatogenesis (ARIA1009) (see appendix D for detailed review):

In the single and repeat-dose volunteer studies, adverse events were in general similar to those reported in the 3 pivotal trials. The following are noteworthy:

a) No deaths were reported during the single-dose and multiple-dose volunteer studies.
b) One pregnancy of a female partner was reported in a repeat-dose volunteer study. When the patient returned for his 2-month post-treatment visit, he still had quantifiable levels of dutasteride in his blood. Shortly thereafter, he learned that his wife was pregnant and had thus been exposed to dutasteride via semen during the first weeks of the pregnancy. The outcome of the pregnancy is unknown; the patient and his wife moved and the investigator was unable to obtain follow-up information about the pregnancy.
c) One patient in ARIA1001 (10 mg dutasteride single dose group) experienced an "increase in total bilirubin beginning at Day 7 that became abnormal at Day 21 and continued abnormal through the rest of the study. High values for ALT and AST at Day 21 were also recorded." Review of the individual laboratory data line listings for this patient (#35) showed that his bilirubin was slightly elevated at baseline (38.7 with normal being 6.3-29.1). At Day 5 his bilirubin was 31.2. The bilirubin was normal at days 8, 15, and 22. At Day 29 the bilirubin was 36.2 and it was normal at Days 57 and 90. The SGOT and SGPT were normal at days 1, 3, 8, 22, and 57. At Day 90 the SGOT was 132 (normal 16-41) and the SGPT was 53 (normal 10-49). Both the SGOT and SGPT were normal at Day 113. In the opinion of the reviewer, it is unlikely that that these changes in liver function studies are drug related.
d) In ARIA2004, five pregnancies were reported by female partners of male patients (one placebo and four dutasteride). Three of the 4 women whose partners received dutasteride had normal births, delivering two healthy boys and one healthy girl. The fourth woman delivered a healthy baby boy at 37 weeks gestation by Cesarean section due to partial placenta previa.

E.3. Summary of 120 Day Safety Update

Year 2 safety data for ARIA3002 was included in the safety update as well as deaths, serious adverse events, and partner pregnancies which occurred after year one in ARIA3001 and ARIB3003. No new safety concerns were identified. At month 12 a mean decrease from baseline in serum PSA of 45.0% was seen in the dutasteride group. At month 24 this mean decrease was 48.2%.

VIII. Dosing, Regimen, and Administration Issues

The 0.5 mg dose of dutasteride was selected based on results from ARIA1003 and ARIA2001. Dutasteride 0.5 mg was the lowest maximally effective dose of dutasteride with regard to DHT suppression (ARIA1003 and ARIA2001) and decreases in prostate volume (ARIA2001). The 0.5 mg dose also appeared to have the best balance between efficacy and safety in the population studied and was chosen as the dose for the phase 3 trials. The 0.01 mg dose appears to be the clinical no effect level based on comparability with placebo results for DHT suppression and prostate volume reduction. In Trial ARIA2001 doses of dutasteride up to 5.0 mg daily were given for 6 months and no significant adverse events were identified.

IX. Use in Special Populations

Gender: Dutasteride is indicated for the treatment of BPH and should not be used in women.

Pediatric use: Dutasteride is indicated for the treatment of BPH, a disease of older men. A pediatric waiver has been granted.

Elderly: The sponsor believes that no dose adjustment is necessary in the elderly and this reviewer agrees. The pharmacokinetics of dutasteride were evaluated in 36 healthy men between the ages of 24 and 87 years following administration of a single 5 mg dose of dutasteride. Exposure to dutasteride, represented by AUC and Cmax, was not statistically different between age groups. Half-life, however, did appear to increase with age. The sponsor also indicated that preliminary population PK studies did not reveal differences in exposure between younger and older men. No differences in drug effect, as measured by DHT reduction, were observed between age groups. Of 2166 men treated with dutasteride in the 3 pivotal studies, 60% were age 65 and over and 15% were age 75 and over. No overall differences in safety or efficacy were observed between these patients and younger patients.

Race: The effect of race on dutasteride pharmacokinetics has not been studied.

Renal impairment: The effect of renal impairment on dutasteride pharmacokinetics has not been studied. Less than 0.1% of a steady-state 0.5 mg dose of dutasteride is recovered in human urine. Thus, the sponsor believes that no dose adjustment is necessary in renal impairment and the reviewer agrees.

Hepatic impairment: The effect of hepatic impairment on dutasteride pharmacokinetics has not been studied. Dutasteride is extensively metabolized. Hepatic insufficiency is likely to increase exposure. Exposure of men at ten times the dose for 6 months did not reveal any significant adverse events. The sponsor proposes a cautionary statement in the label in this special population and the reviewer agrees.

X. Conclusions and Recommendations

In the opinion of this reviewer, dutasteride 0.5 mg should be approved for the indication "treatment of symptomatic hyperplasia (BPH) in men with an enlarged prostate gland." From an efficacy standpoint, all three pivotal trials showed statistically significant changes in the primary endpoint (AUASI) and the main secondary endpoints (Qmax and prostate volume) over baseline when compared to placebo at 12 months. The AUASI decrease is clinically meaningful and the Q_{max} improvement is modest. Although data directly comparing dutasteride and finasteride were not submitted in this application, the efficacy noted in controlled trials studying these 2 drugs appears similar. From a safety standpoint, no significant safety concerns were identified in a review of the 2166 patients who received dutasteride for a total of 1866 patient years during the pivotal trials and Year 2 data from 677 patients enrolled in ARIA3002. Preliminary QT data showed no effect on QT interval at doses which resulted in C_{max} dutasteride levels ranging from 20 to approximately 900 ng/mL.

Several clinical pharmacology issues remain unresolved. The following issues should be addressed in Phase 4 commitments. Approximately 55% of the administered dutasteride dose is not accounted for. Metabolic pathways have not been adequately determined for this drug whose elimination half-life is approximately 5 weeks. The identification of the isoenzymes responsible for the metabolism of dutasteride is incomplete. The available data from *in vitro* studies show that CYP3A4 is responsible for approximately 4% of the metabolism of this drug. No other isozymes were identified as being responsible for the metabolism of dutasteride. Based on *in vivo* data, however, dutasteride is extensively metabolized to approximately 11 metabolites (4 major and 6 minor). The structural identity and pharmacological activity of some of these metabolites is unknown. No information is available concerning the pharmacokinetics of the drug in renal or hepatic impaired patients. No focused drug-drug interaction studies have been conducted which would assess interaction with inhibitors of the CYP450 system.

Recommended Phase 4 commitments:

1) A study of drug-drug interaction with ketoconazole
2) A study of dutasteride use in hepatically impaired patients
3) A study to define the metabolism of dutasteride

The following major labeling changes are recommended and have been made to the proposed label:

1) A cautionary statement for dutasteride in patients with hepatic impairment.
2) A cautionary statement for dutasteride in patients taking ketoconazole and other potent CYP3A4 inhibitors.
3) Men taking dutasteride should not donate blood for 6 months following discontinuation of the drug.

XI. Appendices

Appendix A – Clinical Trial **ARIA3001** ("A Randomized, Double-Blind, Placebo-Controlled, Two Year Parallel Group Study of the Efficacy and Safety of GI198745 0.5 mg in the Treatment and Prevention of Progression of Benign Prostatic Hyperplasia, Followed by a Two-Year Open-Label Treatment Phase (Report on 1 Year Data)"

Appendix B– Clinical Trial **ARIA3002** ("A Randomized, Double-Blind, Placebo-Controlled, Two Year Parallel Group Study of the Efficacy and Safety of GI198745 0.5 mg in the Treatment and Prevention of Progression of Benign Prostatic Hyperplasia, Followed by a Two-Year Open-Label Treatment Phase (Report on 1 Year Data)"

Appendix C– Clinical Trial **ARIB3003** ("A Randomized, Double-Blind, Placebo-Controlled, Two Year Parallel Group Study of the Efficacy and Safety of GI198745 0.5 mg in the Treatment and Prevention of Progression of Benign Prostatic Hyperplasia, Followed by a Two-Year Open-Label GI198745 Treatment Phase (Report on 1 Year Data)"

Appendix D– Clinical Trial **ARIA1009** ("An Investigation of the Pharmacokinetics of GI198745 and of the Effects of GI198745 on Semen Characteristics When Administered Daily for 12 Months to Healthy Male Subjects")

Appendix E: - 120 Day Safety Update (including synopsis of **Trial ARI10010** "A Double-Blind, Placebo-Controlled, Randomized, Parallel Group Study to Investigate the Changes in the Corrected QT Interval Following Repeat Oral Doses of GI198745 in Healthy Male Volunteers: Preliminary Data as of March 7, 2001, for the 120-Day Safety Update for NDA 21-319; Dutasteride Soft Gelatin Capsules" and year 2 safety data for Trial **ARIA3002**

Appendix F: Amendment received June 19, 2001, including study report for **ARIB3004** "A Six-month, randomized, double-blind, placebo-controlled, parallel group study to evaluate the effects of repeat dose oral GI198745 on detrusor pressure and urinary flow in patients with lower urinary tract symptoms suggestive of bladder outlet obstruction, with optional six month open-label extension"

Appendix A – Clinical Trial **ARIA3001** ("A Randomized, Double-Blind, Placebo-Controlled, Two Year Parallel Group Study of the Efficacy and Safety of GI198745 0.5 mg in the Treatment and Prevention of Progression of Benign Prostatic Hyperplasia, Followed by a Two-Year Open-Label Treatment Phase (Report on 1 Year Data)" Study initiation date: September 8, 1997. Study report date: August 31, 2000.

A.1. Objective: This report presents the results from Year 1 of the 2 year double-blind treatment phase. The primary objective for year 1 of the study was to assess the efficacy (AUA-SI) of repeat oral once daily dosing of dutasteride 0.5 mg compared with placebo. The secondary objectives for Year 1 of the study were to assess the effects of repeat oral once daily dosing of dutasteride 0.5 mg compared with placebo on efficacy (prostate volume and urinary flow measurements), humanistic assessments, serum dihydrotestosterone (DHT), testosterone, prostate specific antigen (PSA), and safety and tolerability.

A.2. Design and conduct summary: This was a randomized, double-blind, placebo-controlled, multicenter (105 United States sites), 2-year parallel group study of the efficacy and safety of dutasteride 0.5 mg in patients with BPH followed by a 2 year open-label extension study. A total of 1544 patients were enrolled and entered the 4 week placebo run-in. Of these, 1440 patients were randomized at baseline to treatment with either placebo (n=720) or dutasteride 0.5 mg (n=720). Each patient, once randomized into the study, was to self-administer double-blind study medication for 2 years. Patients who completed 2 years of double-blind therapy were eligible to enter a 2-year open-label extension treatment phase. All patients who participated in the open-label phase received dutasteride 0.5 mg daily. Patients were assessed on a outpatient basis with clinic visits on months 1, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, and 48 post randomization.

This NDA and this study report are concerned only with the data from the first year of the double-blind trial.

The AUASI (primary endpoint) was obtained at screening, baseline (after the 4-week placebo run-in) and at months 1, 3, 6, and 12. (For purposes of statistical analysis, the final value of the AUASI prior to the start of the randomized treatment was used as the baseline value.)

Uroflow (secondary endpoint) was obtained at screening, baseline, and at months 1, 3, 6, and 12.

Prostate volume (secondary endpoint) was determined at screening and at months 1, 6, and 12.

Testosterone, DHT, and PSA (secondary endpoints) were determined at screening and at months 1, 3, 6, and 12.

Humanistic assessments (BPH Impact Index, BPH-specific Interference with Activities, and BPH-Specific Psychological Well-Being) (secondary endpoints) were determined at screening, baseline, and at months 1, 3, 6, and 12. The BPH specific Life-Style Adaptions and Problem Assessment Scale of the Sexual Function Inventory were determined at months 1 and 12.

Genotyping: Blood was collected once (on or after the month 1 visit) from patients who voluntarily submitted this sample.

Safety studies: Clinical laboratory tests (CBC, glucose, sodium, potassium, total protein, total bilirubin, albumin, ALT, alkaline phosphatase, and creatinine) were determined at baseline and at month 12. A 12 lead EKG was performed at baseline. Post-void residual was determined at screening, baseline, and months 1, 3, 6, and 12.

A.3. Study population: One thousand four hundred forty (1440) patients were enrolled. The study population was primarily Caucasian. The 2 groups were comparable with respect to age and prostate size (Table 1).

Table 1. Demographic and Baseline Characteristics.

	Placebo (N=720)	Dutasteride (N=720)
Age (years) – mean	65.9	66.4
Race		
Caucasian	640 (89%)	634 (88%)
Black	41 (6%)	44 (6%)
Asian	5 (<1%)	10 (1%)
American Hispanic	28 (4%)	29 (4%)
Other	6 (<1%)	3 (<1%)
Weight (kg)	86.7	86.2
Prostate volume > 40 cc at baseline	508 (71%)	496 (69%)
Duration of BPH symptoms (years)	5.4	5.6

A.4. Inclusion and exclusion criteria: Inclusion criteria include: 1) men > 50 years of age 2) diagnosis of BPH according to medical history and physical examination including a digital rectal examination (DRE) 3) American Urological Association Symptom Index (AUASI) greater than or equal to 12 at screening (Visit 1) 4) peak urinary flow rate (Qmax) of less than or equal to 15 cc/sec with a minimum voided volume of 125 cc at Visits 1 and 2 5) prostate volume of > 30 cc as determined by transrectal ultrasound (TRUS) and 6) patients must complete the 2 year double-blind treatment phase in order to be eligible to participate in the 2 year open-label treatment phase. Exclusion criteria include: 1) post-void residual urine volume measured by ultrasound of >250 cc at screening and baseline visits (Visits 1 and 2) 2) history or current evidence of prostate cancer 3) serum PSA of <1.5 ng/ml or >10.0 ng/ml. It is the investigators' responsibility to rule-out prostate cancer when the PSA is > 4.0 ng/ml. 4) previous prostate surgery

(including balloon dilatation, thermotherapy, or stent placement) or other invasive procedures to treat BPH 5) history of acute urinary retention or history of repeated catheterizations due to acute urinary retention and BPH within 3 months of Visit 1 6) neurogenic bladder, bladder neck contracture, urethral stricture, bladder malignancy, acute or chronic prostatitis, or acute or chronic urinary tract infection 7) myocardial infarction, coronary artery bypass surgery, unstable angina, cardiac arrhythmias, congestive heart failure, or cerebrovascular accident within 6 months prior to screening visit 8) liver function tests > twice upper limit of normal 9) serum creatinine >1.8 mg/dl 10) previous use of finasteride, investigational 5 alpha-reductase inhibitors, alpha-receptor blockers within 4 weeks of screening, phytotherapy within 8 weeks of screening 11) concurrent use of finasteride, investigational 5 alpha-reductase inhibitors, alpha-receptors blockers, anabolic steroids, drugs with anti-androgenic properties (e.g. spironolactone), or phytotherapy 12) use of alpha adrenergic agonists or cholinergic or anti-cholinergic agents including antihistamines or decongestants within 48 hours of each study visit 13) actively trying to procreate or unwillingness to use a condom during intercourse with a woman of childbearing potential for duration of participation in the study and for 4 months following treatment and 14) history or current evidence of drug or alcohol abuse within the last 12 months.

Reviewer's comment: Patients were required to use a condom during intercourse with a woman of childbearing potential in each of the 3 pivotal trials.

A.5. Endpoints: The primary endpoint at year one of the study is the change in AUASI in the drug group versus placebo. Secondary endpoints at year one of the study include: 1) change in prostate volume in the drug group versus placebo 3) change in Q_{max} in the drug group versus placebo 4) change in the BPH Impact Index, Symptom Problem Index, BPH-Specific Interference with Activities Questionnaire, and Problem Assessment Scale of the Sexual Function Inventory in the drug group versus placebo 5) change in serum testosterone, dihydrotestosterone (DHT), and PSA in the drug group versus placebo, and 6) safety and tolerability of drug versus placebo.

A.6. Withdrawals, compliance, and protocol violations:

Withdrawals: A total of 1544 patients were enrolled and entered into the placebo run-in period. One hundred and four (104 or 7%) of these patients discontinued the study prior to randomization. The main reasons for discontinuation from the placebo run-in phase were inclusion/exclusion criteria violation (44/1544 or 3%) and consent withdrawn (28/1544 or 2%). Additional reason, each listed by <1% of patients, included adverse event, protocol violation, missing reason, and "other" reasons. Of the 1440 patients randomized to double-blind treatment, 1190 (587 placebo and 603 dutasteride) completed treatment through month 12. After randomization to double-blind treatment, a similar proportion of patients in each treatment group prematurely discontinued (133 (18%) placebo and 117 (16%) dutasteride). The primary reasons for discontinuation included adverse event (5% in each treatment group), lack of efficacy (5% placebo and 4% dutasteride), and consent withdrawn (5% placebo and 3% dutasteride).

Protocol violations: Major protocol violations were reported for 129 subjects (76 (11%) placebo and 53 (7%) dutasteride). None of these 129 patients was excluded from any analysis because of violations. The main violations reported were previous use of prohibited medications (3% placebo; and 2% dutasteride), concurrently using prohibited medications at some point during the study (2% for both treatment groups), subjects with $Q_{max} > 15$ cc/sec or a minimum voided volume of < 125 cc at screening (2% for both treatment groups), and reported study drug compliance <75% (2% placebo and <1% dutasteride).

PSA non-reporting: All PSA values for dutasteride-treated subjects were multiplied by a factor of 2 and randomly reported either as such or rounded up or down by 0.1. These adjusted PSA values were to be routinely provided to the investigators (beginning 6 months after treatment initiation and continuing throughout the stuy) who would review the information and take appropriate action. However, during the study, it was learned that a number of PSA values were not reported by Ingenix Pharmaceutical Services in accordance with the study plan. For ARIA 3001, non-reporting occurred for 152 subjects. Study sites for all 152 subjects were contacted and follow-up information was received for 146/152 (96%) of subjects as follows: no action necessary 106 (73%), subject contacted 32 (22%), and lost to follow-up 8 (5%).

Improper conduct by 2 investigators: The participation of 2 ARIA 3001 investigators (A1_11 and A4_08) was terminated due to irregularities in the recording of safety and efficacy data. Irregularities at A1_11 were determined based on site audit findings indicative of irregularities in the recording of safety and efficacy data. Entries on case report forms could not be verified through source document review. As a result, the validity of study data could not be definitely established. Investigator A4_08 withdrew as an investigator in the ARIA 3001 study. His "sudden departure as primary investigator, general unavailability, unwillingness to adequately address study issues at this time, and his exit from all research studies and clinical practice raised multiple concerns." A total of 40 subjects were randomized to double-blind treatment at these two sites (16 at A1_11 and 24 at A4_08). As it is assumed that subjects at these sites did receive study medication, "it was decided to include these subjects in all analyses. However, a separate set of key tables (including the primary endpoint) were produced excluding these subjects to allow for comparison with the overall ITT population."

A.7. Efficacy analysis:

The primary endpoint was the change from baseline in AUASI at month 12 compared to placebo (Table 2).

Table 2. AUASI (LOCF) Mean Values

	Placebo (N=720)	Dutasteride (N=720)
Screening	19.7 (N=717)	19.5 (N=719)
Baseline	17.2 (N=707)	17.2 (N=704)
Month 1	15.8 (N=706)	15.9 (N=703)
Month 3	15.1 (N=709)	14.9 (N=705)
Month 6	14.7 (N=709)	14.3 (N=705)
Month 12	15.2 (N=709)	14.2 (N=705)**

** At month 12, the mean difference (-1.0 units was significantly improved ($p<0.001$; 95% CI: -1.7, -0.5) when comparing dutasteride (-3.0 units) versus placebo (-2.0 units). (No differences were noted when comparing the mean change from baseline AUASI data excluding the 40 patients randomized to double-blind treatment at 2 study sites (A4_08 and A1_11) (see section on major protocol violations).

Among patients with baseline prostate volumes >40 cc, change from baseline AUASI was significantly improved ($p<0.001$ at month 12 in the dutasteride group compared with the placebo group). Within the subgroup of patients with prostate volumes <40 cc, statistical significance for change from baseline AUASI compared with placebo was not achieved (Table 3).

Table 3. AUASI Change from Baseline by Baseline Prostate Volume

	Placebo <40 gm prostate volume	Dutasteride <40 gm prostate volume	p-value	Placebo >40 gm prostate volume	Dutasteride >40 gm prostate volume	p-value
Month 12	N=208	N=218		N=499	N=484	
Mean	-2.5	-2.8		-1.7	-3.2	
Mean difference		-0.3	0.67		-1.4	<0.001

The number and percentage of patients with at least a 20% reduction in AUASI is shown in Table 4.

Table 4. AUASI Improvement from Baseline of >20%.

	Placebo (N=720)	Dutasteride (N=720)
Month 1	211/706 (30%)	222/703 (32%)
Month 3	266/709 (38%)	300/705 (43%)
Month 6	297/709 (42%)	335/705 (48%)
Month 12	281/709 (40%)	344/705 (49%)

The primary secondary endpoints were the changes at 12 months in prostate volume and urinary flow. Changes in prostate volume are shown in Table 5.

Table 5. Prostate Volume Percent Change from Baseline (LOCF)

	Placebo (N=720)	Dutasteride (N=720)	p-value
Month 12	(N=706)	(N=705)	
Mean	-2.0%	-23.2%	
Mean difference		-21.2%	<0.001

The maximum urinary flow (Qmax) mean values (LOCF) are shown in Table 6.

Table 6. Qmax (cc/sec) Mean Values (LOCF)

	Placebo (N=720)	Dutasteride (N=720)
Screening visit 1	9.8 (N= 716)	9.7 (N=717)
Screening visit 2	9.9 (N=716)	9.4 (N=715)
Baseline	10.8 (N=709)	10.2 (N=709)
Month 1	11.2 (N=676)	11.0 (N=686)
Month 3	11.2 (N=702)	11.4 (N=703)
Month 6	11.3 (N=703)	11.4 (N=706)
Month 12	11.2 (N=703)	11.8 (N=706)**

** At month 12, the mean difference (dutasteride minus placebo was 0.6 cc/sec ($p<0.001$; 95% CI: 0.3, 1.1).

The Qmax change from baseline is shown in Table 7.

Table 7. Qmax change from baseline (cc/sec): Mean (LOCF)

	Placebo (N=720)	Dutasteride (N=720)	p-value
Month 1			
Mean	0.5	0.7	
Mean difference		0.2	0.31
Month 3			
Mean	0.6	1.1	
Mean difference		0.5	0.017
Month 6			
Mean	0.7	1.1	
Mean difference		0.4	0.041
Month 12			
Mean	0.7	1.3	
Mean difference		0.7	<0.001

Other secondary endpoints: DHT serum concentration, testosterone serum concentration, humanistic measures

The percent change from baseline in DHT serum concentrations is shown in Table 8.

Table 8. Percent change from baseline in DHT serum concentration (LOCF)

	Placebo (N=720)	Dutasteride (N=720)	p-value
Month 12	(N=655)	(N=647)	
Mean	+1.7	-93.6%	
Mean difference		-95.3%	<0.001

When looking at earlier time points, significant ($p<0.001$) decreases in serum DHT concentrations were noted as early as 1 month after the initiation of dutasteride therapy.

The percent change from baseline in serum testosterone concentration is shown in Table 9.

Table 9. Percent change from baseline in T serum concentration (LOCF)

	Placebo (N=720)	Dutasteride (N=720)	p-value
Month 12	(N=653)	(N=644)	
Mean	-2.0%	16.5%	
Mean difference		18.5%	<0.001

Seven patients (3 in the placebo group and 4 in the dutasteride group) had T levels which exceeded 10,000 pcg/mL (upper limit of normal) at some point during the first year of the study. Five patients (one in the placebo group and 4 in the dutasteride group) had a screening T within the normal range and then an elevated value after treatment with study drug. None of these patients reported any adverse events or clinical symptoms associated with these elevated values. The highest T values were 12,400 pcg/ml which were obtained in two patients after 12 months of dutasteride therapy.

Humanistic studies included the BPH Impact Index (BII), Combined Symptom Problem Index (SPI) and BPH Specific Interference with Activities (BSIA), and Problem Assessment Scale of the Sexual Function Inventory (PASFI).

BII: Mean change from baseline BII was examined at Months 1, 3, 6, and 12 using a LOCF approach. At month 12, dutasteride significantly ($p<0.001$) improved the BII score compared with placebo (mean difference –0.5; 95% CI: -0.8, -0.3). Although statistical significance was achieved at Month 3, significance was not reached at Month 6 and therefore the interpretation of the results at Month 3 is restricted as defined by the multiplicity rules established for this study.

Combined SPI and BSIA: In order to control for multiplicity, change from baseline at Month 12 was compared across the SPI and BSIA in terms of their composite ranking. Based on these summed ranks, results for the dutasteride group were not significantly different ($p>0.082$) from results reported for the placebo group. Therefore, the interpretation is restricted when examining the results for each of these two assessments.

PASFI: At month 12, mean percentage change from baseline PASFI reflected a worsening of sexual function in the dutasteride group whereas for placebo-treated patients a mean increase in the sexual function inventory score was reported.

A.8. Safety analysis:

A.8.1. Extent of exposure: The extent of exposure is summarized in Table 10.

Table 10. Extent of Study Drug Exposure from Week 0 to the End of Treatment (ITT population)

	Placebo (N=720)	Dutasteride (N=720)
N	692	695
Mean (SD)	331.3 (86.16)	331.0 (89.47)
Median	365.0	365.0

A.8.2. Serious adverse events:

Deaths: Two patients in the placebo group and 5 in the dutasteride group died during the trial. None of the AE's leading to death was considered by the investigators to be related to study drug. The causes of death in the placebo group were cardiac arrest in a 72-year-old and disseminated intravascular coagulation in a 67-year-old. The causes of death in the drug group were myocardial infarction in a 72-year-old, bladder cancer in a 70-year-old, worsening of COPD in a 67-year-old, angiosarcoma with liver metastasis in a 74-year-old, and cardiac arrest in an 85-year-old. One additional patient died in his sleep (cause unknown) during the placebo run-in phase.

Serious adverse events: One hundred thirty (130) patients experienced a serious adverse event during the study. Five patients experienced an adverse event prior to randomization. Two of these patients also experienced a serious adverse event after randomization. During the double-blind treatment phase, 127 patients experienced 182 serious treatment-emergent adverse events. The serious adverse events were fatal in seven of these patients (discussed above).

Serious adverse events were reported by 9% of patients in each treatment group (65 in the placebo group and 62 in the dutasteride group). The serious adverse events consisted mainly of cardiovascular (including coronary artery disorders and myocardial infarction) and skin (primary malignant skin neoplasia) events. The only serious adverse events reported by >1% of patients in at least one treatment group were coronary artery disorders (1% placebo and 1% dutasteride) and primary malignant skin neoplasia (<1% placebo and 1% dutasteride). All other serious adverse events were reported by <1% of the patients in either treatment group.

One serious adverse event was considered by the investigator to have a "reasonable possibility" of being caused by the study drug. This 78-year-old man suffered a mild stroke on Study Day 27. He was taking placebo. All of the other serious adverse events were considered by the investigator as not being related to study drug.

A.8.3. Discontinuation due to adverse event: A total of 110 treatment-emergent adverse events in 76 patients (36 (5%) placebo and 40 (6%) dutasteride) resulted in study withdrawal. The most frequently reported adverse events leading to study withdrawal in both treatment groups were associated with the reproductive system (including impotence and altered libido) (1% placebo group and 3% dutasteride group) and the cardiovascular system (including coronary artery disorders and myocardial infarction) (1% placebo group and <1% dutasteride group). No specific adverse event leading to withdrawal from the study had an incidence of >1% in either treatment group.

A.8.4. Frequent adverse events: During year 1 of the double-blind treatment phase, a total of 930 of 1440 (65%) patients experienced 2537 treatment-emergent adverse events (67% of patients in the placebo group and 62% of patients in the dutasteride group). No adverse event had an incidence of >10%. Treatment-emergent adverse events reported in >5% of patients were ear, nose, and throat infections, musculoskeletal pain, impotence, and viral ear, nose, and throat infections.

A.8.5. Adverse events of special interest: The incidence of adverse events of special interest in patients taking 5 alpha-reductase inhibitors are shown in Table 12.

Table 12. Adverse events of special interest in patients taking 5 alpha-reductase inhibitors

	Placebo (n=720)	Dutasteride (n=720)
Altered libido	14 (2%)	30 (4%)
Impotence	22 (3%)	47 (7%)
Ejaculation disorders	6 (<1%)	17 (2%)
Sexual function disorders	2 (<1%)	4 (<1%)
Gynecomastia	3 (<1%)	9 (1%)
Prostate cancer	3 (<1%)	3 (<1%)

The number of patients who withdrew because of an adverse event known to occur with 5 alpha-reductase inhibitors is shown in Table 13.

Table 13. Patients withdrawn because of adverse events of special interest in patients taking 5 alpha-reductase inhibitors.

	Placebo (n=720)	Dutasteride (n=720)
Altered libido	2 (<1%)	8 (1%)
Impotence	3 (<1%)	10 (1%)
Ejaculation disorders	0 (0%)	3 (<1%)
Sexual function disorders	0 (0%)	1 (<1%)
Gynecomastia	2 (<1%)	1 (<1%)
Prostate cancer	2 (<1%)	2 (<1%)

Pregnancy: No pregnancy was reported by a female partner of a patient enrolled in this trial.

A.8.6. Changes in laboratory values:

The frequency of abnormal laboratory values at any post-baseline laboratory assessment (among patients with a normal baseline and at least one post-baseline laboratory value) is shown in Table 14.

Table 14. Abnormal Laboratory Value Frequencies: Normal to Abnormal

	Placebo (n=720)	Dutasteride (n=720)
Any abnormality	217/655 (33%)	236/658 (36%)
Hematology		
WBC	27/617 (4%)	20/616 (3%)
Platelet count	7/620 (1%)	8/621 (1%)
Hemoglobin	21/615 (3%)	17/603 (3%)
Chemistry		
Glucose	92/525 (18%)	94/506 (19%)
Sodium	30/615 (5%)	39/616 (6%)
Potassium	12/634 (2%)	9/642 (1%)
Total protein	9/635 (1%)	10/639 (2%)
Total bilirubin	5/630 (<1%)	10/633 (2%)
ALT	17/616 (3%)	34/617 (6%)
Alkaline phosphatase	9/634 (1%)	9/636 (1%)
Creatinine	16/621 (3%)	15/616 (2%)

The number of patients who had a laboratory value which exceeded "threshold laboratory values" at any post-baseline measurement are shown in Table 15.

Table 15. Threshold laboratory value frequencies.

	Placebo	Dutasteride
Hematology		
WBC >3XULN	1/643 (<1%)	0/644 (0%)
Platelet count <0.75 X LLN	0/631 (0%)	1/643 (<1%)
Hemoglobin <0.75 X LLN	1/643 (<1%)	1/643 (<1%)
Chemistry		
ALT >3 X ILN	1/654 (<1%)	1/656 (<1%)

Changes in PSA: At month 12, a mean decrease from baseline PSA levels of 41.7% was recorded for the dutasteride group whereas an increase in 9.9% was seen in the placebo group. The change from baseline PSA is shown in Table 16.

Table 16. Change from Baseline PSA (ng/mL)

	Placebo (n=720)	Dutasteride (n=720)	p-value
Month 1 Mean Mean difference	0.0	-0.5 -0.5	<0.001
Month 3 Mean Mean difference	0.0	-1.3 -1.3	<0.001
Month 6 Mean Mean difference	0.2	-1.5 -1.7	<0.001
Month 12 Mean Mean difference	0.3	-1.6 -2.0	<0.001

A.9. Reviewer's assessment of safety and efficacy in Trial ARIA3001: In the opinion of this reviewer, clinical trial ARIA3001 supports the approval of dutasteride for the treatment of symptomatic BPH in men with an enlarged prostate gland.

Appendix B– Clinical Trial **ARIA3002** ("A Randomized, Double-Blind, Placebo-Controlled, Two Year Parallel Group Study of the Efficacy and Safety of GI198745 0.5 mg in the Treatment and Prevention of Progression of Benign Prostatic Hyperplasia, Followed by a Two-Year Open-Label Treatment Phase (Report on 1 Year Data)" Study initiation date: September 8, 1997. Study report date: August 31, 2000.

B.1. Objective: This report presents the results from Year 1 of the 2 year double-blind treatment phase. The primary objective for year 1 of the study was to assess the efficacy (AUA-SI) of repeat oral once daily dosing of dutasteride 0.5 mg compared with placebo. The secondary objectives for Year 1 of the study were to assess the effects of repeat oral once daily dosing of dutasteride 0.5 mg compared with placebo on efficacy (prostate volume and urinary flow measurements), humanistic assessments, serum dihydrotestosterone (DHT), testosterone, prostate specific antigen (PSA), and safety and tolerability.

B.2. Design and conduct summary: This was a randomized, double-blind, placebo-controlled, multicenter (89 United States sites), 2-year parallel group study of the efficacy and safety of dutasteride 0.5 mg in patients with BPH followed by a 2 year open-label extension study. A total of 1424 patients was enrolled and entered the 4 week placebo run-in. Of these, 1362 patients were randomized at baseline to treatment with either placebo (n=685) or dutasteride 0.5 mg (n=677). Each patient, once randomized into the study, was to self-administer double-blind study medication for 2 years. Patients who completed 2 years of double-blind therapy were eligible to enter a 2-year open-label extension treatment phase. All patients who participated in the open-label phase received dutasteride 0.5 mg daily. Patients were assessed on an outpatient basis with clinic visits at months 1, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, and 48 post randomization.

This NDA and this study report are concerned only with the data from the first year of the double-blind trial.

The AUASI (primary endpoint) was obtained at screening, baseline (after the 4-week placebo run-in) and at months 1, 3, 6, and 12. (For purposes of statistical analysis, the final value of the AUASI prior to the start of the randomized treatment was used as the baseline value.)

Uroflow (secondary endpoint) was obtained at screening, baseline, and at months 1, 3, 6, and 12.

Prostate volume (secondary endpoint) was determined at screening and at months 3, 6, and 12. (The first post-baseline prostate volume was obtained at month 1 in ARIA3001.)

Testosterone, DHT, and PSA (secondary endpoints) were determined at screening and at months 1, 3, 6, and 12.

Humanistic assessments (BPH Impact Index, BPH-Specific Interference with Activities, and BPH-Specific Psychological Well-Being) (secondary endpoints) were determined at screening, baseline, and at months 1, 3, 6, and 12. The BPH Specific Life-Style Adaptions and Problem Assessment Scale of the Sexual Function Inventory were determined at months 1 and 12.

Genotyping: Blood was collected once (on or after the month 1 visit) from patients who voluntarily submitted this sample.

Safety studies: Clinical laboratory tests (CBC, glucose, sodium, potassium, total protein, total bilirubin, albumin, ALT, alkaline phosphatase, and creatinine) were determined at baseline and at month 12. A 12 lead EKG was performed at baseline. Post-void residual was determined at screening, baseline, and months 1, 3, 6, and 12.

B.3. Study population: One thousand four hundred and twenty-four (1424) patients were enrolled and 1362 patients were randomized.. The study population was primarily Caucasian. The 2 groups were comparable with respect to age and prostate size (Table 1).

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Table 1. Demographic and Baseline Characteristics.

	Placebo (N=685)	Dutasteride (N=677)
Age (years) – mean	66.6	66.7
Race		
Caucasian	637 (93%)	613 (91%)
Black	23 (3%)	25 (4%)
Asian	4 (<1%)	8 (1%)
American Hispanic	20 (3%)	29 (4%)
Other	1 (<1%)	2 (<1%)
Weight (kg)	85.9	86.0
Prostate volume > 40 cc at baseline	489 (71%)	486 (72%)
Duration of BPH symptoms (years)	5.2	5.5

B.4. Inclusion and exclusion criteria: Inclusion criteria include: 1) men > 50 years of age 2) diagnosis of BPH according to medical history and physical examination including a digital rectal examination (DRE) 3) American Urological Association Symptom Index (AUASI) greater than or equal to 12 at screening (Visit 1) 4) peak urinary flow rate (Q_{max}) of less than or equal to 15 cc/sec with a minimum voided volume of 125 cc at Visit 1 and 2 5) prostate volume of > 30 cc as determined by transrectal ultrasound (TRUS) and 6) patients must complete the 2 year double-blind treatment phase in order to be eligible to participate in the 2 year open-label treatment phase. Exclusion criteria include: 1) post-void residual urine volume measured by ultrasound of >250 cc at screening and baseline visits (Visits 1 and 2) 2) history or current evidence of prostate cancer 3) serum PSA of <1.5 ng/ml or >10.0 ng/ml. It is the investigators' responsibility to rule-out prostate cancer when the PSA is > 4.0 ng/ml. 4) previous prostate surgery (including balloon dilatation, thermotherapy, or stent placement) or other invasive procedures to treat BPH 5) history of acute urinary retention or history of repeated catheterizations due to acute urinary retention and BPH within 3 months of Visit 1 6) neurogenic bladder, bladder neck contracture, urethral stricture, bladder malignancy, acute or chronic prostatitis, or acute or chronic urinary tract infection 7) myocardial infarction, coronary artery bypass surgery, unstable angina, cardiac arrhythmias, congestive heart failure, or cerebrovascular accident within 6 months prior to screening visit 8) liver function tests > twice upper limit of normal 9) serum creatinine >1.8 mg/dl 10) previous use of finasteride, investigational 5 alpha-reductase inhibitors, alpha-receptor blockers within 4 weeks of screening, phytotherapy within 8 weeks of screening 11) concurrent use of finasteride, investigational 5 alpha-reductase inhibitors, alpha-receptors blockers, anabolic steroids, drugs with anti-androgenic properties (e.g. spironolactone), or phytotherapy 12) use of alpha adrenergic agonists or cholinergic or anti-cholinergic agents including antihistamines or decongestants within 48 hours of each study visit 13) actively trying to procreate or unwillingness to use a condom during intercourse with a woman of childbearing potential for duration of participation in the study and for 4 months following treatment and 14) history or current evidence of drug or alcohol abuse within the last 12 months.

B.5. Endpoints: The primary endpoint at year one of the study is the change in AUASI compared to baseline in the drug group versus placebo. Secondary endpoints at year one of the study include: 1) change in prostate volume in the drug group versus placebo 3) change in Q_{max} in the drug group versus placebo 4) change in the BPH Impact Index, Symptom Problem Index, BPH-Specific Interference with Activities Questionnaire, and Problem Assessment Scale of the Sexual Function Inventory in the drug group versus placebo 5) change in serum testosterone, dihydrotestosterone (DHT), and PSA in the drug group versus placebo, and 6) safety and tolerability of drug versus placebo.

B.6. Withdrawals, compliance, and protocol violations:

Withdrawals: A total of 1424 patients were enrolled and entered into the placebo run-in period. Sixty-two (62) of these patients discontinued the study prior to randomization. The main reason for discontinuation from the placebo run-in phase was consent withdrawn (24/1424; 2%). Additional reasons, each listed by <1% of patients, included inclusion/exclusion criteria violation, adverse event, protocol violation, missing reason, and "other" reasons. Of the 1362 patients randomized to double-blind treatment, 1083 (542 placebo and 541 dutasteride) completed treatment through month 12. After randomization to double-blind treatment, a similar proportion of patients in each treatment group prematurely discontinued (143 (21%) placebo and 136 (20%) dutasteride). The primary reason for discontinuation included lack of efficacy (7% placebo and 5% dutasteride), adverse event (7% placebo and 5% dutasteride), and consent withdrawn (4% placebo and 6% dutasteride). One per-cent of patients in each treatment group discontinued due to "other" reasons. The "other" reasons mainly occurred in site B1_01 which stopped participation due to closure of the site maintenance organization coordinating the study at that center.

Protocol violations: Major protocol violations were reported for 95 subjects (44 (6%) placebo and 52 (8%) dutasteride). None of these 95 patients was excluded from any analysis because of violations. The main violation reported dealt with exclusion criteria (2% placebo and 3% dutasteride) dealing with the concurrent use of prohibited medications.

PSA non-reporting: All PSA values for dutasteride-treated subjects were multiplied by a factor of 2 and randomly reported either as such or rounded up or down by 0.1. These adjusted PSA values were to be routinely provided to the investigators (beginning 6 months after treatment initiation and continuing throughout the study) who would review the information and take appropriate action. However, during the study, it was learned that a number of PSA values were not reported by [redacted] in accordance with the study plan. For ARIA3002, non-reporting occurred for 157 subjects. Study sites for all 157 subjects were contacted and follow-up information was received for 152/157 (97%) of subjects as follows: no action necessary 110 (72%), subject contacted 35 (23%), and lost to follow-up 7 (5%).

B.7. Efficacy analysis:

The primary endpoint was the change from baseline in AUASI at month 12 compared to placebo (Table 2).

Table 2. AUASI (LOCF) Mean Values

	Placebo (N=685)	Dutasteride (N=677)
Screening	20.0 (n=683)	19.7 (n=676)
Baseline	17.1 (N=678)	17.1 (N=673)
Month 1	15.9 (N=664)	15.8 (N=655)
Month 3	15.2 (N=671)	14.6 (N=663)*
Month 6	15.1 (N=672)	14.3 (N=664)**
Month 12	15.8 (N=672)	14.2 (N=664)***

*p<0.032

** p<0.008

*** At month 12, the mean difference (-1.5 units was significantly improved (p<0.001; 95% CI: -2.1, -0.9) when comparing dutasteride (-2.8 units) versus placebo (-1.3units).

Among patients with baseline prostate volumes >40 cc, mean change from baseline AUASI was significantly improved (p<0.008) beginning at month 3 and persisting through month 12 in the dutasteride group compared with the placebo group. Within the subgroup of patients with prostate volumes <40 cc, statistical significance for change from baseline AUASI compared with placebo was not achieved (Table 3).

Table 3. AUASI Change from Baseline by Baseline Prostate Volume

	Placebo <40 gm prostate volume	Dutasteride <40 gm prostate volume	p-value	Placebo >40 gm prostate volume	Dutasteride >40 gm prostate volume	p-value
Month 12	N=189	N=186		N=481	N=478	
Mean	-1.6	-2.2		-1.2	-3.0	
Mean difference		-0.5	0.36		-1.9	<0.001

The number and percentage of patients with at least a 20% reduction in AUASI is shown in Table 4.

Table 4. AUASI Improvement from Baseline of >20%.

	Placebo (N=685)	Dutasteride (N=677)
Month 1	207/664 (31%)	208/655 (32%)
Month 3	253/670 (38%)	277/663 (42%)
Month 6	268/671 (40%)	289/664 (44%)
Month 12	240/671 (36%)	302/664 (45%)

The primary secondary endpoints were the changes at 12 months in prostate volume and urinary flow. Changes in prostate volume are shown in Table 5.