

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

	Placebo (N=685)	Dutasteride (N=677)	p-value
Month 12	(N=655)	(N=641)	
Mean	-2.0%	-22.9%	
Mean difference		-20.9%	<0.001

The maximum urinary flow (Q_{max}) mean values (LOCF) are shown in Table 6.

Table 6. Q_{max} (cc/sec) Mean Values (LOCF)

	Placebo (N=685)	Dutasteride (N=677)
Screening visit 1	9.8 (N=683)	9.6 (N=677)
Screening visit 2	9.9 (N=684)	9.6 (N=674)
Baseline	10.4 (N=672)	10.0 (N=662)
Month 1	10.9 (N=647)	10.9 (N=629)
Month 3	11.0 (N=664)	11.3 (N=651)*
Month 6	11.0 (N=667)	11.4 (N=653)**
Month 12	11.2 (N=669)	11.8 (N=653)***

* $p < 0.006$

** $p < 0.025$

*** At month 12, the mean difference (dutasteride minus placebo) was 0.8 cc/sec ($p < 0.001$; 95% CI: 0.3, 1.2).

The Q_{max} change from baseline is shown in Table 7.

Table 7. Q_{max} change from baseline (cc/sec): Mean (LOCF)

	Placebo (N=685)	Dutasteride (N=677)	p-value
Month 1			
Mean	0.6	0.8	
Mean difference		0.1	0.47
Month 3			
Mean	0.7	1.2	
Mean difference		0.5	0.006
Month 6			
Mean	0.7	1.2	
Mean difference		0.5	0.025
Month 12			
Mean	0.9	1.7	
Mean difference		0.8	<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=685)	Dutasteride (N=677)	p-value
Month 12	(N=590)	(N=562)	
Mean	+4.5%	-93.5 %	
Mean difference		-98.0%	<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=685)	Dutasteride (N=677)	p-value
Month 12	(N=588)	(N=560)	
Mean	2.1%	21.9%	
Mean difference		19.8%	<0.001

Five patients (3 in the placebo group and 2 in the dutasteride group) had T levels which exceeded 10,000 pcg/mL at some point during the first year of the study. In four of these patients serum T levels were >10,000 pcg/mL at screening and either continued to be elevated or decreased during the study. One patient had a normal screening T level and then had an elevated value after treatment with dutasteride. His T level at screening was 8510 and at month 12 was 11300 pcg/mL. This patient had no adverse events or clinical symptoms.

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 months 6 and 12, dutasteride significantly ($p < 0.012$) improved the BII score compared with placebo. The mean difference at month 12 was -0.4 (95% CI: -0.7, -0.2).

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 significantly lower than results reported for the placebo group based on LOCF ($p = 0.002$).

PASFI: At month 12, the mean score decreased by approximately one point in the dutasteride group (indicating increased problems) whereas the score for the placebo group was essentially unchanged.

B.8. Safety analysis:

B.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=685)	Dutasteride (N=677)
N	660	646
Mean (SD)	328.2 (88.52)	325.7 (96.29)
Median	365.0	365.0

B.8.2. Serious adverse events:

Deaths: One patient in the placebo group and 4 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 cause of death in the placebo group was metastatic bladder cancer. The causes of death in the drug group were CVA in a 68 year-old, coronary artery disease in a 66 year old, CVA in a 63 year-old, and myelogenous leukemia in a 67 year-old. In addition, two patients who were enrolled but not randomized died of cardiac arrest.

Serious adverse events: One hundred thirty-two (132) patients experienced a serious adverse event during the study. Nine patients experienced an adverse event prior to randomization. During the double-blind treatment phase, 123 patients experienced 170 serious treatment-emergent adverse events. The serious adverse events were fatal in five of these patients (discussed above).

Serious adverse events were reported by 9% of patients in each treatment group (59 in the placebo group and 64 in the dutasteride group). The serious adverse events consisted mainly of cardiovascular (including coronary artery disorders, myocardial infarction and tachyarrhythmias) and a variety of cancers. The only serious adverse events reported by >1% of patients in at least one treatment group were coronary artery disorders (1% placebo and 2% dutasteride) and angina pectoris (<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 69-year-old man experienced severe vertigo on study day 257. He was taking placebo. All of the other serious adverse events were considered by the investigator as not being related to study drug.

B.8.3. Discontinuation due to adverse event: A total of 135 treatment-emergent adverse events in 89 patients (50 (7%) placebo and 39 (6%) dutasteride) led to withdrawal from the study. The most frequently reported adverse events leading to study withdrawal in both treatment groups were associated with the reproductive system (including impotence, altered libido and primary malignant reproductive neoplasia) (2% in each treatment group) and the cardiovascular system (including coronary artery disorders and

myocardial infarction) (1% in each treatment group). No specific adverse event leading to withdrawal from the study had an incidence of >1% in either treatment group.

B.8.4. Frequent adverse events: During year 1 of the double-blind treatment phase, a total of 890 of 1362 (65%) patients experienced 2256 treatment-emergent adverse events (66% of patients in the placebo group and 65% 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.

B.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=685)	Dutasteride (n=677)
Altered libido	15 (2%)	26 (4%)
Impotence	28 (4%)	41 (6%)
Ejaculation disorders	3 (<1%)	19 (3%)
Sexual function disorders	0 (0%)	0 (0%)
Gynecomastia	4 (<1%)	10 (1%)
Prostate cancer	6 (<1%)	3 (<1%)

The number of patients who withdrew because of an adverse events of special interest in patients taking 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=685)	Dutasteride (n=677)
Altered libido	4 (<1%)	5 (<1%)
Impotence	4 (<1%)	6 (<1%)
Ejaculation disorders	2 (<1%)	0 (0%)
Sexual function disorders	0 (0%)	0 (0%)
Gynecomastia	0 (0%)	2 (<1%)
Prostate cancer	5 (<1%)	3 (<1%)

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

B.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=685)	Dutasteride (n=677)
Any abnormality	208/626 (33%)	192/604 (32%)
<u>Hematology</u>		
WBC	23/592 (4%)	21/561 (4%)
Platelet count	9/586 (2%)	11/586 (2%)
Hemoglobin	18/583 (3%)	14/557 (3%)
<u>Chemistry</u>		
Glucose	84/490 (17%)	70/483 (14%)
Sodium	26/584 (4%)	17/570 (3%)
Potassium	10/608 (2%)	10/583 (2%)
Total protein	11/609 (2%)	5/590 (<1%)
Total bilirubin	10/605 (2%)	6/582 (1%)
ALT	19/588 (3%)	29/563 (5%)
Alkaline phosphatase	5/602 (<1%)	11/576 (2%)
Creatinine	19/584 (3%)	15/557 (3%)

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

Table 15. Threshold laboratory value frequencies.

	Placebo	Dutasteride
<u>Hematology</u>		
Platelet count <0.75 X LLN	4/597 (<1%)	1/580 (1%)
Platelet count >1.50 X ULN	0 (0%)	1/581 (<1%)
<u>Chemistry</u>		
ALT >3 X ILN	0/619 (0%)	2/600 (<1%)
Alkaline phosphatase >1.5 XULN	0/618 (0%)	1/594 (<1%)

Changes in PSA: At Month 12, a mean decrease from baseline PSA levels of 45.0% was recorded for the dutasteride group whereas an increase in 11.0% was seen in the placebo group. The change from baseline PSA is shown in Table 16.

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

	Placebo (n=656)	Dutasteride (n=677)	p-value
Month 1			
Mean	0.1	-0.3	
Mean difference		-0.4	<0.001
Month 3			
Mean	0.0	-1.2	
Mean difference		-1.2	<0.001
Month 6			
Mean	0.0	-1.6	
Mean difference		-1.7	<0.001
Month 12			
Mean	0.3	-1.8	
Mean difference		-2.1	<0.001

B.9. Reviewer's assessment of safety and efficacy in Trial ARIA3002: In the opinion of this reviewer, clinical trial ARIA3002 supports the approval of dutasteride for the treatment of symptomatic BPH in men with an enlarged prostate gland.

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)” Study initiation date: October 6, 1997. Study report date: August 30, 2000.

C.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.

C.2. Design and conduct summary: This was a randomized, double-blind, placebo-controlled, multicenter (205 international 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 1831 patients were enrolled and entered the 4 week placebo run-in. Of these, 1522 patients were randomized at baseline to treatment with either placebo (n=753) or dutasteride 0.5 mg (n=769). 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 6, and 12. (In ARIA3001 the first post-baseline prostate volume was performed at Month 1 and in ARIA3002 the first post-baseline prostate volume was performed at Month 3.)

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

Blood samples were collected to measure serum dutasteride concentrations at Months 3, 6, and 12 in patients at all centers in Canada, Norway, and the United Kingdom.

Luteinizing hormone (LH) was measured at screening and at Months 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. The translations of the BII, BSIA, and SPI were evaluated against standard psychometric criteria taking into account the psychometric properties of the US English questionnaires.

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.

C.3. Study population: One thousand eight hundred thirty-one patients (1831) were enrolled and 1522 patients randomized. 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=753)	Dutasteride (N=769)
Age (years) – mean	65.7	66.4
Race		
Caucasian	709 (94%)	727 (95%)
Black	15 (2%)	13 (2%)
Asian	11 (1%)	10 (1%)
American Hispanic	12 (2%)	10 (1%)
Other	6 (<1%)	9 (1%)
Weight (kg)	81.8	82.2
Prostate volume > 40 cc at baseline	549 (73%)	556 (72%)
Duration of BPH symptoms (years)	4.7	4.9

C.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 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. A biopsy may be taken if this is the usual clinical practice. 4) previous prostate surgery (including balloon dilatation, thermotherapy, or stent placement) or other invasive procedures to treat BPH 5) history of acute urinary retention 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) history of flexible/rigid cystoscopy or other instrumentation of the urethra (>10F catheter) within 7 days prior to the screening visit 8) liver function tests > twice upper limit of normal 9) serum creatinine >160 umol/L 10) previous use of finasteride, investigational 5 alpha-reductase inhibitors, alpha-receptor blockers within 2 weeks of screening, phytotherapy within 4 weeks of screening 11) concurrent use of finasteride, investigational 5 alpha-reductase inhibitors, alpha-receptor 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 within 48 hours prior to all uroflowmetry assessments 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.

C.5. Endpoints: The primary endpoint at year one of the study is the change in AUASI from baseline in the drug group versus placebo. Secondary endpoints at year one of the study include: 1) change in prostate volume from baseline in the drug group versus placebo 3) change in Q_{max} from baseline 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.

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

Withdrawals: A total of 1831 patients were enrolled and entered into the placebo run-in period. Three hundred and nine (309 or 17%) of these patients discontinued the study prior to randomization. The main reason for discontinuation from the placebo run-in phase was inclusion/exclusion criteria violation (223/1831 (12%)). Additional reasons, each listed by <1% of patients, included adverse event, consent withdrawn, protocol violation, lost to follow-up, and "other" reasons. Of the 1552 patients randomized to double-blind treatment, 1249 (621 placebo and 628 dutasteride) completed treatment through month 12. After randomization to double-blind treatment, a similar proportion of patients in each treatment group prematurely discontinued (132 (18%) placebo and 141 (18%) dutasteride). The primary reason for discontinuation included adverse event (5% placebo and 6% dutasteride), lack of efficacy (5% placebo and 3% dutasteride), consent withdrawn (2% in each group), protocol violation (2% in each group), lost to follow-up (<1% placebo and 1% dutasteride), and "other" reasons (2% placebo and 3% dutasteride).

Protocol violations: Major protocol violations were reported for 129 subjects (62 (8%) placebo and 67 (9%) dutasteride). None of these 129 patients was excluded from any analysis because of violations. The main violations reported were concurrent use of drugs with antiandrogenic properties or anabolic steroids (2% in each treatment group) and reported study drug compliance <75% (2% in each treatment group). Other violations, reported by <1% of patients in each treatment group included no diagnosis of BPH, AUASI <12 at screening, urinary Q_{max} >15 cc/sec, baseline prostate volume <30 cc, previous finasteride or other 5 alpha-reductase inhibitor use, use of alpha blockers, use of phytotherapy, and incorrect study drug consumption.

PSA non-reporting: For the non-US sites, an independent reviewer from [redacted] was unblinded to the PSA values and was to review results which exceeded 25% from the previous reported values or at a level of >10.0 ng/ml. In such cases the investigator was to be notified. For the US sites, 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 ARIB3003, non-reporting occurred for

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 Mean Mean difference	N=193 -3.6	N=202 -4.3 -0.7	0.27	N=542 -2.7	N=545 -4.0 -1.3	<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=753)	Dutasteride (N=769)
Month 1	223/723 (31%)	244/737 (33%)
Month 3	314/738 (43%)	330/750 (44%)
Month 6	344/741 (46%)	373/750 (50%)
Month 12	353/742 (48%)	409/750 (55%)

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=753)	Dutasteride (N=769)	p-value
Month 12 Mean Mean difference	(N=682) -6.0%	(N=682) -27.6% -21.5%	<0.001

The maximum urinary flow (Q_{max}) mean values (LOCF) are shown in Table 6.

Table 6. Q_{max} (cc/sec) Mean Values (LOCF)

	Placebo (N=753)	Dutasteride (N=769)
Screening visit 1	9.5 (N= 750)	9.6 (N=765)
Screening visit 2	9.5 (N=383)	9.4 (N=369)
Baseline	9.9 (N=734)	10.1 (N=753)
Month 1	10.6 (N=693)	11.2 (N=710)
Month 3	10.7 (N=724)	11.8 (N=742)
Month 6	10.8 (N=730)	11.8 (N=743)
Month 12	10.5 (N=732)	12.0 (N=744)**

** At month 12, the mean difference (dutasteride minus placebo) was 1.1 cc/sec ($p < 0.001$; 95% CI: 0.7, 1.5).

The Q_{max} change from baseline is shown in Table 7.

Table 7. Q_{max} change from baseline (cc/sec): Mean (LOCF)

	Placebo (N=753)	Dutasteride (N=769)	p-value
Month 1			
Mean	0.5	1.0	
Mean difference		0.5	0.002
Month 3			
Mean	0.6	1.6	
Mean difference		1.0	<0.001
Month 6			
Mean	0.7	1.5	
Mean difference		0.9	<0.001
Month 12			
Mean	0.6	1.7	
Mean difference		1.1	<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=753)	Dutasteride (N=769)	p-value
Month 12			
Mean	(N=591) -0.5%	(N=609) -93.1 %	
Mean difference		-92.6%	<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			
Mean	(N=653) -2.0%	(N=644) 16.5%	
Mean difference		18.5%	<0.001

Fourteen patients (5 in the placebo group and 9 in the dutasteride group) had T levels which exceeded 10,000 pcg/mL at some point during the first year of the study. Seven patients (two in the placebo group and five 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. In six patients serum testosterone levels were elevated at screening and

either continued to be elevated (one patient) or decreased during the study (4 patients). The highest T values (23100 and 29400 pcg/mL) were present in 2 patients at screening.

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: $-0.7, -0.2$). Statistical significance was not reached at Months 1, 3, or 6.

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 significantly lower than results reported for the placebo group ($p = 0.001$).

Study drug serum concentrations: Mean (SD) dutasteride serum concentrations were 30.1 ng/mL (12.8 ng/mL) at Month 3. Serum concentrations increased to 39.0 ng/mL (18.2 ng/mL) at Month 6. At Month 12, serum concentrations were 38.4 ng/mL (16.7 ng/mL).

C.8. Safety analysis:

C.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=753)	Dutasteride (N=769)
N	735	747
Mean (SD)	327.6 (89.79)	322.3 (97.12)
Median	364.0	364.0

C.8.2. Serious adverse events:

Deaths: Five patients in the placebo group and 3 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 rectal cancer in a 69-year-old, lung cancer in a 73-year-old, lung metastases in a 78-year-old, CVA in a 81 year-old, and myocardial infarction in a 66-year-old. The causes of death in the drug group were lung cancer in a 72-year-old, death due to "natural causes" in a 78-year-old, and myocardial infarction in a 62-year-old.

Serious adverse events: One hundred twenty-four (124) patients experienced 159 serious adverse events during the study. Eleven patients experienced an adverse event prior to randomization. Five of these patients also experienced a serious adverse event after randomization. During the one year double-blind treatment phase, 118 patients

experienced 148 serious treatment-emergent adverse events. The serious adverse events were fatal in eight of these patients (discussed above).

Serious adverse events were reported by 47 (6%) patients in the placebo group and by 71 (9%) of patients in the dutasteride group. The overall incidence of serious adverse events was statistically significantly greater in the dutasteride group compared to the placebo group. The serious adverse events consisted mainly of cardiovascular (including myocardial infarction, angina, cerebrovascular accidents, tachyarrhythmias, and coronary artery disorders) events and cancers and neoplasms (including prostate cancer, skin cancer, colon cancer, bladder cancer, breast cancer, and renal cancer). The only serious adverse event reported by >1% of patients in at least one treatment group was myocardial infarction (1% in each treatment group). All other serious adverse events were reported by <1% of the patients in either treatment group.

Two of the serious adverse events reported during the study were considered by the investigator to have a "reasonable possibility" of being related to study drug. Patient C3_14/51751, a 62-year-old man in the placebo group, experienced an episode of angina pectoris. Patient C2_12/51510, a 62-year-old man in the dutasteride group, experienced a single episode of a severe allergic reaction on Day 370 (study drug was discontinued and the adverse event resolved by Day 11).

C.8.3. Discontinuation due to adverse event: A total of 139 treatment-emergent adverse events in 102 patients (50 (7%) placebo and 52 (7%) dutasteride) led to withdrawal from the study. The most frequently reported adverse events leading to study withdrawal in both treatment groups were associated with the reproductive system (including impotence, altered libido, gynecomastia, and primary malignant male reproductive neoplasia) and the cardiovascular system. No specific adverse event leading to withdrawal from the study had an incidence of >1% in either treatment group.

C.8.4. Frequent adverse events: During year 1 of the double-blind treatment phase, a total of 930 of 1552 (61%) patients experienced 2372 treatment-emergent adverse events (57% of patients in the placebo group and 65% of patients in the dutasteride group). No adverse event had an incidence of >10%. Treatment-emergent adverse events reported in >5% of patients were musculoskeletal pain, impotence, viral respiratory infections, and viral ear, nose, and throat infections.

C.8.5. Adverse events of special interest: The incidence of adverse events which are 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=753)	Dutasteride (n=769)
Altered libido	20 (3%)	32 (4%)
Impotence	26 (3%)	53 (7%)
Ejaculation disorders	9 (<1%)	17 (2%)
Sexual function disorders	0 (0%)	3 (<1%)
Gynecomastia	4 (<1%)	13 (2%)
Prostate cancer	3 (<1%)	5 (<1%)

The number of patients who withdrew because of an adverse event of interest in patients taking 5 alpha-reductase inhibitors is shown in Table 13.

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

	Placebo (n=753)	Dutasteride (n=769)
Altered libido	6 (<1%)	7 (<1%)
Impotence	4 (<1%)	6 (<1%)
Ejaculation disorders	1 (<%)	0 (0%)
Sexual function disorders	0 (0%)	1 (<1%)
Gynecomastia	2 (<1%)	5 (<1%)
Prostate cancer	3 (<1%)	5 (<1%)

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

C.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.

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Table 14. Abnormal Laboratory Value Frequencies: Normal to Abnormal

	Placebo (n=753)	Dutasteride (n=769)
Any abnormality	195/649 (30%)	206/663 (31%)
<u>Hematology</u>		
WBC	17/597 (3%)	22/600 (4%)
Platelet count	9/566 (2%)	10/577 (2%)
Hemoglobin	9/602 (1%)	17/608 (3%)
<u>Chemistry</u>		
Glucose	81/530 (15%)	76/538 (14%)
Sodium	12/630 (2%)	10/646 (2%)
Potassium	2/637 (<1%)	7/644 (1%)
Total protein	4/635 (<1%)	1/651 (<1%)
Total bilirubin	8/610 (1%)	18/621 (3%)
ALT	22/600 (4%)	24/630 (4%)
Alkaline phosphatase	11/595 (2%)	27/604 (4%)
Creatinine	17/605 (3%)	6/624 (<1%)

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

Table 15. Threshold laboratory value frequencies.

	Placebo	Dutasteride
<u>Hematology</u>		
Platelet count <0.75 X LLN	4/598 (<1%)	0/608 (0%)
<u>Chemistry</u>		
Glucose >1.75 X ULN	8/624 (1%)	8/635 (1%)
Total bilirubin >2.5 X ULN	2/641 (<1%)	0/657 (0%)
Alkaline phosphatase >1.5 X ULN	3/639 (<1%)	4/653 (<1%)

Changes in PSA: At month 12, a mean decrease from baseline PSA levels of 41.4 % was recorded for the dutasteride group whereas an increase in 6.9% was seen in the placebo group. The change from baseline PSA is shown in Table 16.

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

	Placebo (n=753)	Dutasteride (n=769)	p-value
Month 1			
Mean	0.0	-0.4	
Mean difference		-0.4	<0.001
Month 3			
Mean	0.0	-1.4	
Mean difference		-1.4	<0.001
Month 6			
Mean	0.2	-1.7	
Mean difference		-1.8	<0.001
Month 12			
Mean	0.2	-1.8	
Mean difference		-2.0	<0.001

Change in LH: At Months 6 and 12, greater mean increases from baseline LH levels were recorded for the dutasteride group (Month 6: mean 29.7%, median 12.0%; Month 12: mean 36.2%, median 18.6%) compared to the placebo group (Month 6: mean 12.5%, median 3.0%; Month 12: mean 16.8%, median 4.8%).

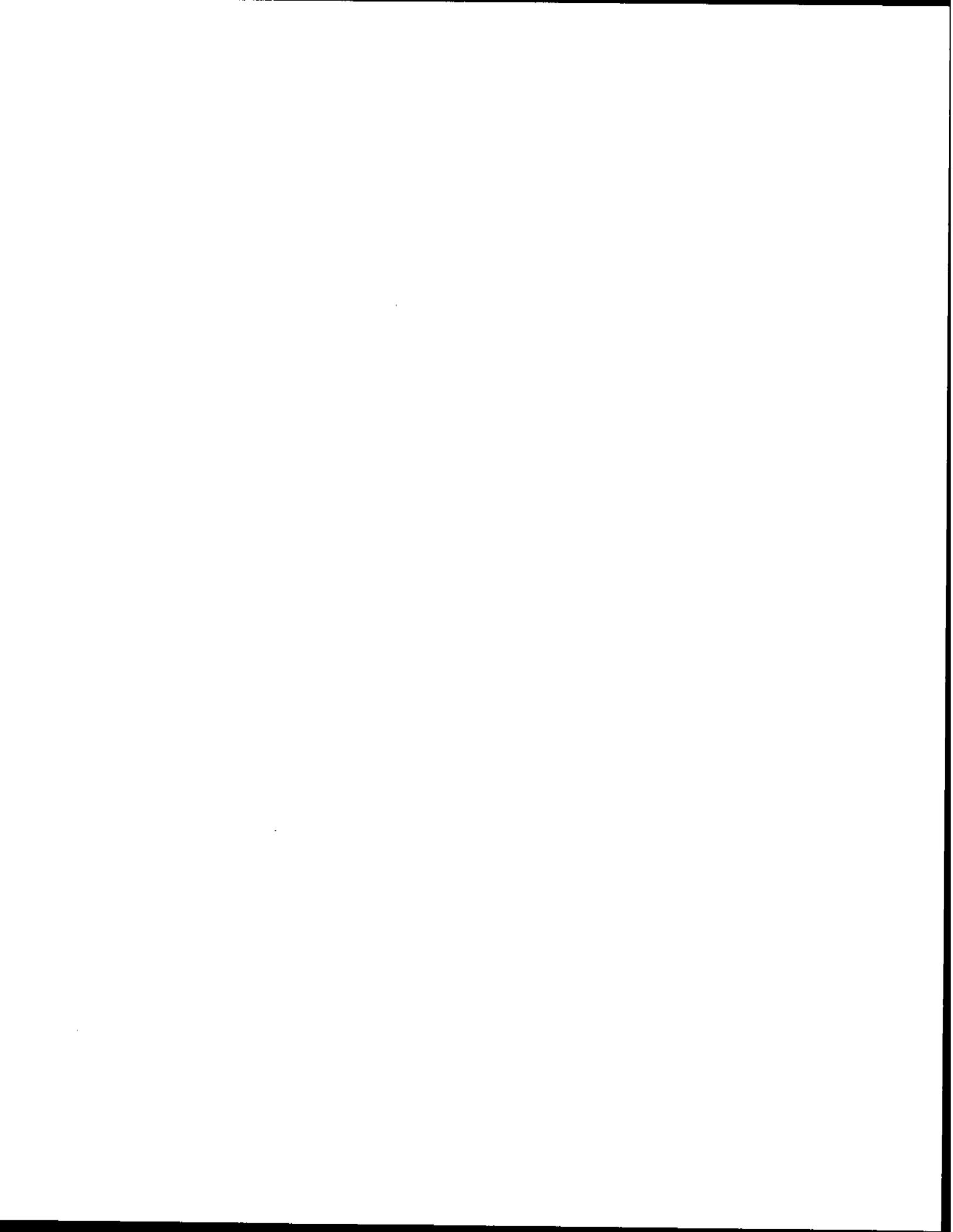
C.9. Reviewer's assessment of safety and efficacy in Trial ARIB3003: In the opinion of this reviewer, clinical trial ARIB3003 supports the approval of dutasteride for the treatment of symptomatic BPH in men with an enlarged prostate gland.

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”) Initiation date: August, 20,1998. Completion date: April 26, 2000.

D.1. Objective: The primary objective of this study was to assess the effects of dutasteride on semen characteristics: sperm count, morphology, motility, and semen volume, and to investigate the pharmacokinetic characteristics of dutasteride in semen. The secondary objectives of the study were to investigate the effects of dutasteride on sexual function, bone metabolism, gonadotropin secretion, and adrenal steroidogenesis.

D.2. Design and conduct summary: This was a double-blind, double-dummy, placebo-controlled, randomized, comparative, parallel-group, multicenter (7 United States sites), 52-week study. Ninety-nine healthy male volunteers aged 18 to 55 were enrolled (approximately 30 per treatment group). Patients were randomized to one of the following 3 groups:

- 1) daily 0.5 mg dutasteride (one 0.5 mg dutasteride gelcap and one finasteride placebo capsule) for 52 weeks
- 2) daily 5.0 mg finasteride (one 5 mg over-encapsulated tablet and one dutasteride placebo gelcap) for 52 weeks



Nocturnal penile tumescence was measured by [redacted] on two consecutive nights between screening and baseline, Weeks 48 and 52, and post-treatment Weeks 20 and 24.

Screening bone scan was to be completed and interpreted before randomization. Bone density was also measured between Weeks 48 and 52 and between follow-up Weeks 20 and 24 using Dual X-ray Absorptiometry.

Hormonal and lipid levels were collected at screening, Week 0 (baseline), and at Weeks 8, 24, 52, and at Weeks 4, 8, 12, and 24 post-treatment. The hormonal profile consisted of total testosterone, free testosterone, LH, FSH, DHEA, FSH, free T, estradiol and sex hormone binding globulin. Blood lipid evaluation consisted of cholesterol, triglycerides, HDL, and LDL.

PSA was determined at screening, baseline, and at Weeks 8, 24, 52 and at post-treatment Weeks 8 and 24.

ACTH stimulation tests were performed between screening and Week 0 (baseline) and at week 52 only at selected sites [redacted]

GnRH stimulation tests were to be performed between screening and Week 0 (baseline). Contrary to the protocol which stipulated that the GnRH stimulation test be performed at Week 52, this was not done because [redacted] was not available from the manufacturer. The GnRH tests were to be performed at only 2 sites [redacted]

Bone metabolism was measured by 2 methods: 1) QDR – Bone Density Scan and 2) Laboratory Bone Markers (serum osteocalcin, serum bone alkaline phosphatase, urinary N-telopeptide, and urine creatinine). These studies were measured at baseline (Week 0) and at Weeks 8, 16, 24, and 52.

Hematology and chemistry assessments were collected at screening, baseline, baseline (Week 0), and at Weeks 8, 24, 52, and at Weeks 8 and 24 post-treatment.

An EKG was performed at screening, Week 52, and at Week 24 post-treatment.

D.3. Study population: Ninety-nine patients were randomized. The study population was primarily Caucasian. The 3 groups were comparable with respect to age.

Table 1. Demographic and Baseline Characteristics.

	Placebo (n=32)	Finasteride (n=34)	Dutasteride (n=33)
Age (yrs) mean	35	35	35
Age (range)	19-52	18-52	23-52
Race			
White	26 (81%)	27 (79%)	28 (85%)
Black	1 (3%)	1 (3%)	0
Asian	0	1 (3%)	3 (9%)
American Hispanic	3 (9%)	5 (15%)	2 (6%)
Other	2 (6%)	0	0
Mean sperm conc.	82 million/cc	94 million/cc	87 million/cc

D.4. Inclusion and exclusion criteria: Inclusion criteria include: 1) healthy men (aged 18-55). Patients with an AUASI <8 and male pattern baldness could be included 2) free from significant cardiac, pulmonary, gastrointestinal, hepatic, renal, endocrinologic, hematologic, neurologic, and psychiatric disease and 3) BMI between 19 and 32 inclusive. Exclusion criteria include: 1) use of the following medications within 6 months prior to screening: finasteride or experimental 5 alpha-reductase inhibitors, phytotherapy, anabolic steroids; drugs with anti-androgen properties (spironolactone, cimetidine), or alpha-receptor blockers 2) actively trying to procreate or unwillingness to use a condom during intercourse with a woman of childbearing potential who is not using an acceptable method of contraception for the duration of the study and for 6 months following treatment 3) patients who have donated more than 450 cc of blood within 30 days of screening 4) patients who have taken prescription or over-the-counter medication that might interfere with steroid hormone action (eg cimetidine) 5) history of alcohol or drug abuse 6) use of tobacco products 7) positive for hepatitis B or C or HIV 8) positive urinary drug screen 8) abnormal screening EKG or laboratory tests 9) history of vasectomy or semen characteristics at screening that show any of the following: (the semen analysis will be performed by CASA) a) sperm concentration of < 30 million/mL b) total sperm count < 45 million c) motility < 40% d) morphology < 10% and e) semen volume < 1.5 mL (If the initial semen analysis does not meet the entry criteria and, in the opinion of the investigator the subject experienced difficulty with the sample collection, the subject may repeat the screening semen analysis one time.) 10) acute illness within 30 days preceding the screening visit 11) subjects who are unable to provide semen analyses according to the protocol 12) history of sexual dysfunction 13) history of sleep disorder and 14) bone density for lumbar spine or hip with a T score less than minus 2 SD at screening.

D.5. Endpoints: The primary "objectives" of this study are: 1) to investigate the effects of dutasteride on semen characteristics: sperm count, morphology, motility, and semen volume and 2) to investigate the pharmacokinetic characteristics of dutasteride in semen. Secondary "objectives" are: 1) to investigate the effects of dutasteride on sexual function 2) to investigate the effects of dutasteride on gonadotropin secretion 3) to investigate the effects of dutasteride on adrenal steroidogenesis and 4) to investigate the effects of dutasteride on bone metabolism.

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

Withdrawals: A total of 99 patients were randomized: 32 to placebo, 34 to finasteride, and 33 to dutasteride. Twenty-four patients (7 placebo, 13 finasteride, and 4 dutasteride) discontinued the study prematurely. The main reason for study withdrawal was withdrawal of consent (Table 1).

Table 1. Reasons for Premature Discontinuation from Drug Dosing After Randomization

	Placebo (n=32)	Finasteride (n=34)	Dutasteride (n=33)
Any reason	7	12	4
Adverse event	2 (29%)	3 (25%)	2 (50%)
Consent withdrawn	4 (57%)	7 (58%)	2 (50%)
Lost to follow-up	1 (14%)	1 (8%)	0
Other	0	1 (8%)	0

Protocol violations: Protocol violations were reported for 69 (70%) of subjects (81% in the placebo group, 62% in the finasteride group, and 67% in the dutasteride group). The most common violation was the semen screen being performed more than 30 days before the start of treatment (59% placebo, 41% finasteride, and 48% dutasteride). Other deviations included violation of the sperm exclusion criteria (47% placebo, 29% finasteride, and 30% dutasteride), start of treatment more than 8 weeks after screening (28% placebo, 12% finasteride, and 27% dutasteride), and violation of the inclusion/exclusion criteria (13% placebo, 6% finasteride, and 12% dutasteride). The treatment blind was broken for one subject in the placebo group and one in the dutasteride group. The reasons for breaking the blind was "wife pregnant" in one and "unblinded himself" in the other.

D.7. Efficacy analysis:

The primary "objectives" of this study are: 1) to investigate the effects of dutasteride on semen characteristics: sperm count, morphology, motility, and semen volume and 2) to investigate the pharmacokinetic characteristics of dutasteride in semen.

Total sperm count data from baseline to Week 52 are shown in Table 2.

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Table 2. Sperm count (in millions) from Baseline to Week 52.

	Placebo	Finasteride	Dutasteride
Baseline			
N	24	23	28
Mean	215.1	250.9	222.6
Median	179.0	213.7	203.1
SD	141.7	161.7	128.9
Min:max			
Weeks 24-28			
N	24	23	27
Mean	202.2	128.2	168.0
Median	182.4	95.1	99.7
SD	115.9	84.3	171.8
Min:max			
Weeks 48-52			
N	23	21	27
Mean	194.1	169.1	154.7
Median	170.5	151.1	137.3
SD	111.7	102.4	129.5
Min:max			

- Semen data is reported for the mean of the three samples at each time period. No patient had a sperm count <30 million at baseline.

In the dutasteride group, total sperm count fell to <30 million at Weeks 24-28 for one subject (#86801; 7.9 million) and at Weeks 48-52 for 2 subjects (#86801; 2.7 million and #86804; 10.6 million). Subject #86801 also had semen volume, sperm concentration, sperm motility, and sperm morphology parameters below threshold. One subject in the finasteride (#73912) had a sperm count <30 million (11.9 million) at Week 48-52. In each of these three patients, the fall in sperm count was to <10% of their baseline values. A fourth patient (#86755) in the finasteride group also had a reduction in sperm count to <10% of baseline value (595.4 million to 53.1 million and 53.8 million at Weeks 24-28 and 48-52 respectively).

The percent change from baseline in sperm count is shown in Table 3.

Table 3. Percent Change from Baseline in Sperm Count.

	Placebo	Finasteride	Dutasteride
Weeks 24-28			
N	24	23	27
Mean	11.4	-39.6	-5.0
Median	13.8	-41.2	-54.2
Weeks 48-52			
N	23	21	27
Mean	2.7	-8.7	-17.3
Median	-15.3	-27.7	-37.6

Semen volume data from baseline to Week 52 are shown in Table 4.

Table 4. Summary of Semen Volume (cc) from Baseline to Week 52.

	Placebo	Finasteride	Dutasteride
Baseline			
N	24	23	28
Mean	2.7	2.9	3.2
Median	2.3	2.7	3.1
Min:Max			
Weeks 24-28			
N	24	23	27
Mean	2.7	2.2	2.5
Median	2.5	1.9	2.5
Min:Max			
Weeks 48-52			
N	23	21	27
Mean	2.8	2.4	2.4
Median	2.2	2.0	2.6
Min:Max			

Individual subject data showed that semen volume fell below 1.0 cc at Weeks 24-28 and Weeks 48-52 for one subject in the placebo group, two subjects in the finasteride group, and four subjects in the dutasteride group. The reduction in semen volume was also calculated as the percent change from baseline. None of the percentage reductions in semen volume in the finasteride and dutasteride groups met the criterion for clinical significance of >30%. At Weeks 24-28, there was a statistically significant difference in semen volume between the finasteride and placebo group (-0.6cc, p=0.007) and the dutasteride and placebo group (-0.6cc, p=0.009). The difference in semen volume between the dutasteride and placebo group was also statistically significant at Weeks 48-52 (-0.7, p=0.004). There was no statistically significant difference between the finasteride and dutasteride groups at any visit.

Sperm concentration data from baseline to Week 52 is shown in Table 5.

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Table 5. Sperm concentration (million/mL) from Baseline to Week 52.

	Placebo	Finasteride	Dutasteride
Baseline			
N	24	23	28
Mean	81.6	91.3	77.2
Median	66.2	86.3	76.8
SD	43.5	48.9	46.3
Min:Max	[REDACTED]		
Weeks 24-28			
N	24	23	27
Mean	83.2	63.2	68.7
Median	81.5	58.0	40.5
SD	47.6	34.4	52.2
Min:Max	[REDACTED]		
Weeks 48-52			
N	23	21	27
Mean	76.3	74.9	75.3
Median	69.6	66.8	48.6
SD	47.1	48.8	59.4
Min:Max	[REDACTED]		

Individual subject data showed one subject in the placebo group, three in the finasteride group, and one in the dutasteride group to have a sperm concentration of <20 million at Weeks 24-28. At Weeks 48-52, one subject in the finasteride group and three in the dutasteride group had a sperm concentration of <20 million/cc.

Sperm motility from baseline to Week 52 is shown in Table 6.

Table 6. Sperm Motility (%) from Baseline to Week 52.

	Placebo	Finasteride	Dutasteride
Baseline			
N	24	23	28
Mean	64.4	61.4	67.3
Median	65.7	56.7	68.3
Min:Max	[REDACTED]		
Weeks 24-28			
N	24	23	27
Mean	65.4	53.0	56.4
Median	67.0	51.7	61.0
Min:Max	[REDACTED]		
Weeks 48-52			
N	23	21	27
Mean	68.5	56.6	60.4
Median	71.3	56.3	64.0
Min:Max	[REDACTED]		

At Weeks 48-52, two subjects in the finasteride group, one in the dutasteride group, and none in the placebo group had sperm motility <30%.

Serum and semen dutasteride concentrations: Of the 33 subjects randomized to dutasteride, 31 were included in the PK population. Serum concentrations were available at Week 8, Weeks 24-28, and Weeks 48-52 for 29, 28, and 28 subjects respectively. Semen concentrations were available at Week 8, Weeks 24-28, and Weeks 48-52 for 29, 29, and 27 patients respectively.

Serum dutasteride concentrations at steady state (>6 months) ranged from 9 [redacted] [redacted]. Mean serum dutasteride concentrations were [redacted] at Week 24 and Week 52 respectively.

Mean semen dutasteride concentrations at Weeks 24-28 and Weeks 48-52 were 3.2 ng/mL and 3.4 ng/mL respectively. The maximum concentration of dutasteride in semen was 14 ng/mL. The mean semen to serum ratio after 52 weeks of dutasteride 0.5 mg/day dosing was 0.115 (11.5% of dutasteride partitions into semen from serum).

Serum DHT concentrations from baseline to week 52 are shown in Table 7.

Table 7. Serum DHT Concentrations (pg/mL) from Baseline to Week 52.

	Placebo	Finasteride	Dutasteride
Baseline			
N	21	20	24
Mean	460.0	437.5	530.1
Week 8			
N	21	20	23
Mean	471.1	156.2	43.3
Week 24-28			
N	21	20	24
Mean	471.0	136.7	35.4
Week 48-52			
N	22	17	26
Mean	490.6	125.8	44.6

Serum T concentrations are from baseline to Week 52 shown in Table 8.

Table 8. Serum T Concentrations (pg/mL) from Baseline to Week 52.

	Placebo	Finasteride	Dutasteride
Baseline			
N	21	20	24
Mean	4741.4	4953.5	5835.0
Week 8			
N	21	20	23
Mean	4860.0	5981.0	7194.8
Week 24-28			
N	21	20	24
Mean	5089.5	6107.5	6625.0
Week 48-52			
N	22	17	26
Mean	4922.3	5679.4	6401.7

D.8. Safety analysis:

D.8.1. Extent of exposure: The extent of exposure is summarized in Table 9.

Table 9. Duration of Study Drug Exposure (Days)

	Placebo (n=32)	Finasteride (n=34)	Dutasteride (n=33)
Mean	305.3	301.4	327.5
Median	364.5	363.5	364.0

D.8.2. Serious adverse events:

Deaths: There were no study deaths.

Serious adverse events: Two subjects experienced serious adverse events. One patient in the finasteride group experienced a mild mental status change and one patient in the placebo group experienced appendicitis.

D.8.3. Discontinuation due to adverse event: Seven subjects withdrew from the study because of adverse events: 2 in the placebo group (impotence and mood swings), 3 in the finasteride group (decreased libido, gynecomastia, and mental status change, and 2 in the dutasteride group (impotence and decreased libido).

D.8.4. Frequent adverse events:

The most common adverse events (reported in >10 % of subjects in any treatment group) are shown in Table 10.

Table 10. Adverse events occurring in >10% of subjects in any treatment group

	Placebo (n=32)	Finasteride (n=34)	Dutasteride (n=33)
Any adverse event	28 (88%)	27 (79%)	28 (85%)
Common adverse events			
Common cold	8 (25%)	3 (9%)	11 (33%)
Headache	3 (9%)	8 (24%)	2 (6%)
Gynecomastia	2 (6%)	7 (21%)	3 (9%)
URI	4 (13%)	5 (15%)	3 (9%)
Decreased libido	1 (3%)	6 (18%)	2 (6%)
Influenza	2 (6%)	5 (15%)	1 (3%)

D.8.5. Adverse events of special interest: The incidence of adverse events which are of special interest in patients taking 5 alpha-reductase inhibitors are shown in Table 11.

Table 11. Adverse events of special interest in patients taking 5 alpha-reductase inhibitors

	Placebo (n=32)	Finasteride (n=34)	Dutasteride (n=33)
Gynecomastia	2 (6%)	8 (24%)	3 (9%)
Decreased libido	1 (3%)	6 (18%)	2 (6%)
Impotence	2 (6%)	1 (3%)	2 (6%)
Ejaculation disorder	0	2 (6%)	1 (3%)
Sexual function disorder	0	0	1 (3%)

No pregnancy was reported by a female partner of a subject enrolled in the study.

D.8.6. Changes in laboratory values: For individual subjects who had a change to a low or a high value, the change was in general transient and was not considered by the investigator to be clinically significant. No abnormalities of hematology or chemistry were reported as adverse events with the exception of one subject in the placebo group who experienced an increase of ALT to 337.

Changes in PSA: At month 12, a mean decrease from baseline PSA level of -3.6% was recorded for the dutasteride group. The placebo group had a mean decrease of 2.4% while the finasteride group experienced a mean decrease of 25%.

Reviewer's comment: It is not clear why the Month 12 data showed a decrease in PSA of only 3.6%.

Although there was an apparent negative trend on tumescence for subjects in both the finasteride and dutasteride groups, there were no statistically significant differences between the placebo and finasteride groups, the placebo and dutasteride groups, or the dutasteride and finasteride groups in event/session duration and average event rigidity at tip and base at Week 48.

Bone density: There was no statistically significant difference in lumbar spine or proximal femur bone density between any of the treatment groups.

D.9. Reviewer's assessment of safety and efficacy in Trial ARIA1009: The number of patients enrolled in this trial was relatively small (approximately 30/group). It is difficult to determine the significance of some of the findings (e.g. decrease in sperm concentration) because of expected effects of 5 alpha-reductase inhibitors on seminal fluid volume.

Appendix E: 120 Day Safety Update (received on April 23, 2001)

Additional safety data included in this update include safety data through year 2 for 1362 patients (677 dutasteride patients) in pivotal study ARIA3002, deaths, serious adverse events, and partner pregnancies which occurred after Year 1 in ARIA3001 and ARIB3003, and data through the double blind treatment phase for 99 patients in ARIA1009 ("An Investigation of the Pharmacokinetics of GII98745 and the Effects of GII98745 on Semen Characteristics When Administered Daily for 12 Months to Healthy Male Subjects"). The synopsis report and safety data related to the QT study ARI10019 and safety related to other ongoing studies are also included.

ARIA1009 (semen analysis study reviewed in detail in Appendix D)

Pertinent information in the safety update regarding ARIA1009:

One pregnancy occurred during the follow-up phase of ARIA1009. The patient's wife had been exposed to placebo (via seminal fluid) and delivered a healthy girl.

Four patients (2 dutasteride and 4 finasteride) had decreases in their sperm count to less than 10% of baseline at the end of 52 weeks drug exposure. All four patients showed recovery at the 26 week follow-up visit, with increases in sperm count above the pre-defined clinically significant threshold.

ARI10010 (QT study reviewed by the CardioRenal Division) (see CardioRenal consult)

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 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 pre-dose 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 interval. 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 of dutasteride 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."

The report consisted of a draft report of preliminary results. (The study was started on October 2, 2000, and all patients had not completed the trial at the time of the submission of the 120 Day Safety Update.)

ARIA3002: Year 2 Safety Data (One year efficacy and safety data for ARIA3002 are reviewed in detail in Appendix B)

In the Intent-to-Treat Population, the mean extent of exposure in the dutasteride group was 592.7 days and in the placebo group was 599.8 days. Sixty-four percent of patients in the placebo group and 68% of patients in the dutasteride group received treatment for more than 720 days.

A similar proportion of patients in each treatment group prematurely discontinued after randomization (240 or 35% placebo and 219 or 32% dutasteride). Ten percent of patients in the placebo group and 9% in the dutasteride group withdrew due to adverse events.

The incidence of adverse events grouped by body system was similar between the 2 treatment groups except for a higher incidence of reproductive adverse events reported in the dutasteride group (24%) than in the placebo group (18%). The frequency of adverse events by age (<65 years versus >65 years) was similar. Cardiovascular adverse events were reported by a slightly higher proportion of older patients (>65 years – placebo 16%; dutasteride 19%) than younger patients (<65 years – placebo 11%; dutasteride 12%). The frequency of adverse events in patients >75 years was similar to patients <75 years. Non-Caucasian patients in the placebo group had a lower incidence of adverse events (60%) than non-Caucasians in the dutasteride group (78%) and Caucasian placebo and dutasteride treated patients (78% and 79%, respectively). The frequency of adverse events occurring at < 1 year was 66% in both the placebo and dutasteride groups while the incidence of adverse events with onset >1 year was 58% in the placebo group and 63% in the dutasteride group. The incidence of reproductive adverse events (impotence, decreased libido, and gynecomastia) with onset <1 year was higher than the incidence with onset >1 year. Adverse events of special interest in patients taking 5-alpha reductase inhibitors is shown in Table 1.

Table 1. Adverse events of special interest.

	Placebo (N=685)	Dutasteride (N=677)
Decreased libido	20 (3%)	31 (5%)
Impotence	42 (6%)	62 (9%)
Ejaculation disorders	4 (<1%)	22 (3%)
Sexual function disorder	0	0
Gynecomastia	6 (<1%)	21 (3%)
Prostate cancer	17 (2%)	9 (1%)

Deaths: Six (<1%) patients in the placebo and 9 (<1%) patients in the dutasteride group died during the study. None of the adverse events leading to death was considered to be related to study drug by the investigator.

All but one serious adverse event was considered by the investigator to be unrelated to study drug. This patient taking placebo experienced vertigo.

Thirty-five (5%) placebo and 25 (4%) dutasteride patients withdrew from the study due to serious adverse events. The most frequent serious adverse events leading to study withdrawal included prostate cancer (12 placebo and 7 dutasteride patients), cerebrovascular accidents (one placebo and 5 dutasteride patients), and coronary artery disorders (3 placebo and 3 dutasteride patients).

Laboratory abnormalities: Three patients in the dutasteride group exceeded pre-defined threshold values of clinical significance for liver function tests (3 X ULN for ALT and 1.5 X ULN for alkaline phosphatase) compared with 6 patients in the placebo group. When examining the proportion of patients with abnormal laboratory values by age >75 years and <75 years, a higher incidence of abnormal laboratory values was reported for dutasteride treated patients >75 years (54%) than placebo treated patients >75 years (43%) or patients in either treatment group younger than 75 years (47%). Dutasteride treated patients >75 years had a higher incidence of normal to abnormal change in platelet count (10% versus 2 to 3% in the other 3 subgroups).

Reviewer's comment: Only 16% of the study population was comprised of men >75 years of age and meaningful conclusions concerning laboratory abnormalities in this age group are difficult to draw.

Change from baseline in PSA: 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%.

Change from baseline in serum testosterone: Six dutasteride treated patients had elevated serum T levels at at least one time-point during the trial. The highest value recorded was 12,400 pcg/mL (normal <10,000 pcg/mL).

Open label phase of ARIA3002:

During the open label phase of ARIA3002, patient #40091 developed infiltrating ductal carcinoma of the left breast 340 days after initiating open-label treatment. The tumor was estrogen receptor and progesterone receptor positive. He had received placebo for 2 years during the double-blind phase of the study.

Appendix F: Amendment received by the Division on June 19, 2001

Preclinical data as well as the clinical study report for ARIB3004 and its open label extension phase entitled "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" was received by the Division on June 19, 2001.

Trial ARIB3004:

One hundred fourteen patients were randomized to placebo or dutasteride 0.5 mg/day for 6 months. The primary endpoint was the change in detrusor pressure at maximum flow compared to baseline. Sixteen patients withdrew. The mean detrusor pressure at maximum flow increased (1.4 cm H₂O in the placebo group and 4.0 cm H₂O in the dutasteride group) from baseline in both treatment groups. A positive trend was seen in secondary endpoints AUASI, prostate volume, and Qmax, but statistical significance was not reached. No new safety concerns were observed in either the double-blind or open-label extension phases of the study.

**APPEARS THIS WAY
ON ORIGINAL**