Figure 23. Dutasteride Concentration-Time Profiles Following 5 mg Single Dose Alone (Open circle) or with Cholestyramine (open square)

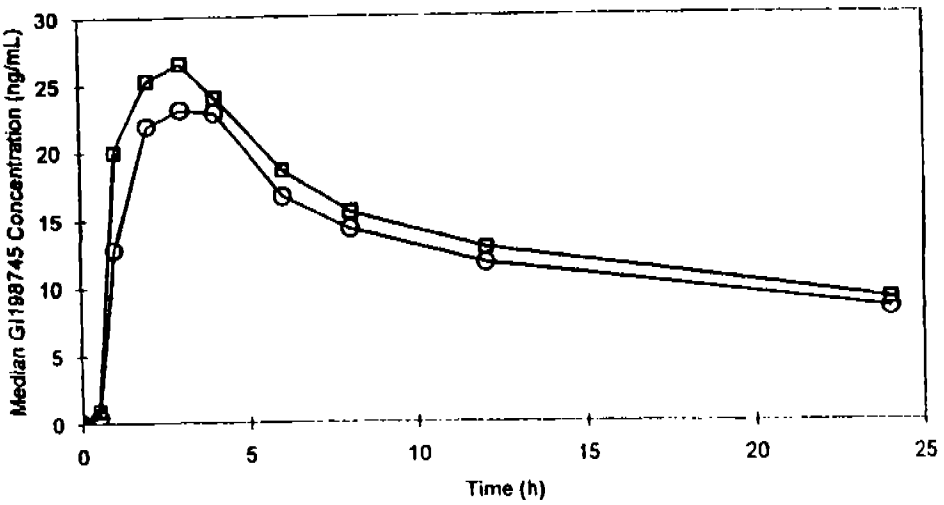
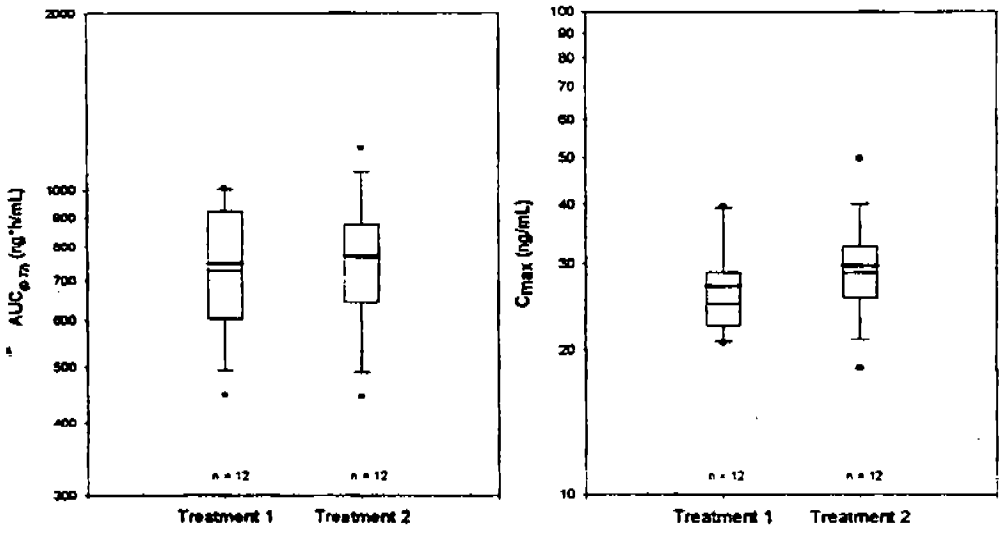


Figure 24. Comparative Box Plot for Dutasteride AUC and Cmax for treatment 1 (alone) and treatment 2 (with cholestyramine)



Is There any PK/PD or Dose-Response Relationship With Dutasteride?

With respect to PK/PD relationship, the three most relevant studies that were conducted are ARIA2001, ARIB2002 and ARIA1003. The latter study was discussed earlier. Study ARIA2001 was dose ranging up to 5 mg in BPH patients. However, study ARIB2002 was conducted in BPH patients awaiting trasurethral resection of the prostate (TURP) at one dose level of 5 mg. The concentration of the DHT was determined in prostate tissues and serum. These two studies are discussed briefly below:

Study ARIA2001:

This was a double blind, placebo controlled, dose ranging in patients with BPH. The main objectives of this study were to establish the safety and efficacy of the drug as well as the PK/PD characteristics following repeated doses. In this study the drug was administered daily up to 24 weeks and 16 weeks follow up. The following five-dose levels were administered:

Dose (mg)	Number of subjects for PK Blood Collection	Number of Subjects for Efficacy and PD*
Placebo	N/A	59
0.01	30	58
0.05	31	53
0.5	32	57
2.5	26	57
5	28	60
5 (Finsateride-PROSCAR)	N/A	55

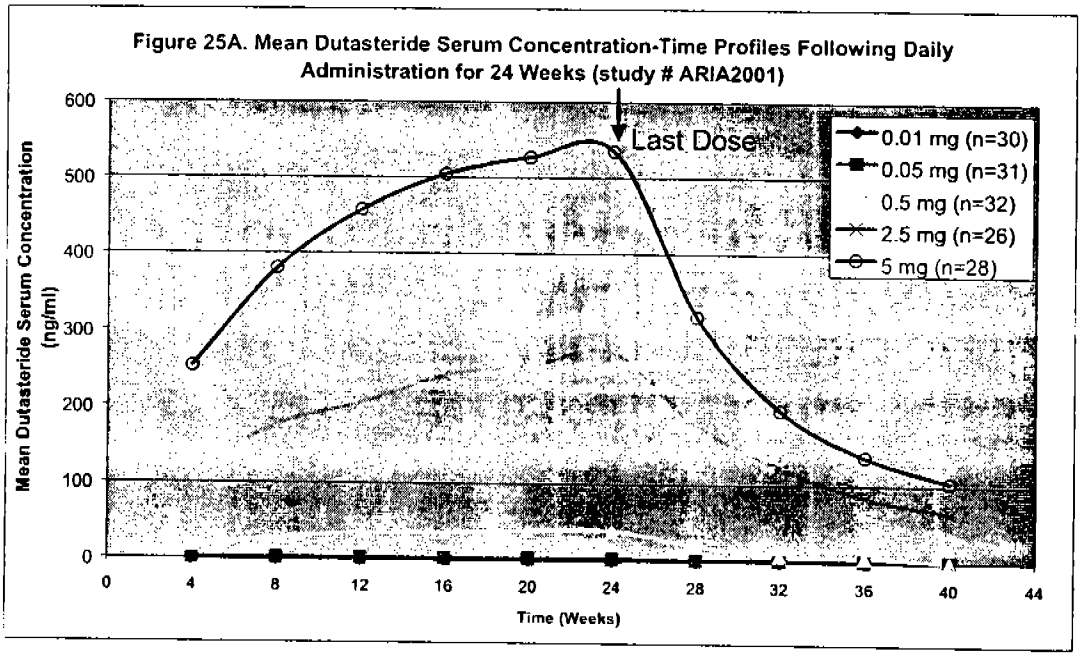
*This includes parameters such as serum DHT, testosterone, and prostate volume. Blood samples were collected on weeks 4, 8, 12, 16, 20, and 24 after drug administration. In addition on weeks 4, 8, 12, and 16 after the last dose which correspond to weeks 28, 32, 36, and 40 after the first dose.

From this study, the following conclusions can be made:

1. The drug levels continued to rise up to week 24 as seen from dutasteride serum concentration-time profiles (**Figures 25A&B**).
2. The steady- state was almost achieved by week 24 (i.e., after 6 months) following all doses. The drug was still detectable in the serum at week 40 after termination of 2.5 and 5 mg doses at week 28 (**Figures 25 A&B**).
3. In terms of efficacy, there was a dose-response relationship in relation to DHT inhibition (**Figures 26 and 27**). By Week 24 there was almost 97% reduction in DHT serum levels relative to base line at doses 0.5 mg and above. However, testosterone

serum levels resulted in a moderate increase (~25%) relative to baseline at doses of 0.5 mg and above (**Figure 28**). The effect of Finasteride 5 mg doses on DHT inhibition was much lower than that of the corresponding 5 mg doses of dutasteride. By Week 24, the maximum reduction in DHT levels produced by finasteride was approximately 70% of the baseline.

4. The effect on prostate volume correlates well with DHT inhibition (**Figure 28**). No further effect on prostate volume was observed at the doses above 0.5 mg (**Figure 29**).
5. Dutasteride as well as finasteride had no effect on urine flow (**Figure 28**). In addition, both drugs had no effect on symptoms and quality of life scales as shown from IPSS scores (**Figure 30**).
6. There was little changes in serum level of Prostate Specific Antigen (PSA) as shown from the dose-response relationship (**Figure 31**).



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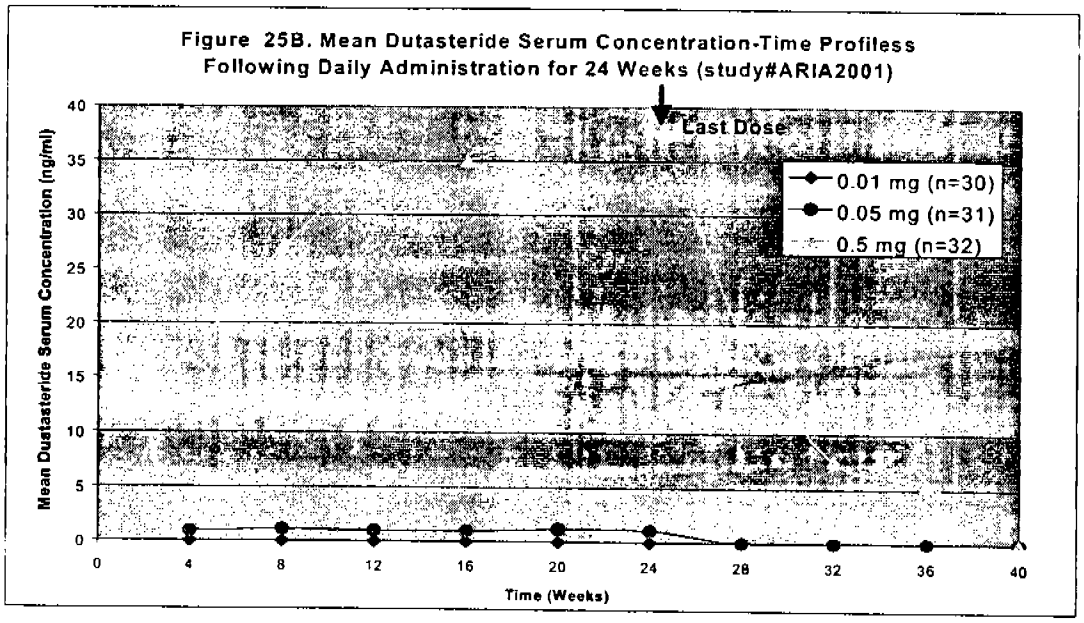


Figure 26. Dose-Response Relationship for DHT inhibition represented as % change in from baseline on Week 24 (Study # ARIA2001)

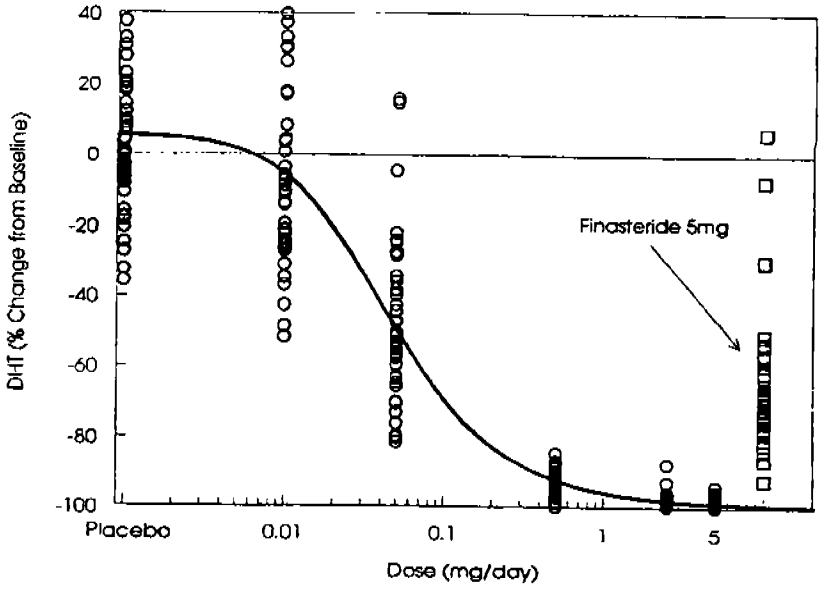


Figure 27. Mean DHT Serum Concentration-Time Profiles Following Daily Administration of Dutasteride and Finasteride Up to 24 Weeks (n=11-12) (study #

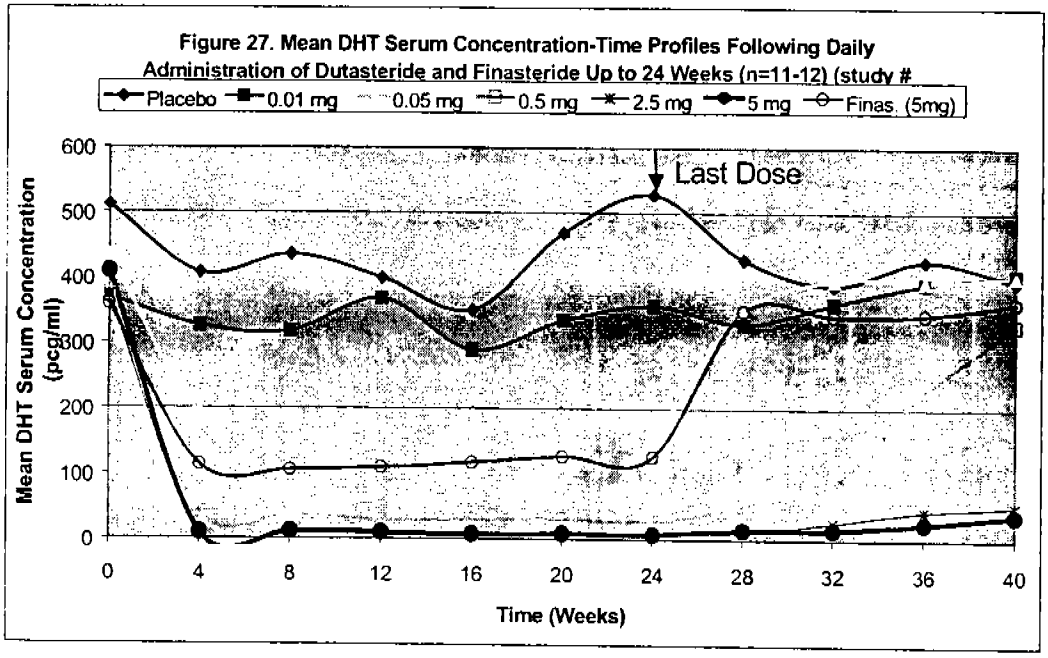
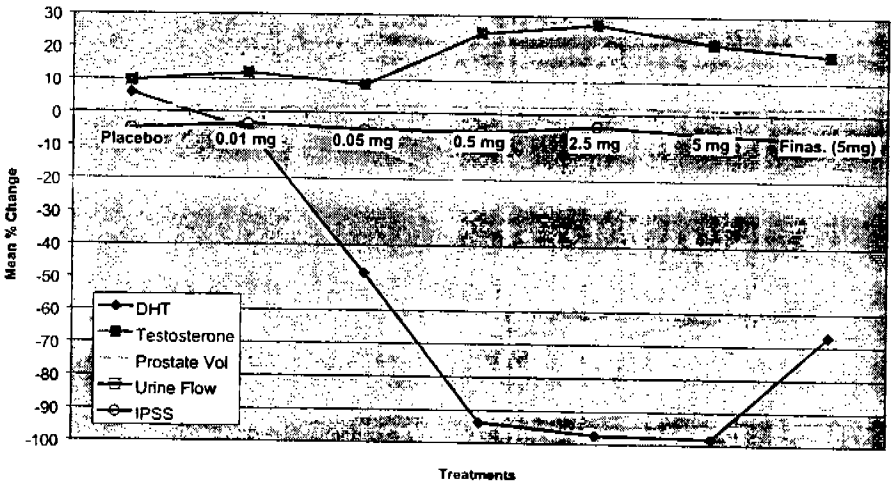


Figure 28. Mean % Change in Efficacy (PD) Parameters on Week 24 (Study # ARIA2001)



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Study ARIB2002:

This study was double-blind, placebo-controlled, double-dummy in PBH patients awaiting trasurethral resection of the prostate (TURP). Dutasteride and finasteride were administered daily at 5 mg doses with matching placebo. The total number of patients that completed the study is 58 who received one of the following pre-defined treatment time-frames: 0-3 weeks, >3-6 weeks, or >6-12 weeks, prior to TURP:

Group A (n=24): Dutasteride 5 mg and finasteride (PROSCAR)-matched placebo
Group B (n=22): Dutasteride-matched placebo soft-gelatin capsules and finasteride 5 mg
Group C (n=19): Dutasteride-matched placebo and finasteride-matched placebo.

In this study the following parameters were collected:

- Prostate tissue concentration of dutasteride, DHT and testosterone (T).
- Serum dutasteride, DHT, and testosterone concentration
- Degree of apoptosis/atrophy of prostate tissue based on histological examination.

Comments:

From this study the following observation and conclusions are made:

1. There is an excellent correlation between the following parameters (**Figure 32**).

    - Dutasteride prostate tissue concentration and serum dutasteride concentration. The ratio is almost unity (i.e., 1.0)
    - Dutasteride prostate tissue concentration and study day.
    - Dutasteride serum concentration and study day.

2. Dutasteride resulted in >95% inhibition in serum DHT (**Table 16**).

3. There is a relatively poor correlation between dutasteride serum concentration and the following PD parameters (**Figures 34 A& D**):

    - DHT prostate tissue concentration
    - Testosterone prostate tissue concentration
    - DHT serum concentration
    - Testosterone serum concentration.

4. There is a trend for an inverse relationship between DHT concentration in prostate and apoptotic cell count (**Figure 35**).

Figure 32. Relationship Between Dutasteride Prostate Tissue Concentration and Serum Concentration

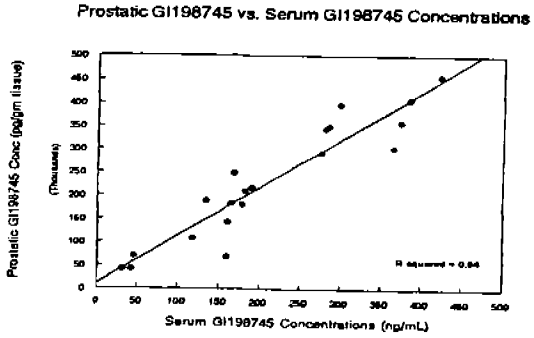

Figure 33. Relationship Between Dutasteride Prostate Tissue Concentration and Study Day

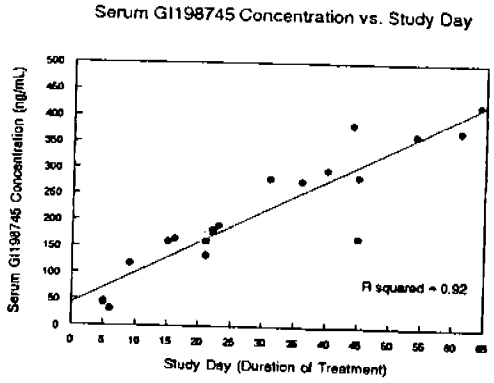

Figure 34. Relationship Between Dutasteride Prostate Tissue Concentration and Serum Concentration

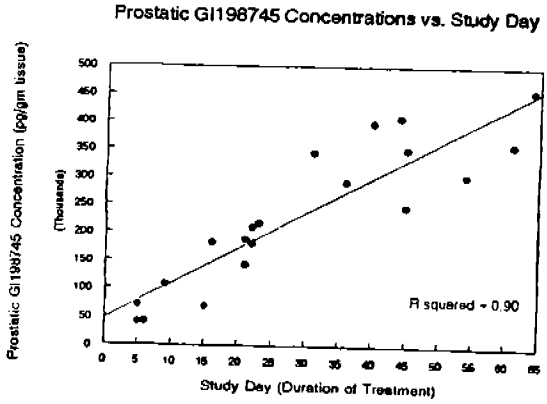

Table 16. Summary of DHT and Testosterone Parameters

Serum DHT and testosterone adjusted mean percentage changes from baseline			
	Placebo	Dutasteride	Finasteride
Number of subjects randomised	19	24	22
Serum DHT at TURP	+3.1% (17)	-96.2% (22)	-72.8% (18)
Serum DHT at 16 weeks FU	+21.0% (18)	-84.3% (21)	-15.4% (18)
Serum DHT (median) at 32 weeks FU	-2.1% (3)	-18.7% (14)	-11.6% (5)
Serum testosterone at TURP	-13.9% (17)	+38.3% (23)	+31.5% (18)
Serum testos. At 16 weeks FU	+2.4% (18)	+20.8% (21)	-9.4% (18)
Serum testosterone (median) at 32 weeks FU	-8.4% (3)	+1.4% (14)	-22.9% (5)

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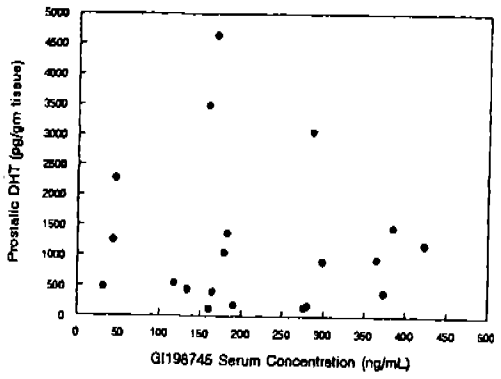
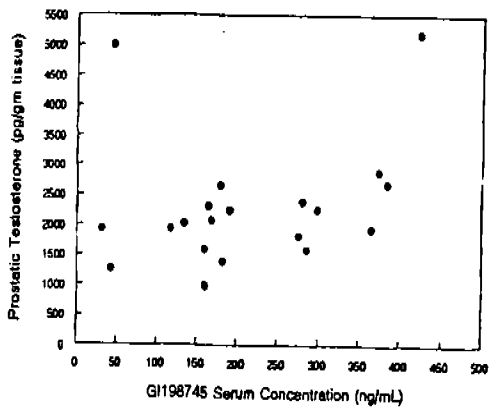
Figure 34 A-D. Summary of Derived PD Parameters For Dutasteride

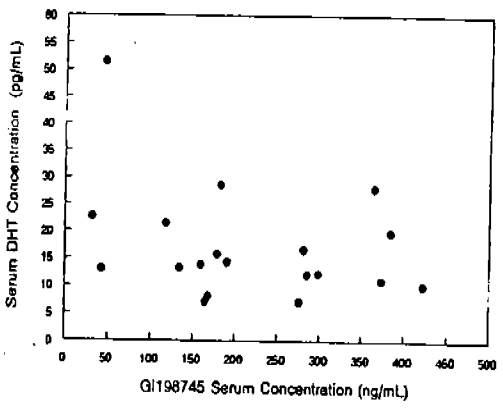
(A)



(B)



(C)



(D)

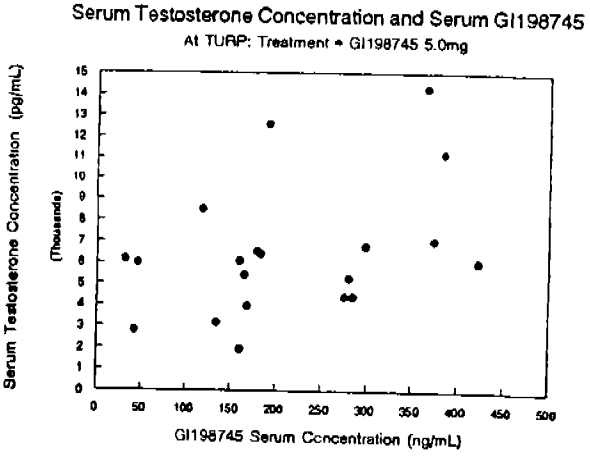


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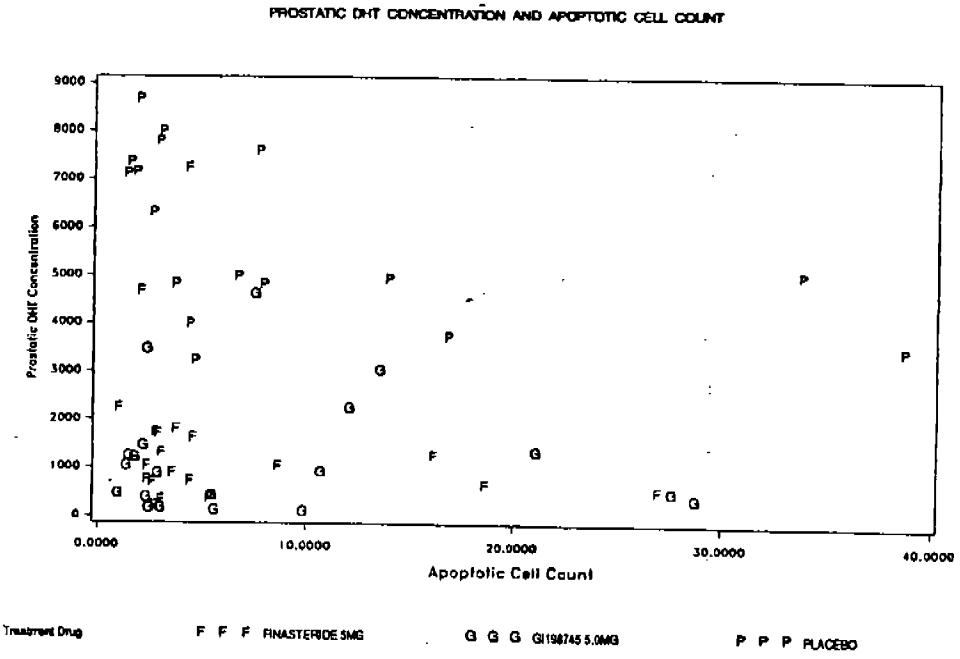
Figure 35. Relationship Between DHT Concentration in Prostate and Apoptotic Cell Count



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Is There Any Safety Related Issues:

The data discussed below are based on a 52 weeks placebo controlled double-blind study (#ARIA1009). Dutasteride was administered at a dose of 0.5 mg and finasteride (PROSCAR) was at dose of 5 mg daily for 52 weeks to healthy subjects. The total number of subjects completed the 52 weeks dosing were 29, 25, and 22 for dutasteride, finasteride, and placebo arms, respectively. In this study several PK/PD parameters were determined such as: serum, semen concentration of dutasteride and finasteride, DHT inhibition, serum testosterone, sperm count, sperm concentration, and semen volume etc.

a) Semen/Serum Ratio

From this study it was shown that semen dutasteride steady-state concentration is about 10% of that of serum concentration. In this study the average semen concentration at steady-state was approximately 3.3 ng/ml (**Table 16**). The highest concentration of dutasteride in semen was 14 ng/ml. The average steady-state serum concentration of dutasteride was approximately 31 ng/ml after daily administration of 0.5 mg doses.

Table 16. Mean (± SD) of serum and semen concentration of dutasteride (study # ARIA10009)

Duration	Serum (ng/ml)	Semen (ng/ml)	Ratio (Semen/Serum)
Baseline	BQL	BQL	0
Week 8	25.43 (8.28)	2.13 (1.15)	0.083
Week 24-28	32.62 (15.31)	3.23 (2.66)	0.099
Week 48-52	30.14 (12.56)	3.42 (2.65)	0.011

Based on this study, exposure of pregnant woman to dutasteride appears to be minimal. However, this depends on the degree of the toxicity of the drug and its metabolites. It should be noted that based on animal studies, the "no effect dose" on the embryo fetal development of male primate is 260 ng/kg. The exposure of fetus to a high level of DHT inhibitor may be associated with high risk of inadequate development of male genitalia.

b) **Effect on Spermatogenesis**

There is a clear trend that dutasteride and also finasteride have some effect on spermatogenesis in one form or another compared to placebo (**Figures 36 A-E**.). In all cases, there is a sharp drop in sperm count, sperm concentration, sperm motility, sperm morphology, and semen volume in week 24-28 from the baseline. Finasteride, however. appears to exhibit a more pronounced effect in all cases than dutasteride. This observation can be explained by the differences in the doses administered for both drugs, i.e., 0.5 mg for dutasteride and 5 mg finasteride. It should be noted, however, that these are the recommended daily doses for both drugs. The clinical significance of these observations remains to be established after the chronic administration of the drug.

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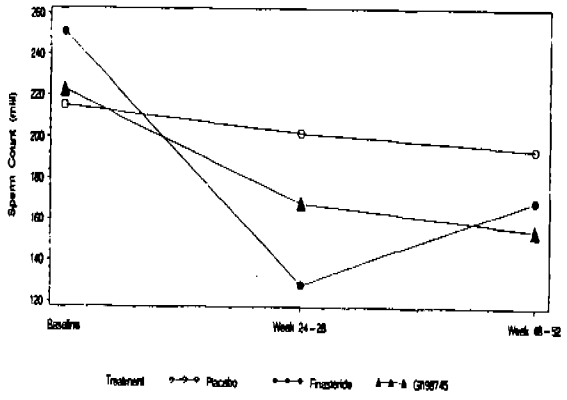
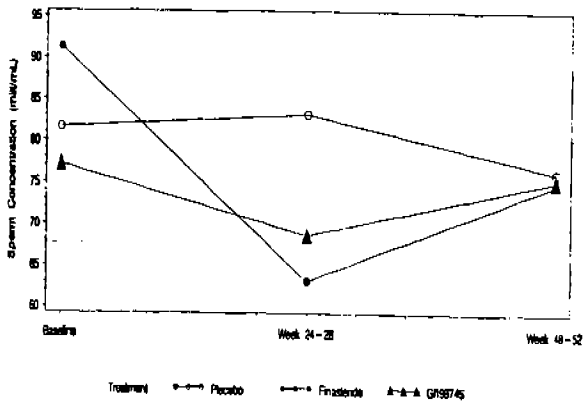
Figures 36. Effect of dutasteride on spermatogenesis (study # ARIA1009)

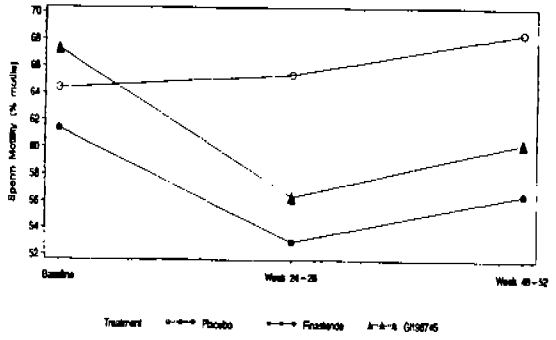
A. Sperm Count



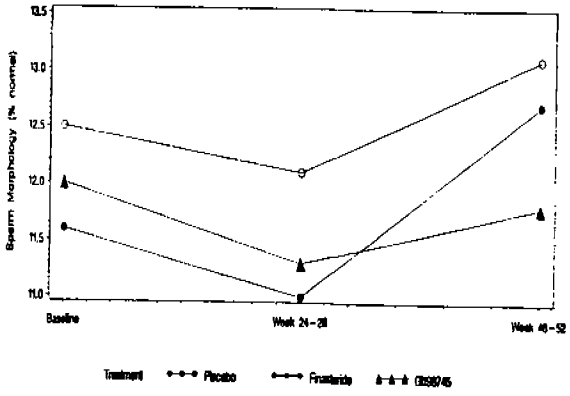
B. perm Concentration



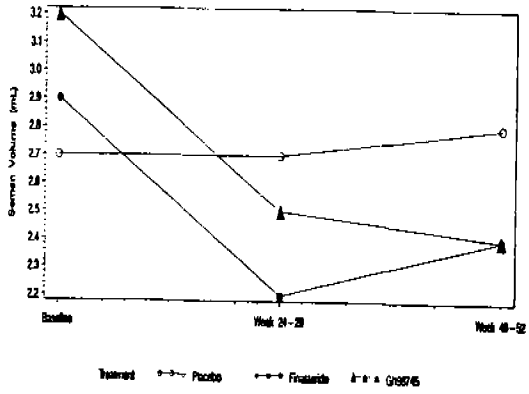
C. Sperm Motility



D. Sperm Morphology



E. Semen Volume



b) Effect on DHT and Testosterone:

Figure 37 A-C shows the effect of dutasteride and finasteride on DHT and testosterone serum levels. Dutasteride as well as finasteride caused marked reduction in DHT serum level from the baseline compared to placebo (**Figure 37 A**). There is no difference between week 8 and week 52 in terms of DHT suppression. Dutasteride at a dose of 0.5 mg appears to exhibit a more pronounced effect on DHT compared to 5 mg finasteride. Similarly, the effect of dutasteride on the total and the free (unbound) testosterone serum levels are greater than finasteride (**Figure 37 B,C**). Both the total and the free testosterone serum levels were markedly increased from the baseline with greater extent shown for dutasteride compared to finasteride. With this respect, placebo virtually had no effect.

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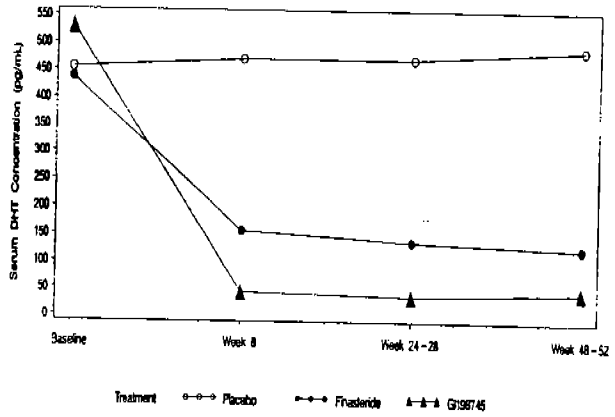
Figures 37 A-C. Effect of dutasteride on serum DHT and testosterone levels (study # ARIA1009)

(A) DHT Level



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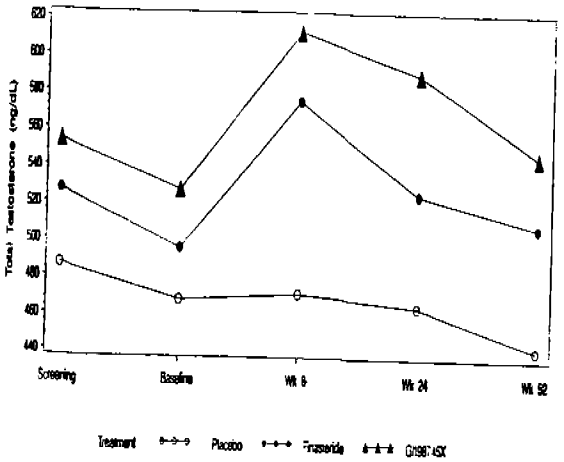
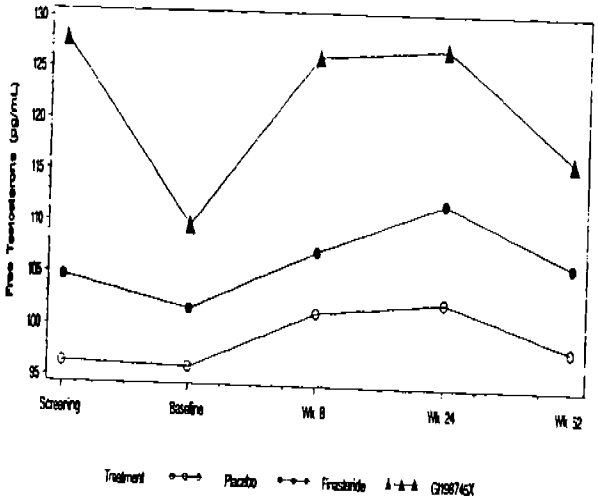
(B) Total Testosterone Concentration



(C) Free Testosterone Concentration



Is there any Effect of dutasteride on QTc interval?

The sponsor has conducted a study to specifically investigate the effect of dutasteride on QTc prolongation (study # ARI10019). At the time of review, the Agency received a draft report and preliminary analysis of the data. Therefore, the study is considered ongoing. Briefly, this is a placebo-controlled double blind study in healthy subjects. The first group received a loading dose of 25 mg on Day 1 followed by a daily dose of 0.5 mg for 28 days (n=31). The second group received a loading dose of 40 mg followed by a daily dose of 5 mg for 28 days (n=32). The third group received placebo (n=34) for 28 days. Serial 12-lead ECG monitored for baseline and on Day 1 and Day 28 at the following time points: predose, 1, 2, 3, 4, 6, 8, 10, and 12 hours and predose on the following days: Day 7, 14, and 21. Additional ECG monitoring were done at approximately 10 days and 2 months after the last dose as a follow up.

Blood samples for PK and PD (e.g., DHT) assessments were collected at 2 hours post dose **only** on Day 1 and pre-dose on Days 7, 14, 21, and 28. Additional blood samples were collected at approximately 10 days and 2 months after the last dose.

Comments:

1. According to the protocol, serum concentration of dutasteride and its metabolite (s) (e.g., 4-hydroxy metabolite) are to be measured for PK analysis.

2. For the PD analysis, serum DHT, free and total testosterone and sex hormone binding globulin (SHBG) are to be measured. At the time of review, only preliminary serum dutasteride data was available. In terms of PD data, only preliminary analysis of QTc data was available. Other PD data such as DHT, SHBG and testosterone were not available. In addition, the serum concentrations of 4-hydroxy metabolite were not available from this study.

3. The study design was not optimal in order to establish the relationship between the serum concentration and the changes in QTc. The full PK profiles should have been characterized on Day 1 and Day 28 to correspond to the times of ECG readings.

4. Blood samples should have been collected at 2 hours after each dose rather than pre-dose on each day. In this case the relationship between serum dutasteride concentration and the changes in QTc can be adequately established at the time of Cmax.

5. The mean QTc intervals-time profiles on Day –1, Day 1, and Day 28 are shown in **Figures 38 and 39.** In all cases, including placebo, there was a progressive prolongation in QTc intervals with time relative to the baseline. This prolongation peaks at 4 to 5 hour post the baseline and sharply dropped at 6 hours. This pattern appears to mimic some kind of diurnal variation. On Day –1 the QTc values following

placebo are consistantely longer than after drug treatment (**Figure 38**). The QTc profiles from Day 1 to Day 28 are shown in **Figure 40**.

6. The mean serum concentration-time profiles for dutasteride from Day 1 throughout the follow up Day 10 are shown in **Figure 41**. It should be noted that these profiles represent concentrations prior to each dose at the respective days, expect Day 1 which were at 2 hours after the loading dose. Therefore, this could be attributed to the lack of the relationship between dutasteride serum concentrations and QTc intervals as shown in **Figure 42**.

Note: The Division of the Cardio-Renal Drug Products was consulted in relation to QTc prolongation with dutasteride. The conclusion of the Cardio-Renal Division was that dutasteride had no effect on QTc intervals. In addition, the available data should not rule out the effect of dutasteride at higher drug concentration than that reported in the study. Furthermore, potential drug-drug interaction or certain diseases may interfere with the metabolism of dutasteride and hence may increase serum level. The full review of Cardio-renal Division is posted in DFS dated July 30, 2001.

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Figure 38. Mean QTc Intervals-Time Profiles in Day -1 and Day 1 Following Administration of 25 mg and 40 mg Loading Doses of Dutasterid on Day 1 (study # ARI1009)

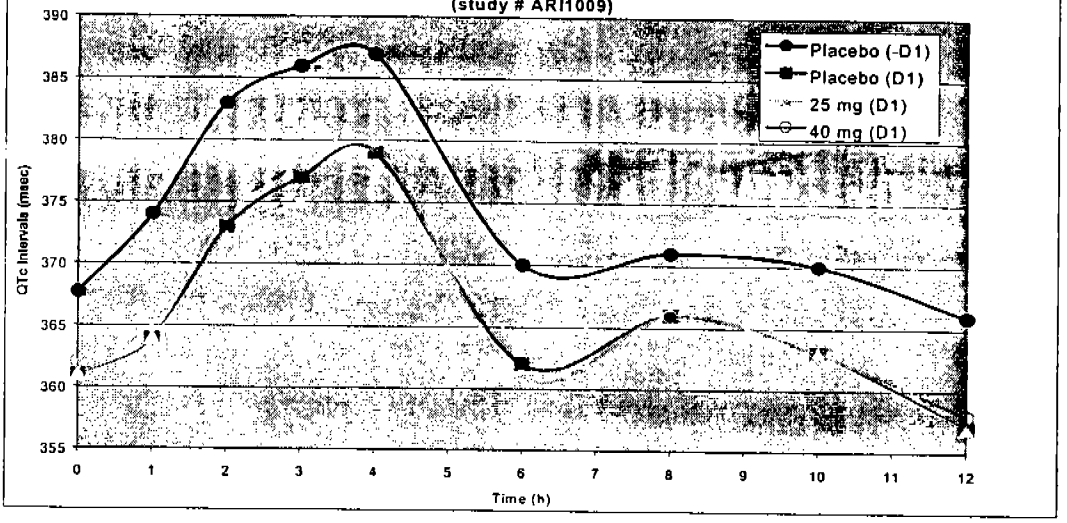


Figure 39. Mean QT intervals-Time Profiles in Day 28 Following Administration of 25 mg or 40 mg Loading Doses on Day 1 and 0.5 or 5 mg Dutasteride Daily Doses For 28 Days

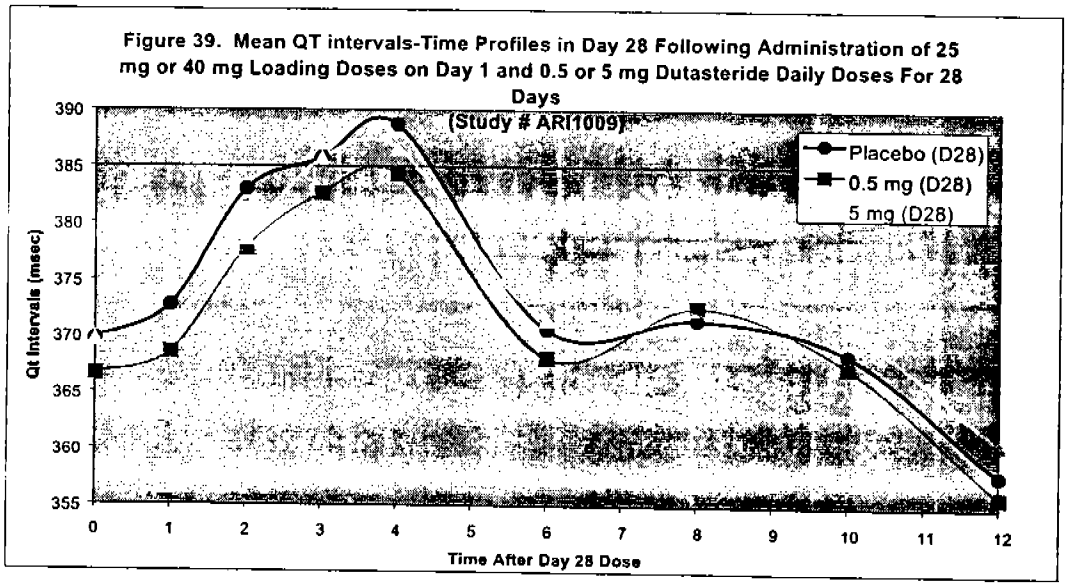


Figure 40. Mean QTc Intervals-Time Profiles Following Loading Doses of 25 mg or 40 mg on day 1 and Daily Doses of 0.5 mg and 5 mg Dutasteride Doses for 28 Days

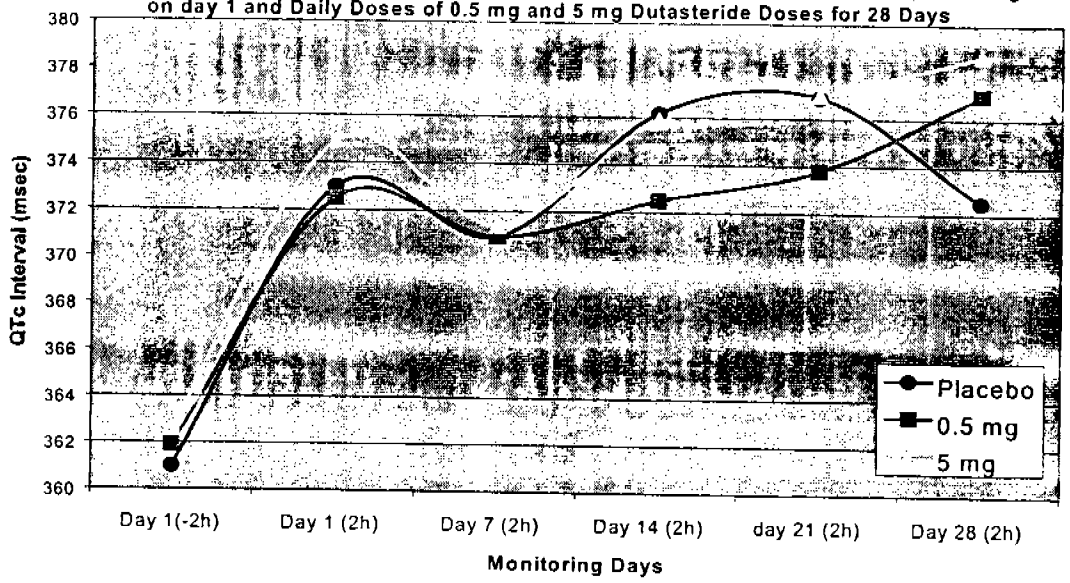


Figure 41. Mean Dutasteride Serum Concentration Following Loading Doses of 25 mg or 40 mg on Day 1 and Daily Doses of 0.5 mg or 5 mg to Healthy Volunteers, Respectively

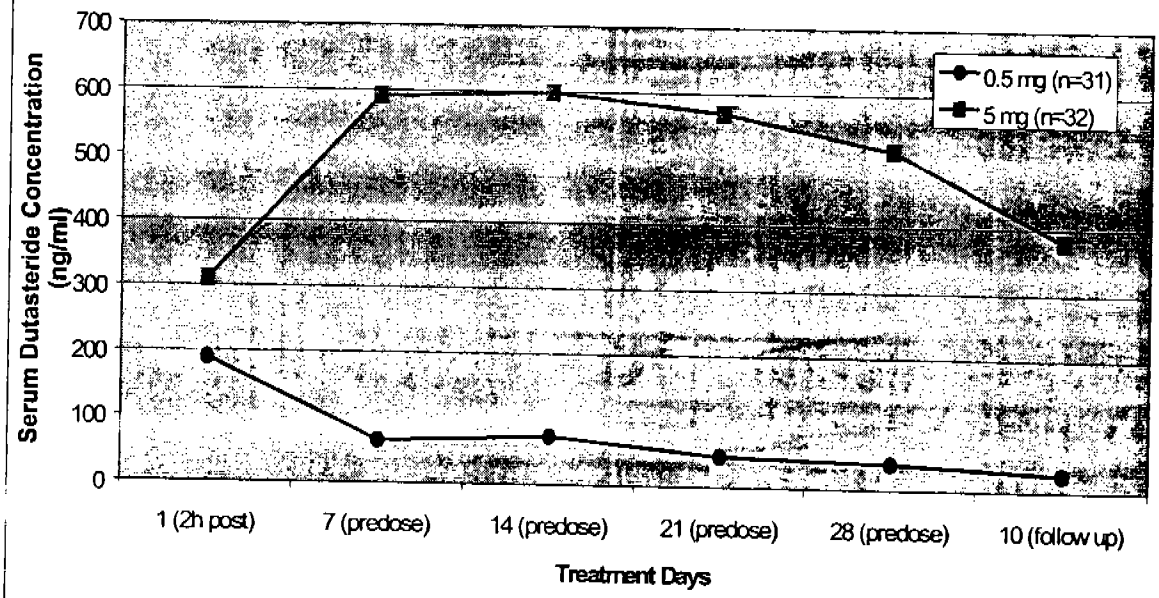
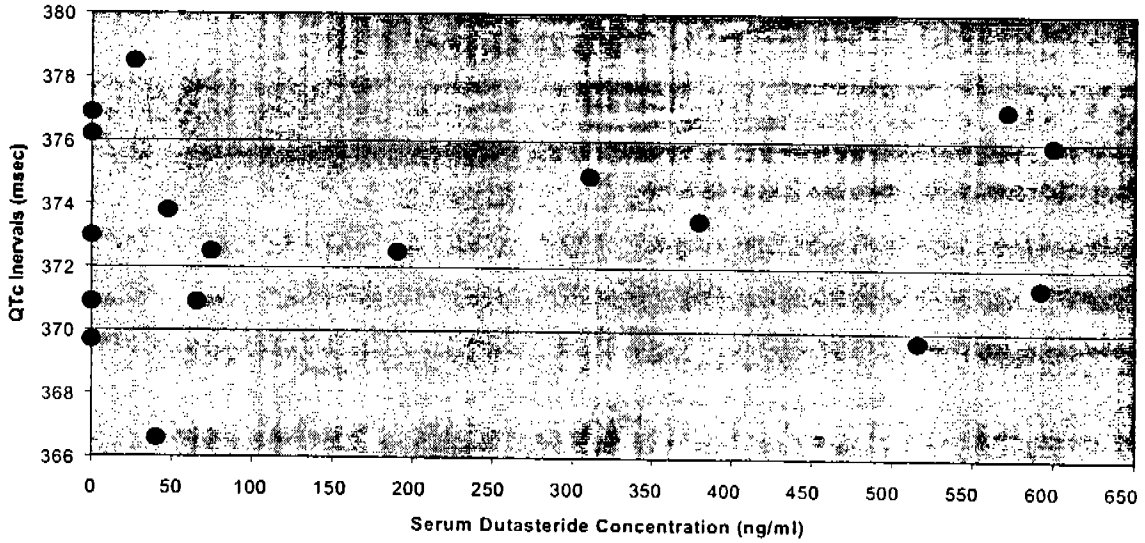


Figure 42. Relationship Between Mean Serum Dutasteride Concentrations and Mean QTc Intervals Following Loading Doses of 25 mg or 40 mg on Day 1 and Daily Doses of 0.5 mg or 5 mg For 28 Days in Healthy Subjects, Respectively



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ClinPharm/Biopharm Briefing on: September 21, 2001.

Briefing Attendees: Drs. Florence Houn, Mark Hirsch, Henry Malinowski, George Benson, John Strong, Jerry Collins, John Hunt, Myong-Jin kim, Johnny Lau, Shiew Mei Huang, Laurie Mcleod, Jean Salemme, Venkat Jarugula, Ameeta Parekh, Sam Haider, Chandra Sahajawalla, John Lazer, Jim Wei, Steve Johnson, and Sayed Al Habet

Reviewed by:

Sayed Al-Habet, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

RD/FT initialed by Ameeta Parekh, Ph.D. _____

cc: NDAs # 21-319: HFD-580, HFD-860 (Al-Habet, Parekh, and Malinowski), and Drug files (Biopharm File, CDR).

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23 page(s) of revised draft labeling has been redacted from this portion of the review.