# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-319**

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
# (Final Version October 5, 2001)

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| NDAs: 21-319<br>Category: IS | Submission Date:<br>January 13, 1999 (IND 47,838)<br>December 15, 2000 (for IND # 47-838)<br>December 21, 2000 (original NDA submission)<br>March 1, 2001<br>April 20, 2001<br>June 15, 2001<br>July 20, 2001<br>August 23, 20001 |
| **Generic Name:** | Dutasteride (code name **GI198745**) |
| **Brand Name:** | DUAGEN™ |
| **Formulations:** | Soft Gelatin Capsules 0.5 mg |
| **Route of Administration:** | Oral |
| **Indication:** | Benign Prostatic Hyperplasia (BPH) |
| **Sponsor:** | GlaxoSmithKline.<br>Research Triangle Park, North Carolina |
| **Type of Submission:** | NME |
| **Reviewer:** | Sayed Al-Habet, Ph.D. |
| **Dates of Review:** | |

| | |
|---|---|
| Received for Review: | March 12, 2001 |
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| Briefing Draft: | September 14, 2001 |
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## Synopsis:

DUAGEN (dutasteride also known as GI198745) is a synthetic 4-azasteroid compound that is a selective inhibitor of both type 1 and type 2 isoforms of steroid 5α-reductase (5AR), an intracellular enzyme that converts testosterone to 5α-dihydrotestosterone (DHT). The drug is indicated for the treatment of symptomatic Benign Prostatic Hyperplasia (BPH). The recommended dose of DUAGEN is 0.5 mg once daily. The drug may be administered with or without food.

DUAGEN is available as Soft Gelatin Capsules for oral administration containing 0.5 mg of the active ingredient dutasteride. The molecular weight of the drug is 528.5 and it is insoluble in water.

## RECOMMENDATION:

Based on the information submitted this NDA was found to be deficient from clinical pharmacology and biopharmaceutics (OCPB) perspective. However, based on the information available on safety and efficacy, discussion with review team, and OCPB management, this NDA is acceptable provided that the sponsor addresses these deficiencies as Phase IV commitments. These deficiencies are listed below:

**List of Deficiencies**

1. Approximately 55% of the administered dose is unaccounted for. In addition, the metabolism and metabolic pathways were not adequately determined.

2. The identification of the isoenzymes responsible for the metabolism of dutasteride have not been appropriately characterized. The available data from *in vitro* study show that CYP 3A4 is responsible for approximately 5% of the metabolism of the drug. No other isoenzymes were found or identified that can be responsible for the metabolized of dutasteride. This may be due to the high concentration of dutasteride used in this study. However, based on *in vivo* data, the drug is extensively metabolized to approximately 11 metabolites (four major and 6 minor).

3. Due to inadequate information on metabolism of the drug, it is difficult to predict any potential drug-drug interaction with dutasteride.

4. Since the drug is extensively metabolized and a study in hepatically impaired subjects has not been undertaken, it should be contraindicated in patients with hepatic impairment.

**Comments to Sponsor:**

1. The sponsor may consider conducting a study to investigate the effect of hepatic impairment on the PK of dutasteride..

2. The Agency is still awaiting the population PK analysis to verify certain drug-drug interaction claims. For example, data regarding increase in dutasteride exposure by 37% to 44% with calcium channel antagonists should be submitted.

**Phase IV Commitments:**

The limitations and deficiencies in the clinical pharmacology and biopharmaceutics studies should be addressed as phase IV studies. The sponsor should make a commitment to address the above deficiencies as well as conduct the following studies within 1 year of approval of this NDA. The protocols for the following list of studies should be submitted to the Agency for review within 3 months of the action letter.

**List of Phase IV Commitment Studies:**

1. Mass balance study and characterization of parent and metabolites profiles in serum, urine, and feces following oral administration.
2. *In vitro* metabolism study using therapeutically relevant dutasteride concentration to characterize the metabolic pathways.
3. Drug interaction with ketoconazole in humans.

# Executive Summary
# Clinical Pharmacology and Biopharmaceutics

**Background:**

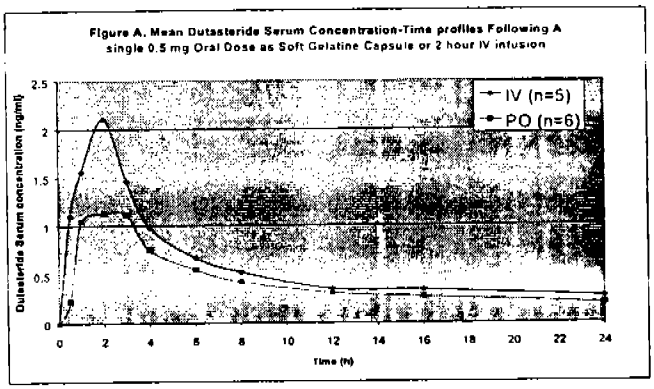
Benign Prostate Hyperplasia (BPH) is one of the most common conditions in men over 50 years of age. The condition normally manifests itself as lower urinary tract symptoms including symptoms related to bladder function (e.g., urgency, frequency, and nocturia) and those related to obstruction of urine flow (e.g., hesitation, weak stream, and terminal dripping). Apart from surgery, the most commonly used class of drugs are $\alpha_1$-receptor blockers such as tamsulosin (FLOMAX), terazosin (HYTRIN), and doxazosin (CARDURA) or Type II 5α-reductase inhibitor such as finasteride (PROSCAR).

DUAGEN™ (dutasteride also known as GI198745) is a 5α-reductase inhibitor that inhibits the conversion of testosterone to dihydrotestosterone (DHT) in the prostate gland. There are two isoenzymes for 5α-reductase, namely Type I which is the predominant form present in non genital tissue such as skin and liver and Type II form present in prostate gland and other reproductive tissues. DHT is normally responsible for the maturation and the growth of the prostate. However, its over production leads to the enlargement of the prostate and hence causing hyperplasia of the gland. Unlike finasteride (PROSCAR) which inhibits only Type II α-reductase, dutasteride is targeted to inhibit both Type I and Type II 5α-reductase. The recommended dose of dutasteride is 0.5 mg daily.

**General Clinical Pharmacology and Pharmacokinetics:**

**Biopharmaceutics:**

Absorption of dutasteride following oral administration of soft gelatin capsules is rapid with $T_{max}$ of 1-4 hours. The absolute bioavailability from soft gelatin capsules is approximately 60% based on study conducted in 5 subjects (**Figure A**). Food reduced the AUC by approximately 10-15%. The drug exhibits large volume of distribution (300 to 500 L) and is highly bound to plasma proteins (99.0%). The terminal elimination half-life of dutasteride is approximately 5 weeks. Therefore, accumulation of the drug is expected after daily administration. Following repeated doses of 0.5 to 5 mg the plasma levels after 28 days is about 14-16 folds higher than after a single dose.



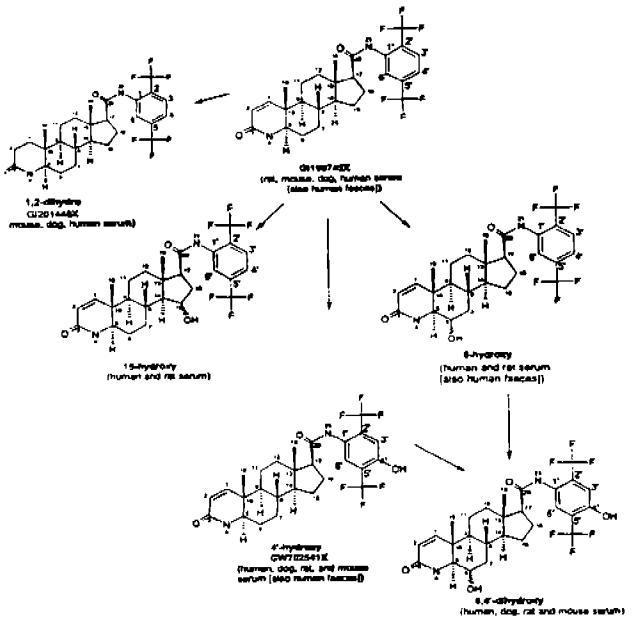

**Metabolism:**

A mass balance study using radiolabeled dutasteride was not conducted for this drug. Based on a preliminary (pilot) metabolism study (ARIA10012) with "unlabeled" dutasteride, the data show that the drug is extensively metabolized to approximately 10 metabolites (four major and six minor). The parent drug and its metabolites were primarily excreted in the feces, indicating biliary excretion and/or incomplete absorption. Without the availability of the IV data, the exact mechanism of excretion can not be fully explained. Virtually, nothing was found in urine that can be related to dutasteride. Therefore, the drug should be contraindicated in patients with hepatic impairment and bile obstruction. Overall, approximately 5% of the dose was excreted unchanged in feces and approximately 40% excreted as unidentified pooled metabolites. Approximately 55% of the dose is unaccounted for.

While *in vivo* data suggests that dutasteride is extensively metabolized in humans, these findings are not in agreement with the *in vitro* data. *In vitro* data showed that CYP 3A4 isoenzyme is responsible for about 5% of the metabolism. No other tested isoenzymes or enzymes (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP 2D6, and CYP2E1, glucuronyltrasferase, and sulphotrasferase) were found to be responsible for the metabolism of the drug using either cDNA-Expressed CYP450 enzymes, liver microsomes, or hepatocytes. This is critical information relative to potential drug-drug interaction with dutasteride. This potential drug-drug interaction has not been adequately characterized for this drug. It should be noted that the concentrations of dutasteride used in the *in vitro* metabolism study is 200 and 2000 ng/ml. The steady state concentration of dutasteride is approximately 40 ng/ml.

The metabolic pathways of the drug is not well known. However, based on the Agency's request, the sponsor has submitted a proposed metabolic pathway in animals and human on August 23, 2001 (**Figure B**). In this metabolic pathway, no information on isoenzymes was included for any of the proposed pathway. The main metabolites were 4-hydroxydutasteride and 6- hydroxydutasteride. The former is the major circulating metabolite in humans. The activity of the metabolites is mostly unknown.

**Figure B. Proposed Metabolism of Dutasteride in Animals and Humans**



**Special Population:**

The half-life of dutasteride increased almost linearly with age. It should be noted that, the half-life is a function of clearance. Since the renal status (e.g., GFR) decreases with age by approximately 1% per year after the age of 30, the increase in the half-life with age is not a surprising observation. However, based on the current knowledge, 45% of the administered dose is excreted in feces..

In addition, considering the extensive metabolism of the drug and the unaccountability of 55% of the dose, no study was conducted in hepatic impairment patients. Therefore, dutasteride should be contraindicated in this population.

**Drug-Drug Interactions:**

No relevant metabolically based drug-drug interactions studies were conducted by the sponsor (e.g., with ketoconazole). However, the sponsor conducted drug-drug interaction with the following drugs: tamsulosin, terazosin, warfarin, digoxin, and cholestyramine. These drug-drug interaction studies are considered chemically or physically based. Dutasteride was found to have little effect (<10%) on the PK or PD of warfarin, tamsulosin, or terazosin. Similarly, cholestyramine increased the AUC and Cmax of dutasteride by approximately 10%. No other drug-drug interaction studies were conducted to investigate their effects on the PK or PD of dutasteride.

**Efficacy Biomarkers and PK/PD Relationship:**

In terms of PK/PD relationship relevant to DHT inhibition (biochemical marker) the maximum effect is dose and time dependent. Daily administration of 0.5 mg dose produces about 80% reduction in DHT after 7 days with a maximum effect observed within 1 to 2 weeks. The administration of 5 mg dose causes almost complete inhibition of serum DHT. In repeat dose studies the highest dose group produced 80% reduction in DHT within one day, 95% reduction within one week and 98% reduction in 6 months. The mean data for plasma concentration-time profiles, DHT, and some of efficacy parameters are shown **Figures C-G**. Steady-state dutasteride concentration was almost achieved by six months (**Figure D**).

**Figures C and G. Dose-Response Relationship for DHT inhibition represented as % change from baseline on Week 24 and Plasma Concentration-Time Profiles Following Daily Administration for 24 Weeks (Study # ARIA2001)**

**Figure C**

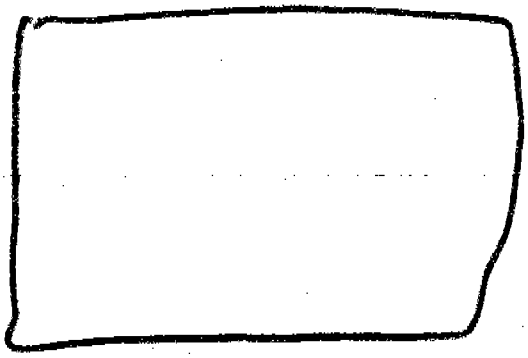


**Figure D**

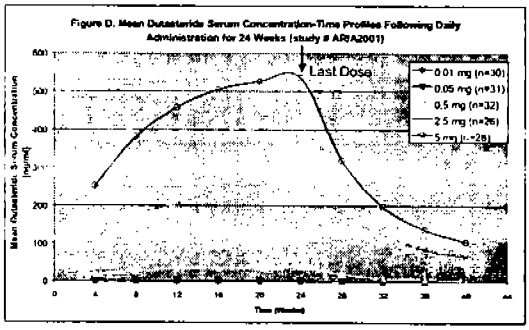
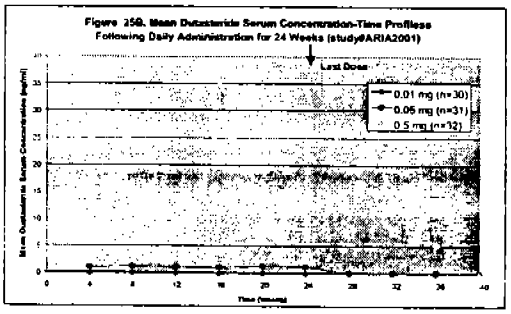



**Figure E.**

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**Figures F and G: Mean % Change in Efficacy Parameters on Week 24 and Dose-Prostate Response Relationship (study # ARIA2001)**

**Figure F**

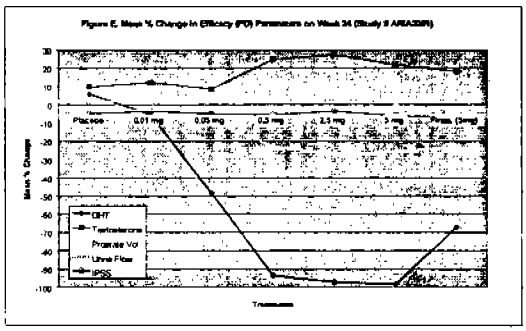
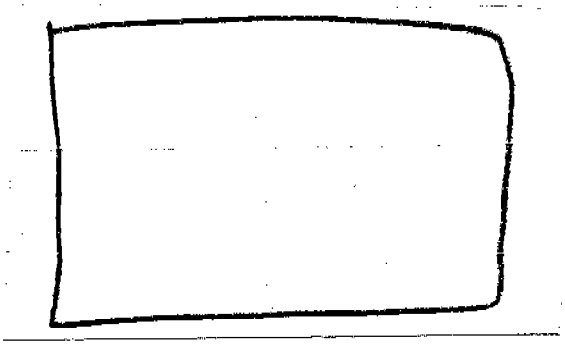
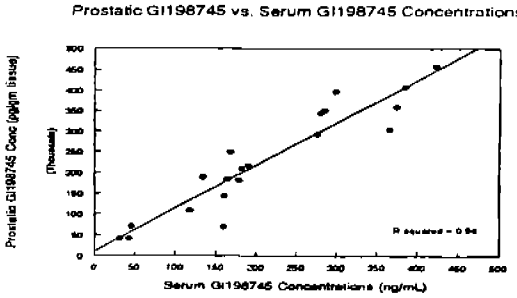



**Figure G.**



In addition, serum dutasteride concentration correlates well with prostate tissue dutasteride concentration in patients who had undergone trasurethral resection of the prostate (**Figure H**). The ratio is almost 1 (unity).

**Figure H. Relationship Between Dutasteride Prostate Tissue Concentration and Serum Concentration**

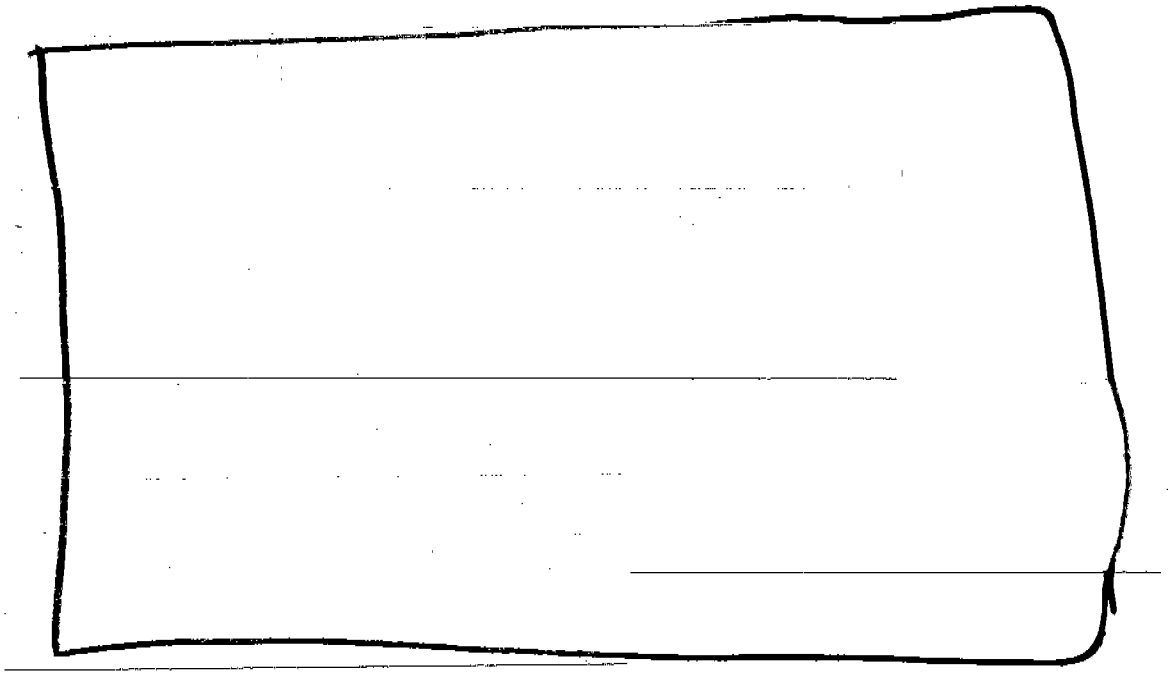



The Division of Cardio-Renal Drug Products was consulted on QTc prolongation study. The potential for QTc prolongation was studied at 10 times the proposed therapeutic dose, administered over 28 days.

The drug is excreted in semen and therefore the potential for its effect on the development of male organs in the fetus of the pregnant women exposed to drug during the intercourse was explored. About 12% of the serum concentration is present in semen following 0.5 mg dose.

**Summary:**

- The drug exhibits a high inter-subject variability (>50% CV)
- The submitted information on the metabolism of dutasteride is inadequate and deficient in many aspects.
- The drug is extensively metabolized in human. However, the drug is virtually unchanged *in vitro*. This may be due to the high drug concentration used in the *in vitro* studies.
- The activity of the metabolites is mostly unknown.
- The half-life increases almost linearly with age.
- Although the drug is extensively metabolized and there is approximately 55% of the dose unaccountable for, the sponsor did not conduct either hepatic or renal impairment studies or appropriate drug interaction studies.
- Based on the present data, biliary excretion is the main route of elimination or the drug is not well absorbed.
- No clinical significant QTc prolongation was observed at 10 times the recommended therapeutic dose administered over 28 days.
- The drug demonstrated excellent dose-response relationship relative to DHT inhibition. The dose of 0.5 mg daily is the best dose selected by the sponsor. No additional benefits were found using higher doses than 0.5 mg.
- In vitro dissolution method and specification is acceptable as follows:

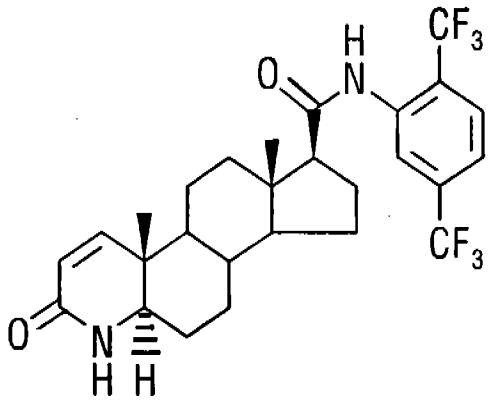


# SUMMARY REVIEW
# OF PHARMACOKINETICS AND BIOAVAILABILITY
# (Question Based Review, QBR)

## A) BACKGROUND:

**What are the Physico-Chemical Properties of Dutasteride?**

Dutasteride is chemically designated as (5α, 17β)-N-{2, 5 bis(trifluoromethyl) phenyl}-3-oxo-4-azaandrost-1-ene-17-carboxamide. The empirical formula of dutasteride is $C_{27}H_{30}F_6N_2O_2$, representing a molecular weight of 528.5 with the following structural formula:




Dutasteride contains seven chiral centers. The drug is white to pale yellow powder. It is insoluble in water in which its solubility is below the quantitation limit of the assay (0.038 ng/ml). However, the drug is soluble in various organic solvents including alcohol (ethanol and methanol). Since the drug is insoluble in water the best estimate of the $pK_a$ is approximately 13.5. The drug is lipophilic as indicated by the high octanol/water partition coefficient of 5.09 (logP).

**What are the Indications for Dutasteride?**

Dutasteride ™ is indicated for the treatment of symptomatic benign prostate hyperplasia (BPH) in men with an enlarged prostate gland.

**What is the Mechanism of Action of Dutasteride?**

Dutasteride is a competitive inhibitor to Type I and Type II 5α-reductase isoenzymes, with which it forms a stable enzyme complex. In that it inhibits both Type I and Type II

forms of this enzyme. Tis enzyme is responsible for the metabolism of testosterone to DHT (dihydrotestosterone) and its inhibition leads to reduction in circulating DHT. Since DHT is responsible for the growth and maturation of the prostate, its inhibition causes atrophy (shrinking) of the enlarged prostate.

**How Will Dutasteride be Supplied?**

Dutasteride will be available 0.5 mg Soft Gelatin Capsules.

The drug substance will be manufactured by Glaxo SmithKline Pharmaceuticals, Montrose, Angus, United Kingdom. Manufacturing of 0.5 mg dutasteride soft gelatin capsule 0.5 mg will be at RP Scherer S.A., Beinheim, France. The final product release will be by Glaxo SmithKine Pharmaceuticals, Zebulon, North Carolina

**What is the Proposed Dosage and Administration of Dutasteride?**

The recommended dose of DUAGEN is 1 capsule (0.5 mg) taken orally once a day. The capsules should be swallowed whole. DUAGEN may be administered with or without food.

## B) CLINICAL PHARMACOLOGY STUDIES:

### I. Biopharmaceutics

**1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.**

**Formulation Development:**

Study ARIA1004 was conducted with the following main objectives:

1. Compare the relative bioavailability of MDC soft gelatin capsules to PEG400 soft gelatin capsules.
2. Investigate the effect of high fat meal on the relative bioavailability of MDC soft gelatin capsules.

Briefly, the study was a parallel, single dose in four groups of healthy subjects as follows:

Group A (n=18): 0.5 mg PEG400 soft gelatin capsules
Group B (n=18): 0.5 mg MDC soft gelatin capsules.
Group C (n=18): 0.5 mg MDC soft gelatin capsules with food
Group D (n=18): (2 X 0.5 mg) MDC soft gelatin capsules.

For PK, serial blood samples were collected over 24 hours and at 3, 7, 14, 21, and 28 days. For DHT and testosterone measurement, blood samples were collected at pre-dose, 24 hours, 3, 7, 14, 21, and 28 days post administration.

**Comments:**

1. MDC formulation produced higher dutasteride serum levels than PEG400 formulation and the bioavailability was approximately 60% higher than PEG400 formulation (**Table 2 and Figures 1-3** ).
2. By doubling the dose, it appears that the $AUC_{0-\infty}$ is increased more than twice, but not $AUC_{0-72h}$ (**Table 2**). In addition, the half-life after 1 mg dose is about twice longer than after 0.5 mg dose.
3. Food appears to reduce the AUC by approximately 10-15%. In terms of 90% CI, there, the $AUC_{0-\infty}$ was 0.6-1.3 and for Cmax was 0.7-1.0. Based on the therapeutic window of this drug, this difference should not be considered of any clinical significance. Therefore, the drug can be administered with or without food.
4. In terms of PD effect, there is little difference that can be seen among all treatments related to DHT inhibition (**Table 3 and Figure 4**)

Conclusions:

1. MDC is the preferred formulation since it was demonstrated to be superior to PEG400 formulation in terms of bioavailability.
2. Food had little effect on the bioavailability of dutasteride. However, in terms of 90% CI, food has some effect on bioequivalence limits.
3. Based on this study MDC formulation where selected as a clinical trial

formulation. This formulation was used in Phase II and III clinical trials.

**Table 2**

**Summary of Pharmacokinetic Parameters**
**(All Subjects Enrolled in Protocol ARIA1004)**

| Group | GI198745 0.5mg PEG400 (N=18) | GI198745 0.5mg MDC (N=18) | GI198745 0.5mg MDC with food (N=18) | GI198745 1.0mg (2x0.5mg) MDC* (N=18) |
|---|---|---|---|---|
| $AUC_{0-72}$ (ng*h/mL) | | | | |
| Geometric LS Mean (95% CI) | 27 (20-36) | 43 (32-57) | 35 (26-47) | 65 (48-86) |
| Geometric LS Mean ratio/ PEG400 (90%CI) | – | 1.6† (1.1-2.2) | – | – |
| Geometric LS Mean ratio/ MDC 0.5mg (90% CI) | – | – | 0.8 (0.6-1.2) | 1.5† (1.1-2.1) |
| $AUC_{\infty}$ (ng*h/mL) | | | | |
| Geometric LS Mean (95% CI) | 37 (26-51) | 59 (42-83) | 53 (38-74) | 129 (93-181) |
| Geometric LS Mean ratio/ PEG400 (90%CI) | – | 1.6† (1.1-2.4) | – | – |
| Geometric LS Mean ratio/ MDC 0.5mg (90% CI) | – | – | 0.9 (0.6-1.3) | 2.2† (1.5-3.2) |
| $C_{max}$ (ng/mL) | | | | |
| Geometric LS Mean (95% CI) | 1.6 (1.3-1.9) | 2.2 (1.9-2.7) | 1.9 (1.6-2.3) | 3.0 (2.5-3.5) |
| Geometric LS Mean ratio/ PEG400 (90%CI) | – | 1.4† (1.1-1.7) | – | – |
| Geometric LS Mean ratio/ MDC 0.5mg (90% CI) | – | – | 0.8 (0.7-1.0) | 1.3† (1.1-1.6) |
| $t_{max}$ (h) | | | | |
| Median Range | 2.0 1.0-4.0 | 3.0 2.0-4.0 | 3.5 1.0-12.0 | 2.0 2.0-4.0 |
| Estimated difference from PEG (90% CI) | – | 0.5† (0.0-0.5) | – | – |
| Estimated difference from MDC (90% CI) | – | – | 0.5 (0.0-1.5) | 0.0 (-0.5-0.0) |
| Half-life (h) | | | | |
| Geometric LS Mean (95% CI) | 29 (22-38) | 38 (29-51) | 37 (28-48) | 75 (57-100) |
| Geometric LS Mean ratio/ PEG400 (90%CI) | – | 1.3 (1.0-1.9) | – | – |
| Geometric LS Mean ratio/ MDC 0.5mg (90% CI) | – | – | 1.0 (0.7-1.3) | 2.0† (1.4-2.7) |

* $AUC_{0-72}$, $AUC_{\infty}$, and $C_{max}$ for the 1 mg group are normalized to the 0.5mg dose
† $p<0.05$

**Figure 1. Mean Serum Dutasteride Concentration-Time Profiles**

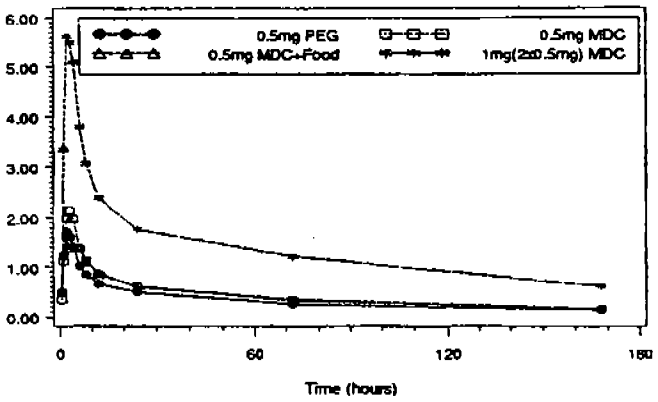



**Figure 2. Individual and Mean Box Plots For $AUC_{0-\infty}$**

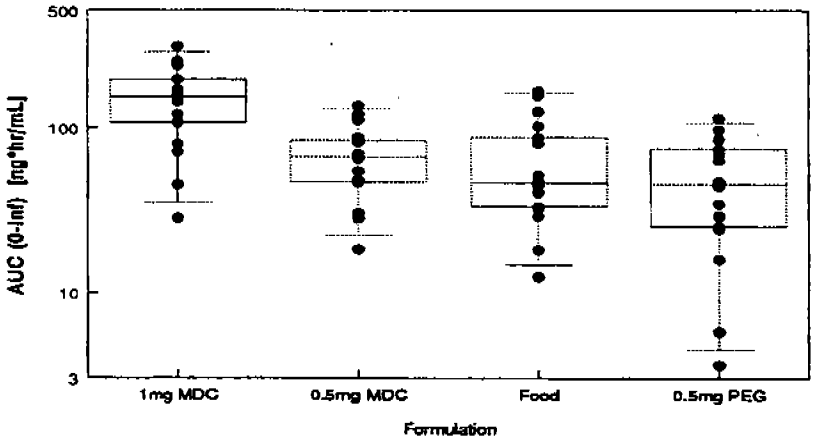



**Figure 3. Individual and Mean Box Plots Fr Camx**

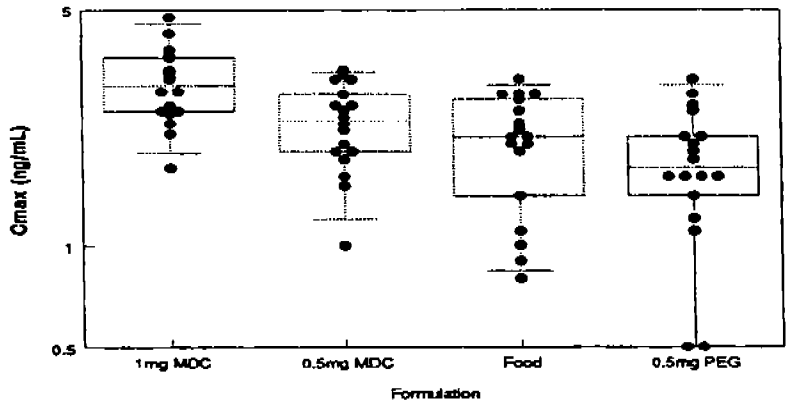


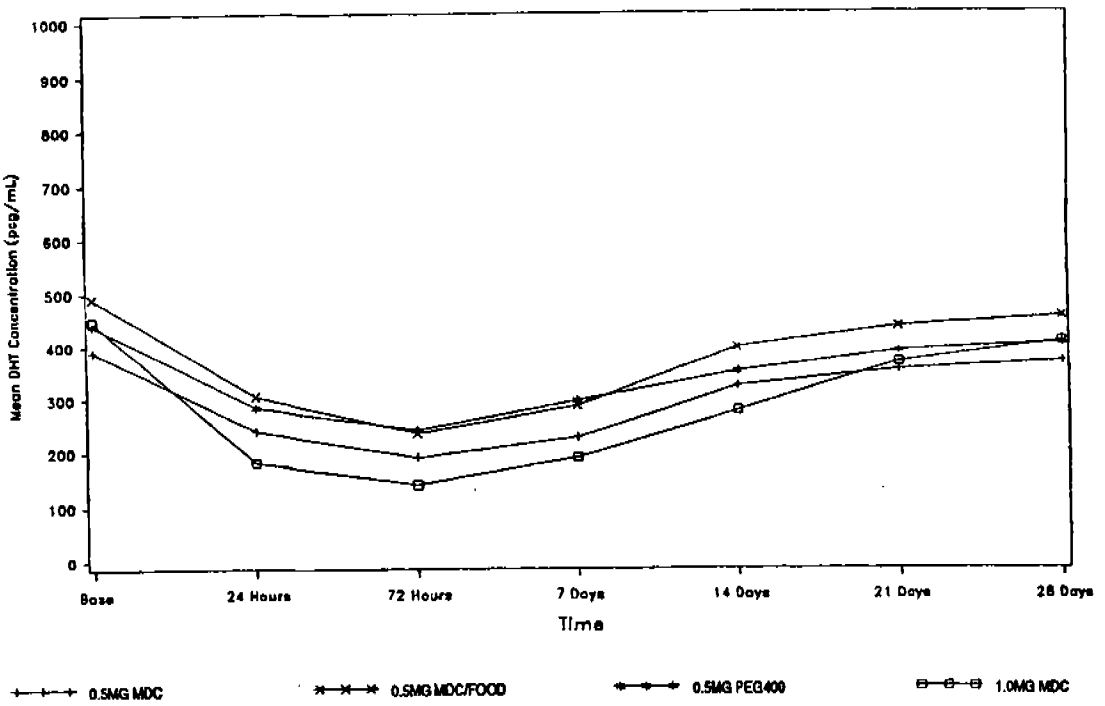
Table 2.

**Maximum Percent Change in Dihydrotestosterone and Testosterone Serum Concentrations from Baseline Values**
(All Subjects Enrolled in Protocol ARIA1004)

| | GI198745 0.5mg PEG400 (N=18) | GI198745 0.5mg MDC (N=18) | GI198745 0.5mg MDC with food (N=18) | GI198745 1.0mg (2x0.5mg) MDC (N=18) |
|---|---|---|---|---|
| DHT<br>Mean (SD)<br>(90%CI)* | -46 (13.6)<br>(-5, 11) | -49 (15.2)<br>NA | -51 (11.8)<br>(-9, 6) | -68 (7.2)†<br>(-25, -12) |
| T<br>Mean (SD)<br>(90%CI)* | 19 (19.2)<br>(-18, 5) | 26 (21.9)<br>NA | 19 (14.6)<br>(-17, 4) | 42 (50.3)<br>(-6, 38) |

Note: DHT= dihydrotestosterone; T= testosterone
*90% CI for the mean difference between 0.5mg MDC and the other treatment groups
†p<0.001 versus 0.5mg MDC group based upon t-tests from a general linear model

Figure 4. Mean DHT Serum Levels



**Formulation Development (Continued):**

**Does *in vitro* capsule cross-linking affect *in vivo* performance?**

There was no effect of capsule cross-linking on *in vivo* performance. This was based on a crossover study with 4-weeks washout period in 22 healthy subjects (study #ARI10018). In this study subjects received either "fresh" non-crossed-linked capsules or cross-linked capsules. Briefly, the study design is as follow:

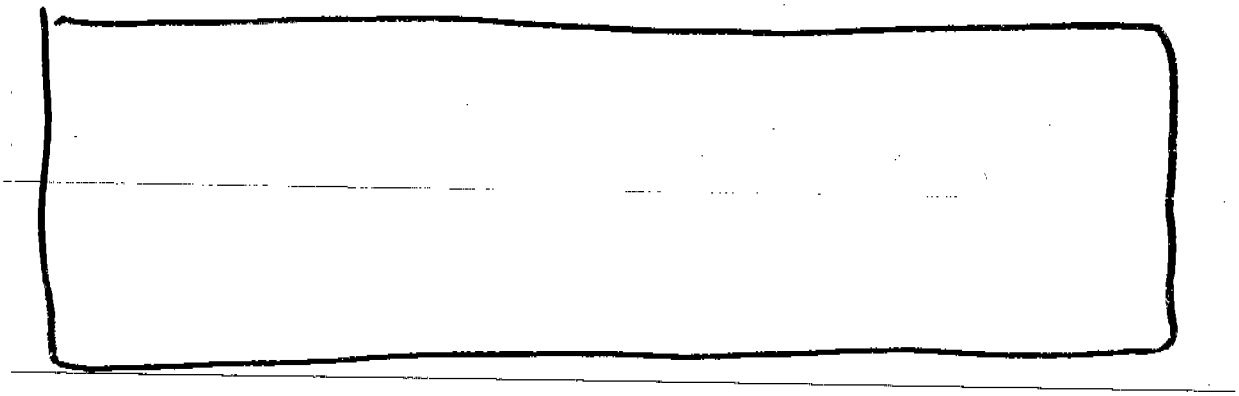
Treatment A (n=22): 0.5 mg fresh non-cross-linked soft gelatin capsule (**reference**)

Treatment B (n=22): 0.5 mg cross-linked soft gelatin capsule (**test**).

The crossed-linked capsules were stored for 17 months at controlled room temperature. In addition, cross-linking of the capsules was verified by the *in-vitro* test as shown **Figure 5 A & B.** .

**Figure 5. *In vitro* Dissolution Profiles for Fresh Non-crossed Linked MDC Soft Gelatin Capsules (A) and Crossed-Linked 17 Months Old Capsules (B).**

**(A)** **(B)**



**Conclusions:**

In terms of 90% CI limits, the all parameters were within 80-125%except for $AUC_{0-\infty}$ which was 79% to 123%. However, overall, it can be concluded that the data show comparable concentration-time profiles and PK parameters for both formulations (**Figure 6 and table 4**). Therefore, cross-linking has no effect on the *in vivo* performance of the tested capsule formulation.

**Figure 6. Mean Serum Dutasteride Concentration-Time Profiles**

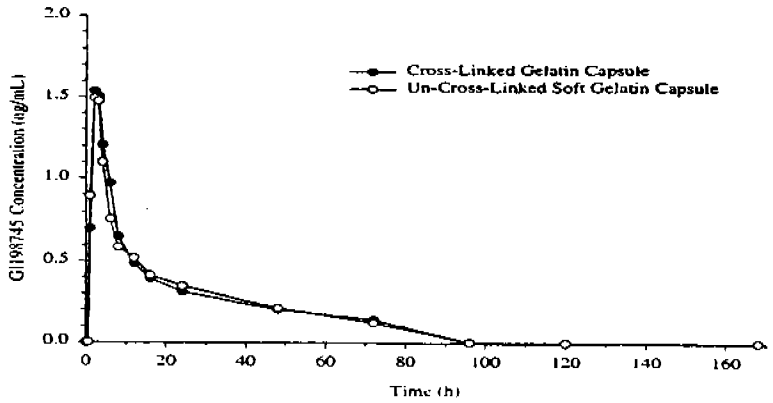



**Table 4. Summary of PK data**

| Parameter | Treatment B GI198745 Cross-Linked Soft Gel Caps | Treatment A GI198745 Non-Cross-Linked Soft Gel Caps | Comparison (Treatment B:A) |
|---|---|---|---|
| $AUC_{24}$ (ng*h/mL) | | | |
| Mean (SD) | 14.41 (5.36) | 15.68 (9.10) | |
| Geo. LS Mean | 13.34 | 13.20 | |
| Geo. LS mean ratio | | | 1.01 |
| 90% CI | | | (0.90, 1.14) |
| $AUC_{72}$ (ng*h/mL) | | | |
| Mean (SD) | 26.21 (14.07) | 28.80 (20.16) | |
| Geo. LS mean | 21.11 | 21.32 | |
| Geo. LS mean ratio | | | 0.99 |
| 90% CI | | | (0.85, 1.15) |
| $AUC_{last}$ (ng*h/mL) | | | |
| Mean (SD) | 29.51 (22.84) | 34.05 (33.67) | |
| Geo. LS mean | 22.03 | 21.70 | |
| Geo. LS mean ratio | | | 1.02 |
| 90% CI | | | (0.84, 1.23) |
| $AUC_{\infty}$ (ng*h/mL) | | | |
| Mean (SD) | 41.03 (29.48) | 46.27 (43.10) | |
| Geo. LS mean | 28.94 | 29.34 | |
| Geo. LS mean ratio | | | 0.99 |
| 90% CI | | | (0.79, 1.23) |
| $C_{max}$ (ng/mL) | | | |
| Mean (SD) | 1.66 (0.45) | 1.82 (0.85) | |
| Geo. LS mean | 1.59 | 1.62 | |
| Geo. LS mean ratio | | | 0.98 |
| 90% CI | | | (0.88, 1.10) |

**What are the proposed in vitro Dissolution Method and Specifications:**

As discussed above, due to the problems with cross-linking of the capsules, the sponsor had conducted several experiments after the consultation with the Agency prior to the NDA submission. Some of the *in vitro* data and proposed method and specifications were submitted to the Agency under IND # [redacted] on January 13, 1999 (serial # 104). An update on the method and specification were submitted to the Agency on March 1, 2001. The following is the summary of the overall and final proposal for the new two-tiered dissolution methods:

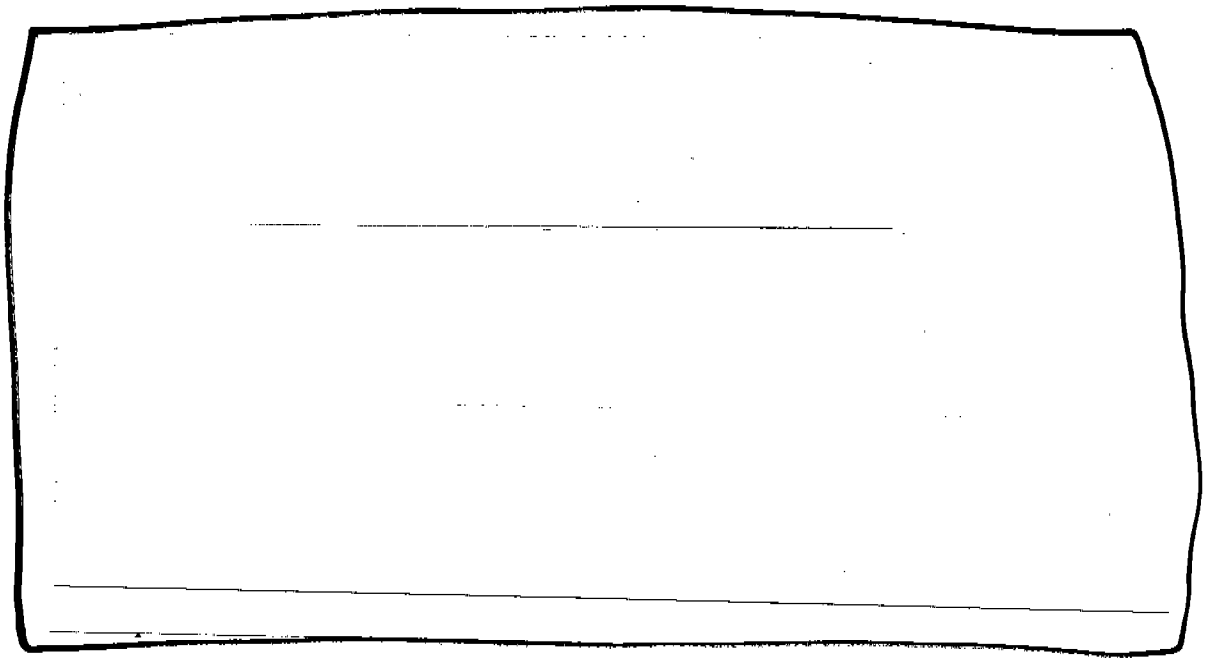


**Table 5 and Figure 5 A & B** (see above) show individual dissolution data using the above proposed method. Based on these data it can be concluded that at 45 minutes [redacted] was dissolved for all tested crossed linked and non-crossed linked capsules. Therefore, the specification proposed by the sponsor is acceptable.

**Conclusions:**

1 The proposed method is granted.
2 The proposed specification is acceptable

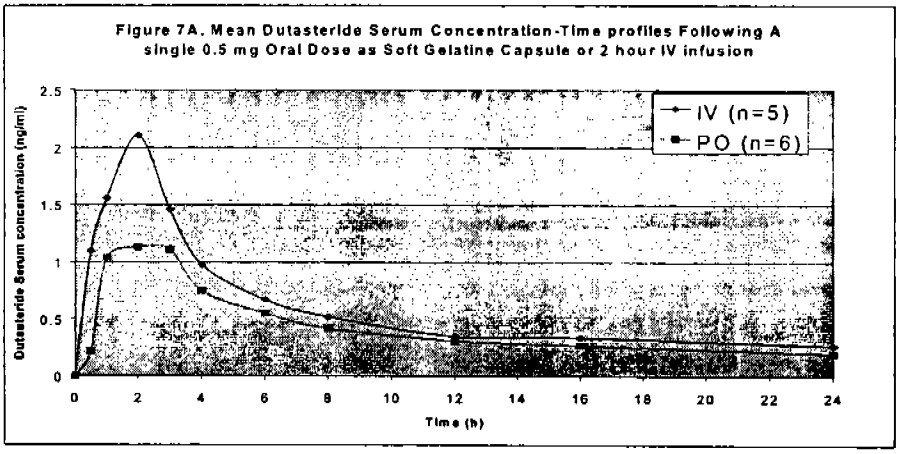
**1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.**

**What is the absolute Bioavailability of Dutasteride ?**

The absolute bioavailability of Dutasteride is 59% (ranged from [redacted]). This was based on a crossover study with 4-weeks washout period following 0.5 mg soft gelatin capsule or 0.5 mg IV infusion over 2 hours (study # ARI10015). The major drawback of this study is that the number of subjects is rather too small (n=5 for IV and n=6 for capsule). The mean data are shown in **Figure 7A & B and Table 6.**

**Conclusions:**

1. There is a wide variability in the data. The %CV is >50% (**Table 6**).
2. The absolute bioavailability of dutasteride is approximately 60% with a very wide range in the data [redacted]
3. The drug is virtually undetectable at 48 hours after administration (**Figure 7 B**)
4. The major drawback of this study is the lack of adequate power due the small number of subjects.
5. This study is considered inadequate, but sufficient as a pilot study.



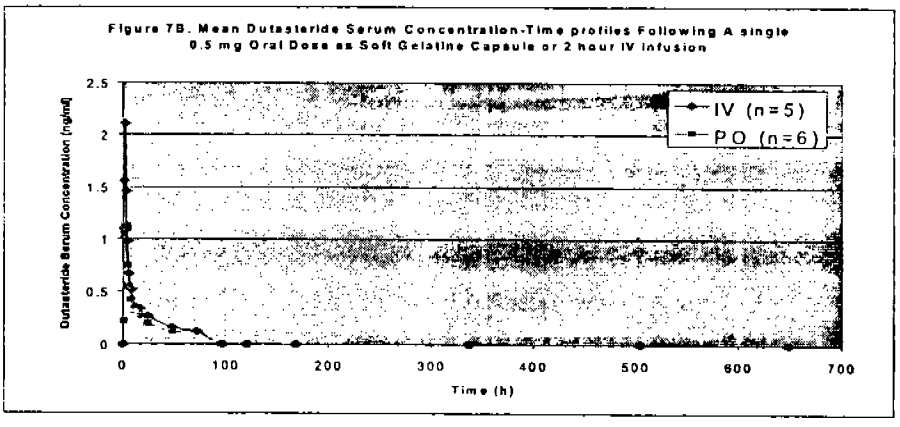



**Table 6. Mean PK Data of Dutasteride After Single Doses of 0.5 mg as Soft Gelatin Capsule and 2 hours IV Infusion.**

| Subjects | Treatments | Cmax (ng/ml) | $AUC_{0\text{-last}}$ (ng.h/ml) | $AUC_{0\text{-}\infty}$ (ng.h/ml) | F (%) ($AUC_{0\text{-}\infty}$) | 90% CI ($AUC_{0\text{-}\infty}$) |
|---|---|---|---|---|---|---|
| 1 | IV | 1.4 | 8.7 | 10.1 | 68 | |
| | P | 1.1 | 5.9 | 6.9 | | |
| 2* | IV | - | - | - | - | - |
| | PO | 2.5 | 69 | 92.3 | | |
| 3 | IV | 2.9 | 36.8 | 45.5 | 94 | |
| | PO | 2.1 | 35.4 | 42.9 | | |
| 4 | IV | 2.9 | 77.8 | 86.2 | 56 | |
| | PO | 1.5 | 42.4 | 48.1 | | |
| 5 | IV | 1.5 | 5.0 | 5.6 | 40 | |
| | PO | 0.6 | 1.9 | 2.2 | | |
| 6 | IV | 2.0 | 11.1 | 13.2 | 64 | |
| | PO | 1.1 | 7.1 | 8.5 | | |
| | | | | | | |
| **Mean** | IV | 2.11 | 27.88 | 32.10 | | 0.47,0.75 |
| | PO | 1.27 | 18.53 | 21.70 | 64.4 or 59** | |
| **SD** | IV | 0.73 | 30.58 | 34.09 | | |
| | PO | 0.54 | 18.83 | 21.89 | 19.7 | |
| **%CV** | IV | 35 | 110 | 106 | | |
| | PO | 42 | 102 | 101 | 30.6 | |

***Subject excluded from the analysis and summary statistics**
**** 59% based on geometric means**

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- **Is There Any Effect of Food on Dutasteride Absorption and Bioavailability?**

There was no effect of food on dutasteride absorption and bioavailability. This study was discussed earlier under Formulation Development Section (study # ARIA1004).

## II. Clinical Pharmacology

**What is the Degree of the Plasma Protein Binding of Dutasteride?**

Base on *in vitro* study (UDM/94/057) the plasma protein binding in human plasma is greater than 99.5%. This data are based on spiked dutasteride with whole blood at concentration ranging from approximately [redacted]. The binding was independent of dutasteride concentration.

**What is the PK in Relationship to Dose? (i.e., is there dose proportionality?)**

Study # ARIA1003 was double blind, placebo controlled in 8 male subjects with BPH at each dose level of 0.1, 0.5, 2.5, and 5 mg daily up to 28 days. In one arm of the study (n=8) a loading dose (LD) of 40 mg was also administered followed by a maintenance daily dose of 2.5 mg. Moreover, an additional arm (n=8) was for finasteride (PROSCAR), a marketed 5-alpha-reductase inhibitor, which was administered at a dose of 5 mg daily for 28 days. This serves as an active control. Blood samples were collected at appropriate intervals for PK and PD (DHT level) determination.

From this study, the $C_{max}$ and AUC appear to increase proportionally over a dose range of 0.1 to 5 mg administered as single daily doses up to 28 days (**Figures 8 and 9, and Table 6B**). In addition, drug accumulates in the body following multiple administration as shown in **Figures 10 and 11.** After multiple administration, the serum concentration on day 28 is about 7 to 16 folds higher than after a single dose administration (Day 1).

**Table 6B.**

**Summary of Pharmacokinetic Parameters: Mean (SD)**
(Subjects Evaluated for Pharmacokinetics in Protocol ARIA1003)

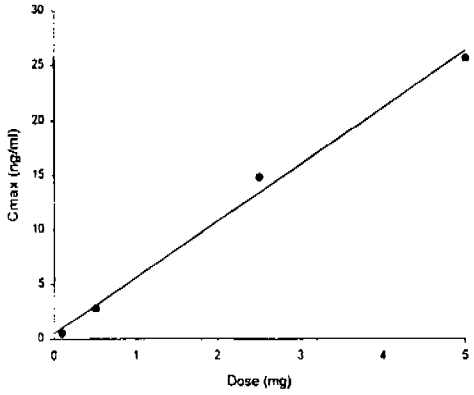
| GI198745 Dose | $C_{max}$ (ng/mL) | DN-$C_{max}$ (ng/mL) | $AUC_{(0-24)}$ (ng*h/mL) | DN-$AUC_{(0-24)}$ (ng*h/mL) |
|---|---|---|---|---|
| 0.1mg, Day 1 (N=8) | 0.5 (0.24) | 4.8 (2.36) | 1.6 (1.20) | 15.7 (12.04) |
| 0.1mg, Day 28 (N=8) | 2.7 (0.83) | 26.5 (8.27) | 49.3 (16.87) | 492.7 (168.70) |
| 0.5mg, Day 1 (N=8) | 2.8 (0.81) | 5.6 (1.63) | 30.1 (12.17) | 60.1 (24.34) |
| 0.5mg, Day 28 (N=8) | 23.6 (5.97) | 47.1 (11.94) | 480.6 (130.81) | 961.1 (261.61) |
| 2.5mg, Day 1 (N=8) | 14.8 (5.01) | 5.9 (2.00) | 158.0 (47.95) | 63.2 (19.18) |
| 2.5mg, Day 28 (N=8) | 118.5 (32.09) | 47.4 (12.84) | 2500.3 (680.74) | 1000.1 (272.30) |
| 40mg LD+2.5mg, Day 1 (N=8) | 158.5 (73.40) | 3.7 (1.73) | 1819.5 (793.11) | 42.8 (18.66) |
| 40mg LD+2.5mg, Day 28 (N=7) | 138.3 (26.44) | 55.3 (10.58) | 3052.6 (641.55) | 1221.1 (256.62) |
| 5mg, Day 1 (N=9) | 25.6 (13.00) | 5.1 (2.60) | 286.3 (129.09) | 57.3 (25.82) |
| 5mg, Day 28 (N=8) | 203.2 (87.35) | 40.6 (17.47) | 4311.1 (1897.91) | 862.2 (379.58) |

Note: DN = dose normalized to a 1mg dose.
Note: 40mg LD +2.5mg = 40mg loading dose on Day 1 followed by 2.5mg daily on Days 2-28.

**Figure 8 A & B. Relationship Between Dutasteride Dose and Cmax on Day 1 (A) and on Day 28 (B) (study # ARIA1003)**

**Day 1 (Single dose)**

**(A)**




**Day 28 (Multiple dose)**

**(B)**

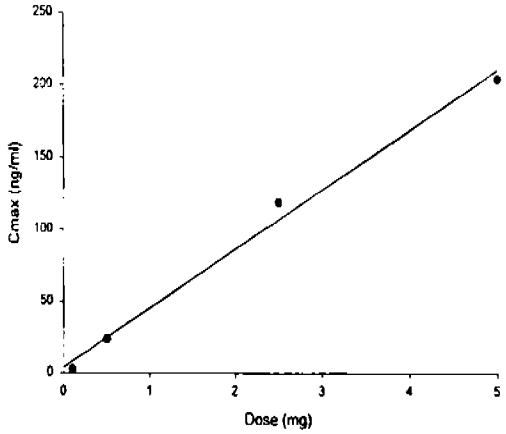
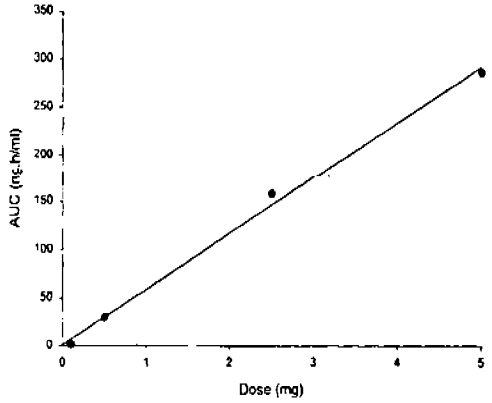



**Figure 9 A & B . Relationship Between Dutasteride Dose and AUC on Day 1 (A) and on Day 28 (B) (study # ARIA1003)**

**Day 1 (single dose)**

**(A)**




**Day 28 (Multiple dose)**

**(B)**

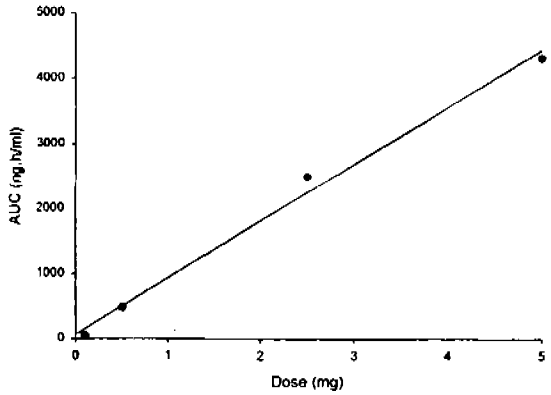


**Figure 10. Relationship Between Dutasteride Dose and AUC on Day 1 (single dose) and Day 28 (multiple dose) (study # ARIA1003)**

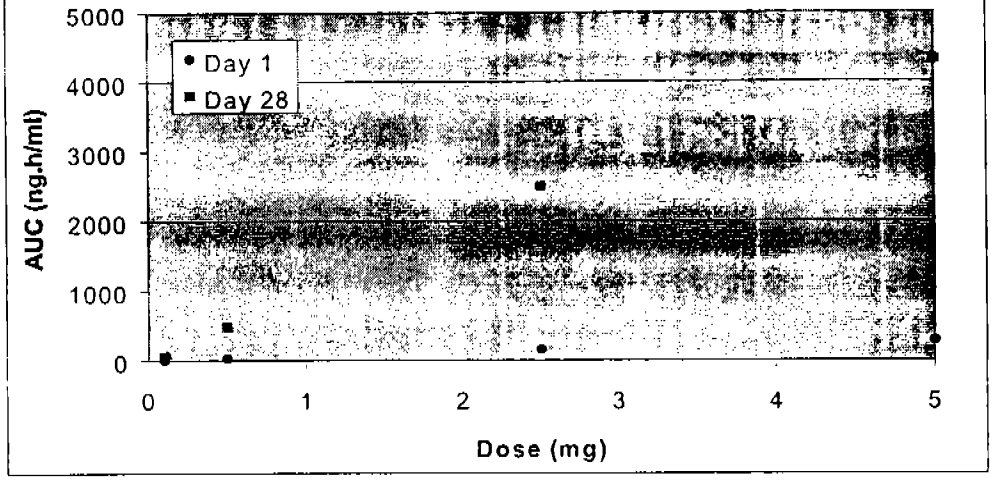
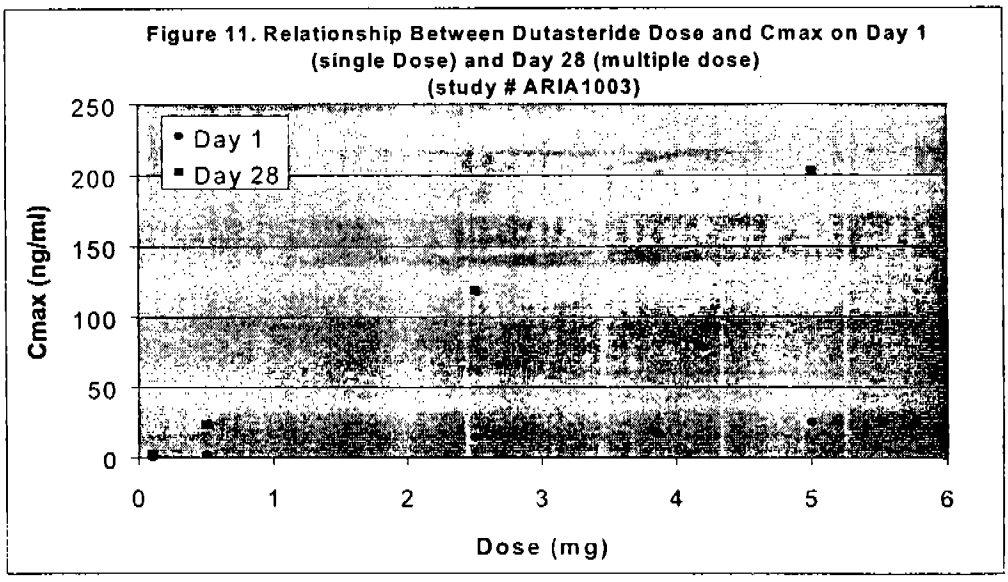


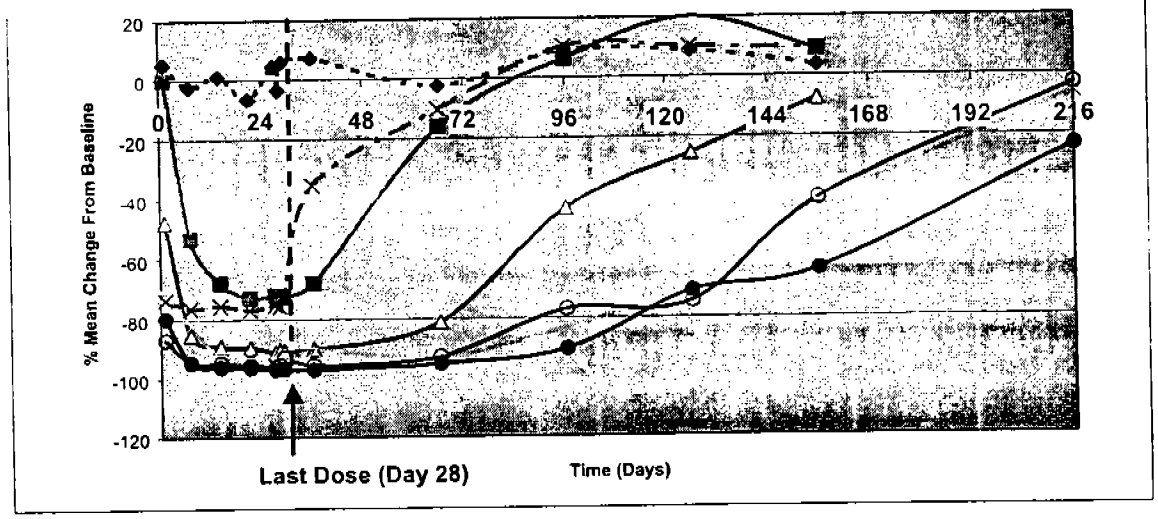

**Figure 11. Relationship Between Dutasteride Dose and Cmax on Day 1 (single Dose) and Day 28 (multiple dose) (study # ARIA1003)**



In terms of pharmacodynamic effect as exemplified by DHT inhibition, the following observations can be made from this study (**Figures 12 A&B**)

- There is a dose-dependent inhibition in DHT. The maximum observed inhibition on day 28 was approximately 90% which occurred after 0.5 mg dose.
- There was no difference in the degree of DHT inhibition with the use of the loading dose. However, there was a quicker action with the loading dose.
- Finasteride 5 mg dose showed more rapid recovery from inhibition compared to dutasteride at all tested doses in this study.

**Fugure 12A. Percent Changes From Baseline in DHT Concentration as a Function of Dutasteride Dose (Study # ARIA 1003)**

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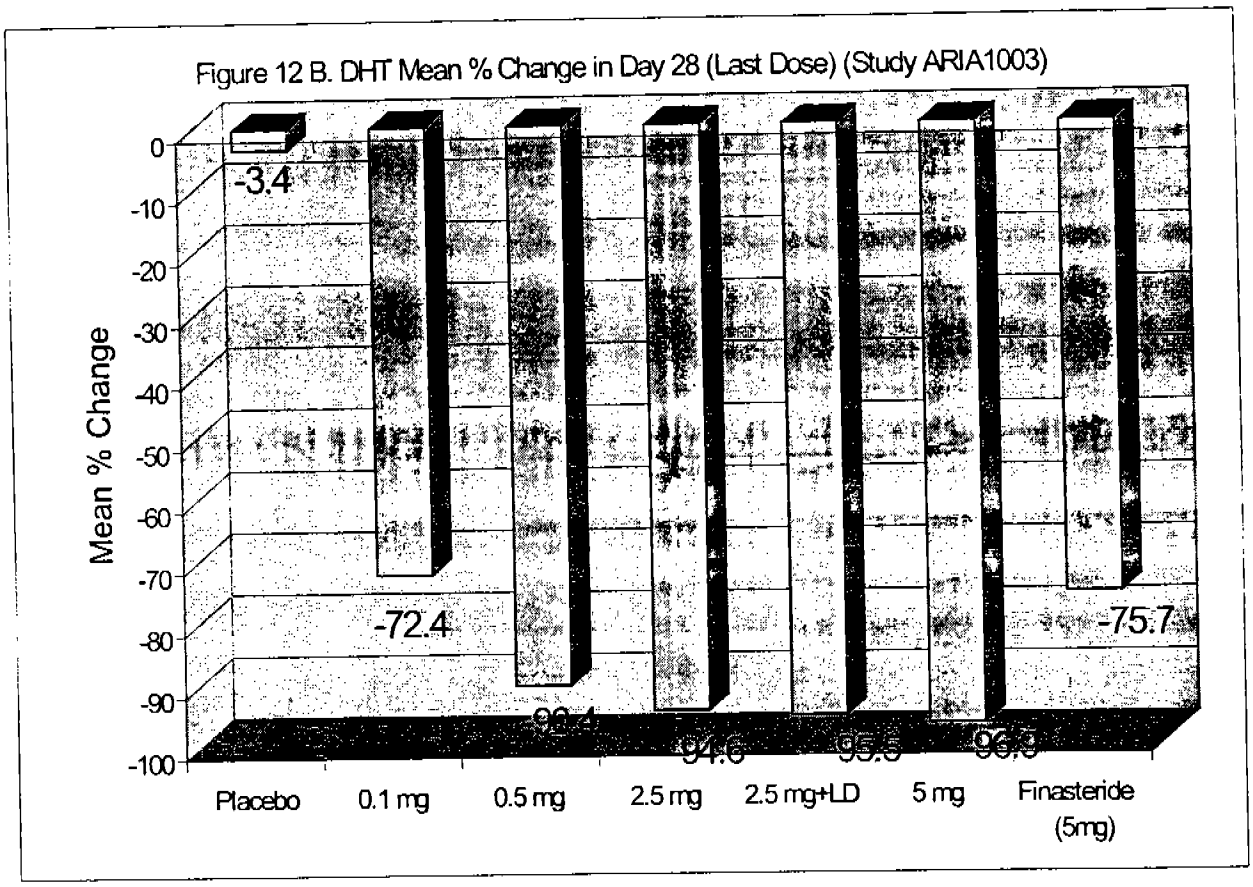


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**What is the Elimination Pathways of Dutasteride (Metabolism and Excretion)?**

**a) *In vitro* metabolism:**

CYP 3A4 appears to be responsible for approximately 4% of dutasteride metabolism. No other tested isozymes were found to be associated with the metabolism of dutasteride. The *in vitro* metabolism experiment was conducted using cDNA expressed CYP 450 microsomes and hepatocytes (study # RD1999/00424/01). Briefly, pooled human liver microsomes containing 2 mg/ml proteins were incubated with 0.2 or 2 µg/ml of $^{14}C$-dutasteride for 1 hour. cDNA-expressed CYP 1A2, 2D6, 2C9, 2C19, and 3A4 were used in the incubation. [redacted]coupled with UV and radiochemical detection was used to the determination of dutasteride concentration and its possible metabolites.

**Conclusions:**

1. It appears that dutasteride undergoes little or no *in vitro* metabolism. This is in sharp contrast to the data from *in vivo* human studies where the drug was found to be extensively metabolized (se below). Therefore, this raises the questions on the validity of the *in vitro* study as well as human metabolism study. This may be due to high concentrations used in the *in vitro* study (200 ng/ml and 2000 ng/ml) compared to the expected steady state level in human (40 ng/ml). Unless proven otherwise, in terms of metabolism, no *in vitro*/*in vivo* correlation should be expected for this particular drug.

2. The drug is not metabolized by any of the known isozymes, except CYP 3A4 which appears to be responsible for only 4% or less of the metabolism of the drugs. However, since high concentrations were used *in vitro* experiment, the conclusions are questionable.

**b) *In vivo* Metabolism:**

By sharp contrast to *in vitro* data, *in vivo* study has clearly demonstrated that the drug is extensively metabolized in humans to several metabolites/components.

Study ARIA10012 is, in part, an extension of the semen (spermatogenesis) study # ARIA1009 (see below). Briefly, 8 and 2 healthy subjects were on 0.5 mg or 5 mg daily doses of dutasteride for at least 6 months, respectively. Urine and feces were collected in two separate occasions. Each occasion included 3 consecutive days with three 24-hour collection intervals. In addition, daily trough serum concentrations were determined to ensure steady-state concentrations. The concentrations of dutasteride and its metabolite, 4-hydoxy-dutasteride in urine, feces, and serum were determined by [redacted] and LC/MS/MS techniques. The proposed metabolic pathway is shown in **Figure 13A**. The data are summarized in **Table 7 A** and detailed in **Tables B-D**. Individual subject dutasteride serum concentration at steady-state is shown in **Figure 13B**.

**Figure 13A. Proposed Metabolism of Dutasteride in Animals and Humans**

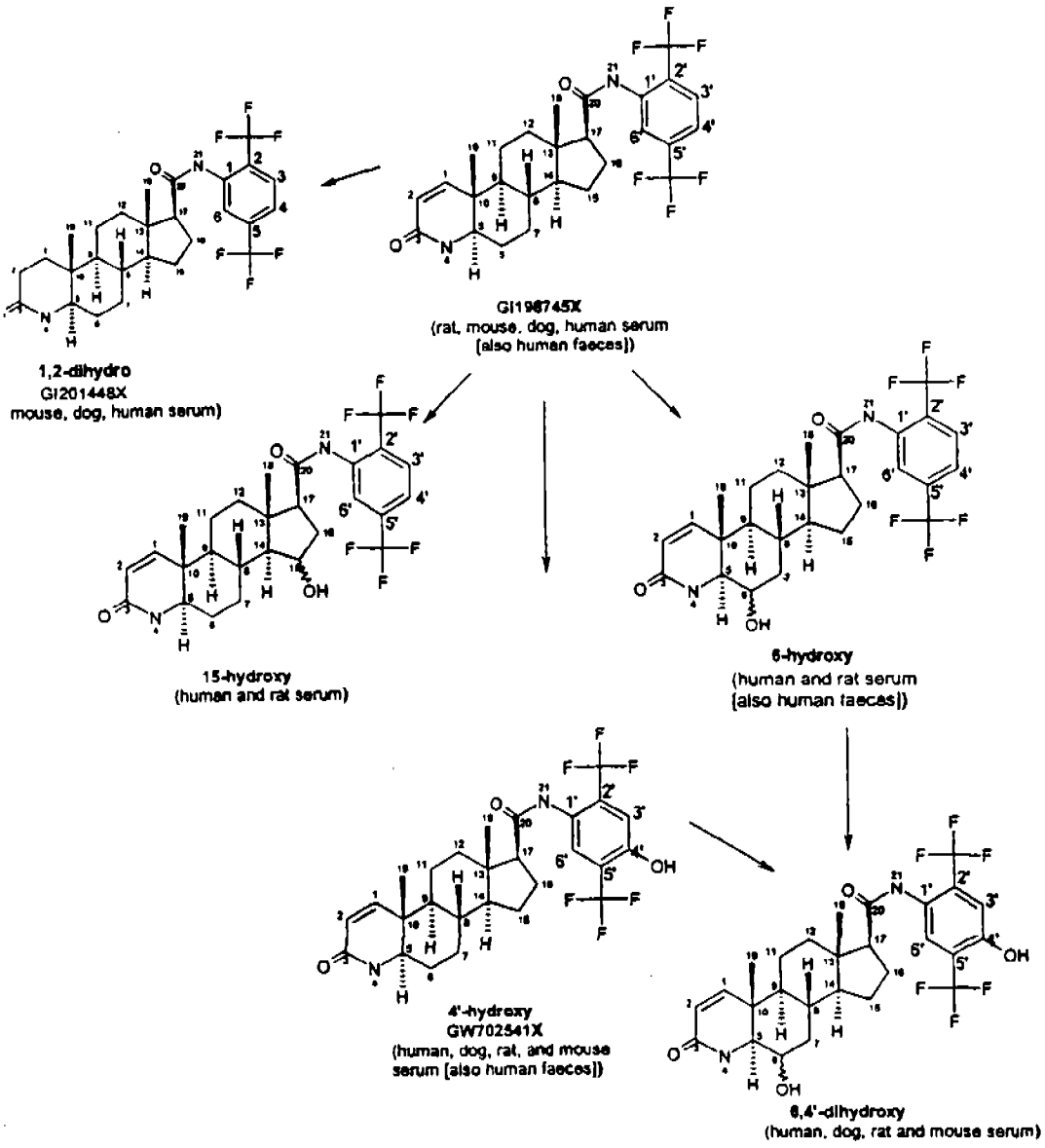


**Table 7A. Approximated Summary Data for Dutasteride Metabolism**

| Matrices (Fluids) | Dutasteride | 4-hydroxydutasteide | % Dose Recovered |
|---|---|---|---|
| Serum (n=8) | 40 ng/ml<br>(16 ng/ml-78 ng/ml) | 10 ng/ml<br>(2 ng/ml-30 ng/ml) | - |
| Urine (n=8) | <0.1 ng/ml | - | <0.06%<br>(0%-0.06%) |
| Feces (n=8) | 80 (µg)<br>(15 µg- µg 230) | - | 5%<br>(1%-15%) |
| **Feces (Parent + all Metabolites)** | | | **45%<br>(6%-97%)** |
| **Note: 4-hydroxydutasteride concentration was not reported in urine or feces. The total is for parent and all dutasteride related materials.** | | | |

**Table 7B. Summary of Period 1 as a mean Trough on Day 1, Day 2, and Day 3 for the Dutasteride and 4-Hydroxydutasteride in Serum and Total Amount Excreted in Urine and Feces.**

| Subjects | Parent | | | | | 4-Hydroxydutasteride | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Serum | Urine | | Feces | | Serum | Urine | | Feces | |
| | Conc (ng/ml) | Conc (µg) | % | Conc. (µg) | % | Conc. (ng/ml) | Conc. (µg) | % | Conc. (µg) | % |
| 1 | 46.6 | 738 | 0.05 | 54.8 | 3.7 | 3.3 | - | - | - | - |
| 2 | 69.8 | 876 | 0.06 | 230 | 15.4 | 3.8 | - | - | - | - |
| 3 | 32.8 | 0 | 0 | 100 | 6.7 | 5.8 | - | - | - | - |
| 4 | 25.1 | 0 | 0 | 106 | 7.1 | 17.6 | - | - | - | - |
| 5 | 31.5 | 0 | 0 | 39.9 | 2.7 | 3.8 | - | - | - | - |
| 6 | 30.5 | 0 | 0 | 73.1 | 4.9 | 22.0 | - | - | - | - |
| 7 | 39.1 | 0 | 0 | 49.2 | 3.3 | 6.1 | - | - | - | - |
| 8 | 48.2 | 737 | 0.05 | 74.7 | 5.0 | 9.8 | - | - | - | - |
| | | | | | | | | | | |
| **Mean** | **40.4** | **293.7** | **0.02** | **91.0** | **6.1** | **9.0** | - | - | - | - |
| SD | 14.3 | 407.6 | 0.03 | 60.8 | 4.1 | 7.0 | - | - | - | - |
| %CV | 35.3 | 139 | 138.7 | 66.8 | 67.1 | 78.2 | - | - | - | - |
| Min | [redacted] | | | | | | | | | |
| Max | | | | | | | | | | |

**(-) 4-hydroxydutasteride concentration was not reported in urine or feces.**
**Mean urine volume was 5984 ml ± 1628 ml (ranged fro[redacted]**

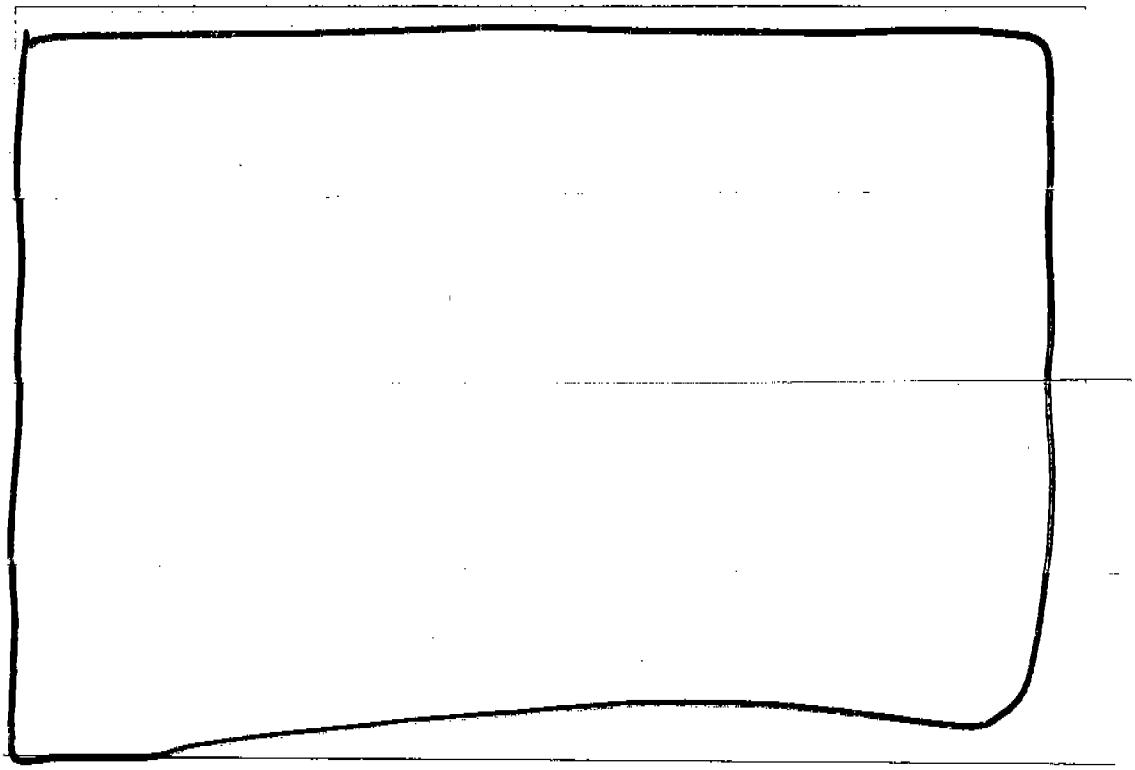
**Table 7C. Summary of Period 2 as a mean Trough on Day 1, Day 2, and Day 3 for Dutasteride and 4-Hydroxydutasteride in serum and Total Amount Excreted in Urine and feces**

| Subjects | Parent | | | | | 4-Hydroxydutasteride | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Serum | Urine | | Feces | | Serum | Urine | | Feces | |
| | Conc (ng/ml) | Conc (µg) | % | Conc. (µg) | % | Conc. (ng/ml) | Conc. (µg) | % | Conc. (µg) | % |
| 1 | 47.0 | 0 | 0 | 91.2 | 6.1 | 3.2 | - | - | - | - |
| 2 | 68.1 | 765 | 0.05 | 140.0 | 9.3 | 4.5 | - | - | - | - |
| 3 | 34.8 | 0 | 0 | 69.9 | 4.7 | 5.5 | - | - | - | - |
| 4 | 26.8 | 0 | 0 | 56.9 | 3.8 | 12.6 | - | - | - | - |
| 5 | 35.4 | 0 | 0 | 14.9 | 1.0 | 3.0 | - | - | - | - |
| 6 | 32.3 | 440 | 0.03 | 107.0 | 7.1 | 9.0 | - | - | - | - |
| 7 | 27.5 | 880 | 0.06 | 28.9 | 1.9 | 6.8 | - | - | - | - |
| 8 | 34.6 | 834 | 0.06 | 53.1 | 3.5 | 9.4 | - | - | - | - |
| | | | | | | | - | - | - | - |
| **Mean** | **38.3** | **364.9** | **0.02** | **70.2** | **4.7** | **6.75** | - | - | - | - |
| SD | 13.5 | 411.2 | 0.03 | 41.2 | 2.7 | 3.3 | - | - | - | - |
| %CV | 35.3 | 113 | 112.7 | 58.7 | 58.7 | 49.9 | - | - | - | - |
| Min | [redacted] | | | | | | | | | |
| Max | | | | | | | | | | |

**(-) 4-hydroxydutasteride concentration was not reported in urine or feces**
**Mean urine volume was 4577 ml ± 1547 ml (ranged from [redacted]**

**Table D. Combined Urine and Feces (parent and all dutasteride related materials) in period 1 and 2**

| Subjects | Period 1 | | Period 2 | |
|---|---|---|---|---|
| | Concentration (µg) | % | Concentration (µg) | % |
| 1 | 473 | 31.5 | 592 | 39.5 |
| 2 | 1048 | 69.8 | 645 | 43.0 |
| 3 | 687 | 45.8 | 686 | 45.7 |
| 4 | 1458 | 97.2 | 759 | 50.6 |
| 5 | 191 | 12.7 | 81 | 5.4 |
| 6 | 881 | 58.7 | 598 | 39.9 |
| 7 | 266 | 17.7 | 176 | 11.8 |
| 8 | 655 | 43.7 | 625 | 41.7 |
| | | | | |
| **Mean** | **707.4** | **47.1** | **520.3** | **34.7** |
| SD | 419.0 | 27.9 | 248.9 | 16.6 |
| %CV | 59.2 | 59.3 | 81.0 | 47.8 |
| Min | [redacted] | | | |
| Max | | | | |



**Comments:**

The following observations can be made from this study:

1. The drug is extensively metabolized in humans.

2. The average serum concentration of unchanged dutasteride was approximately 40 ng/ml compared the average concentration of 10 ng/ml for the major metabolite 4-hydroxydutasteride.

3. Other minor metabolites were found in human serum such as 6- hydroxydutasteride and di-hydroxylated metabolites. The activity of these metabolites is unknown.

4. In terms of urine, virtually nothing was detected related to dutasteride (i.e., 0 % to 0.06 % of the dose). Therefore, based on these data it can be concluded that bile is the major route of elimination of dutasteride.

5. In feces, there were about eleven $^{19}F$ peaks observed using $^{19}F$-NMR techniques. The most abundant peaks are related to the parent drug and its major metabolite, 4-hydroxydutasteride. The unchanged drug excreted in feces ranged from approximately

1% to 15% of the dose with an average of approximately 5%. In terms of all dutasteride's related materials recovered in feces the average was approximately 45% of the dose ranging from approximately 6 % to 97%.

6. In addition to 4-hydroxymetabolite, three major and at least six minor metabolites have been detected in feces. No quantitative data was reported for 4-hydroxydutasteride in urine or feces. Instead, urine and feces data were reported as pooled metabolites (referred to as all dutasteride related metabolites).

7. The structural identity of most of the metabolites and the metabolic pathway were not reported by the sponsor.

**Conclusions:**

1. Based on this study, the total percent of dose recovered in urine and feces was about 45% including the parent and all metabolites. Therefore, there is approximately 55% of the dose that is unaccountable for.
2. Based on in vitro study, the drug undergoes no or little metabolism. Therefore, there appear to be a lack of correlation between *in vitro* and *in vivo* metabolic profiles. However, this may be due to the high concentrations (200 and 2000 ng/ml) used *in vitro* study.
3. The activity of the metabolites and the metabolic pathways are not well characterized.
4. The data from this study is considered to be inconclusive and the study is deficient and inadequate.

**What is the Active Moiety?**

At the time of review, the activity of the metabolites is unknown. According to the sponsor, there is an on-going study to characterize the activity of the metabolites.

**What is the Pharmacokinetics of Dutasteride in Special Populations?**

**A) Hepatic Disease**

The PK of dutasteride was not conducted in this population.

**B) Renal Disease**

The PK of dutasteride was not conducted in this population.

**C) Gender:**

Not applicable.

**Conclusions:**

1. AUC appears to increase with age, but not Cmax.
2. There is clear relationship between half-life and age.

**Figure 13B. Mean Dutasteride Serum Concentration-Time Profiles**

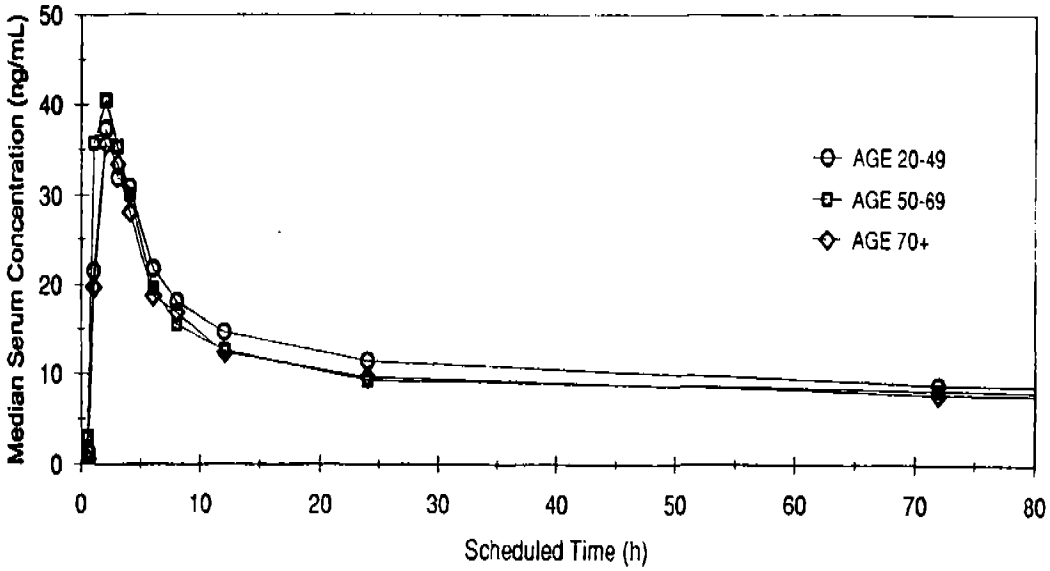



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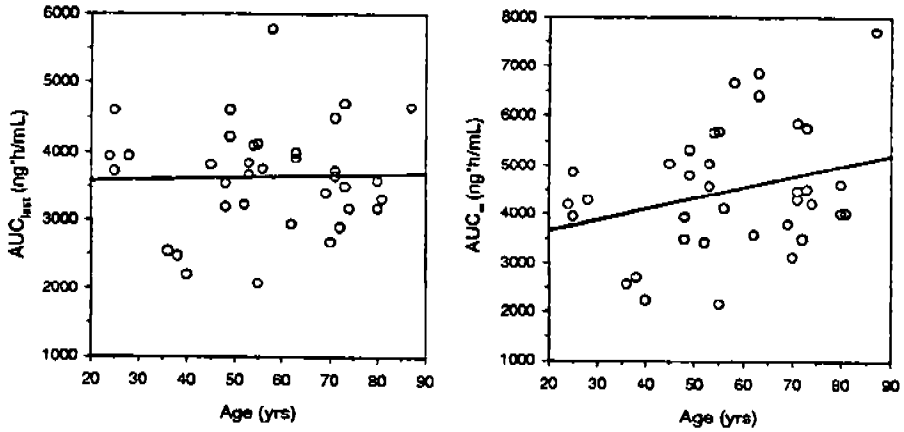
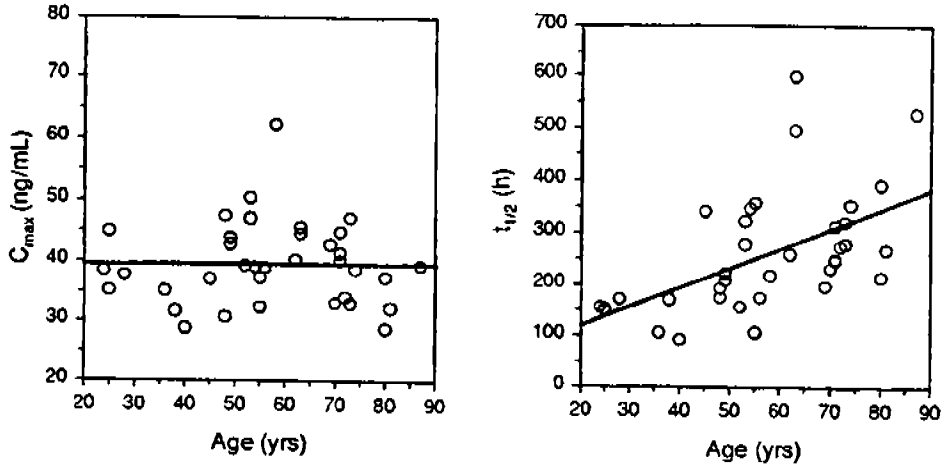
**Figure 14. Serum $AUC_{0\text{-last}}$ ands $AUC_{0\text{-}\infty}$ for Dutasteride Relative to Age**




Note: Linear regression analysis: $AUC_{last}$: Y = 1.62(AGE) + 3549.30; $r^2$ = 0.001; p = 0.8355
$AUC_{\infty}$: Y = 22.20(AGE) + 3212.00; $r^2$ = 0.087; p = 0.0804

**Figure 15. Serum Cmax and Half Life Values for Dutasteride Relative to Age**




Note: Linear regression analysis: $C_{max}$: Y = 0.001(AGE) + 39.38; $r^2$ = 0.001; p = 0.9873
$t_{1/2}$: Y = 3.76(AGE) + 43.89; $r^2$ = 0.300; p = 0.0005

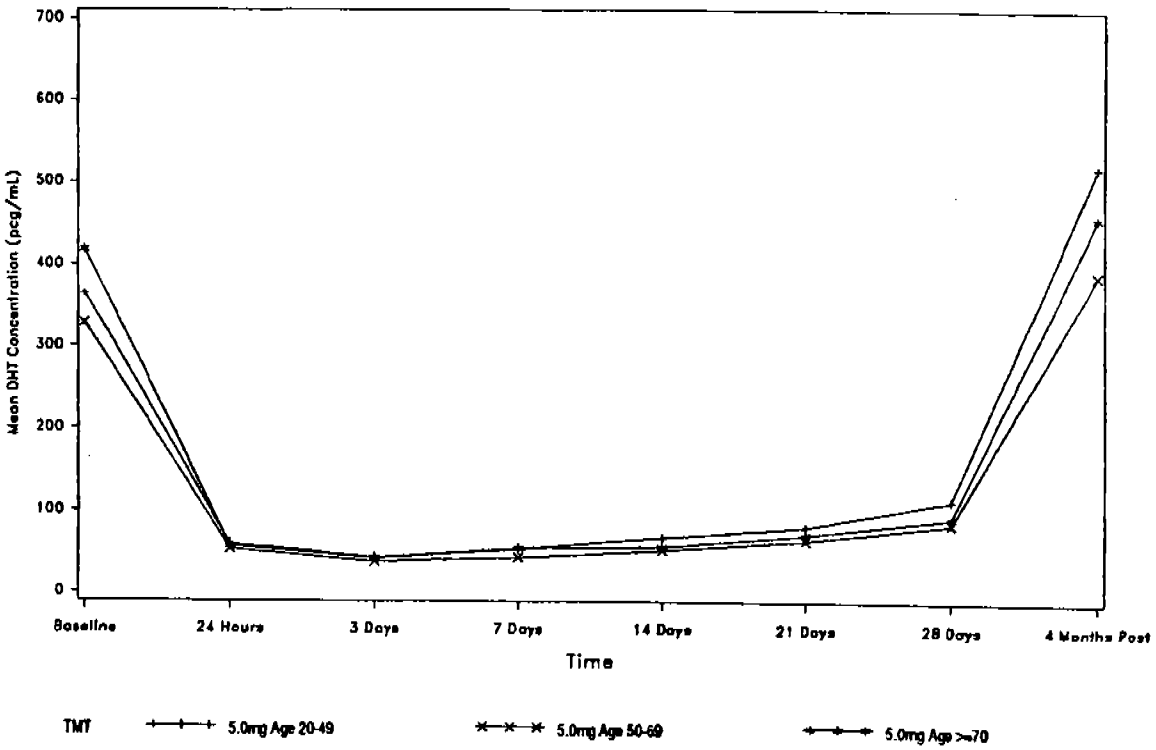
Table 8.

**Noncompartmental Pharmacokinetic Parameters by Age**
**Geometric LS Means (95% CI)**

| Dosing Group | $AUC_{last}$ (ng*h/mL) | $AUC_{\infty}$ (ng*h/mL) | $C_{max}$ (ng/mL) | $t_{1/2}$ (h) | $t_{max}$[a] (h) |
|---|---|---|---|---|---|
| Young (n=12) (20-49 Years) | 3472.22 (3041.47, 3963.97) | 3808.95 (3208.25, 4522.14) | 37.27 (33.96, 40.89) | 167.91 (134.78, 209.19) | 2.01 (2.00 - 3.00) |
| Middle (n=12) (50-69 Years) | 3638.08 (3186.76, 4153.33) | 4592.86 (3868.52, 5452.82) | 42.64 (38.86, 46.79) | 261.62 (210.00, 325.94) | 2.00 (1.05 - 2.00) |
| Elderly (n=12) (70+ Years) | 3571.49 (3128.42, 4077.30) | 4532.78 (3817.92, 5381.49) | 37.04 (33.76, 40.64) | 295.94 (237.54, 368.70) | 2.01 (2.00 - 3.00) |

[a] $t_{max}$ statistics are median (95% CI) values determined nonparametrically

Figure 16. Mean DHT Serum Concentration-Time Profiles



**What Drugs Could Potentially Interact with Dutasteride?**

**Is there any potential drug-drug interactions?**

**i) Is There Any Effect of Dutasteride on Other Drugs**

**A) *In vitro* drug-drug interaction**

**Metabolism Based Interactions:** Based on in vitro study (#97/AVT/0004) dutasteride had no inhibitory effect on CYP-2C9, 2C19, 2D6, or 3A4 isozymes in human microsomes at dutasteride concentration of 1.9 μM (~1000 ng/ml). Since this concentration is about 25-fold higher than the anticipated clinical concentration, inhibition of the major human hepatic CYP P450 isozymes by dutasteride is unlikely.

**Displacement Based Interactions:** Dutasteride did not displace other highly bound drugs such as warfarin, diazepam, and phenytoin. This was based on *in vitro* study (#96AVT0006) using $^{14}C$ labeled warfarin (2-20 μg/ml), diazepam (0.5-2 μg/ml), or phenytoin (10-20 μg/ml). The drugs were incubated in human plasma proteins using ultrafiltration as a separation technique.

**Physically/Chemically Based Interactions:** A study was conducted to investigate the binding of dutasteride to charcoal and cholestyramine in case of accidental ingestion of large doses of dutasteride (study # 98/AVT/0019). The study was conducted to mimic the stomach environment. $^{14}C$-dutasteride was incubated for 24 hours at 1 and 50 μg/ml concentrations in the following two media:

- 0.5 L Simulated Gastric Fluid (SGF) containing 40 mg/ml bovine serum albumin (BSA) and either 10 gram of charcoal or 50 gram cholestyramine.
- 0.5 L Simulated intestinal fluid (SIF) containing 40 mg/ml BSA and either 10 gram of charcoal or 50 gram cholestyramine.

The addition of BSA to the media is to improve the solubility of dutasteride and also to mimic a small amount of ingested protein. The low and high concentrations of dutasteride used in this experiment simulate the ingestion of one capsule of 0.5 mg and 50 capsules of 0.5 mg, respectively.

**Conclusions:**

1. Dutasteride avidly binds to charcoal and cholestyramine in both media **(Tables 9 and 10)**

2. Dutasteride binds to cholestyramine, but not charcoal, and the binding appears to increase with incubation time only in SIF media, but not in SGF.

3. Considering the objective of the study (i.e. accidental ingestion of large dose of dutasteride) the data from this *in vitro* experiment is somehow in conflict with the data shown from human study. Cholestyramine at a dose of 12 gram did not affect the absorption and the bioavailability of dutasteride (study # ARIA1010, discussed later). Therefore, both human and *in vitro* data should be interpreted carefully.

**Table 9. *In vitro* Binding of Dutasteride to Charcoal and Cholestyramine in Simulated Gastric Fluid**

| GI198745 Concentration | Binding Agent | % GI198745 Bound in Simulated Gastric Fluid over time (mean) | | |
|---|---|---|---|---|
| | | 1.5 h | 4 h | 24 h |
| 1 µg/mL | Charcoal | ≥ 99.8 | ≥ 99.8 | ≥ 99.8 |
| 1 µg/mL | Cholestyramine | 97.2 | 97.1 | 96.3 |
| 50 µg/mL | Charcoal | ≥ 99.8 | ≥ 99.8 | ≥ 99.8 |
| 50 µg/mL | Cholestyramine | 98.2 | 98.4 | 98.6 |

**Table 10. *In vitro* Binding of Dutasteride to Charcoal and Cholestyramine in Simulated Intestinal Fluid**

| GI198745 Concentration | Binding Agent | %GI198745 Bound in Simulated Intestinal Fluid over time (mean) | | |
|---|---|---|---|---|
| | | 1.5 h | 4 h | 24 h |
| 1 µg/mL | Charcoal | ≥ 99.8 | ≥ 99.8 | ≥ 99.8 |
| 1 µg/mL | Cholestyramine | 91.1 | 92.9 | 95.5 |
| 50 µg/mL | Charcoal | 99.8 | ≥ 99.8 | 99.8 |
| 50 µg/mL | Cholestyramine | 78.9 | 82.7 | 95.5 |

**B) *In vivo* drug-drug interaction**

**ii) Is There Any Effect of Dutasteride on Other Drugs**

**1) Warfarin:**

Dutasteride had little effect on the PK or the PD of warfarin. This was based on study # ARI10016 in which dutasteride was administered for 21 days to 23 healthy subjects. Briefly, during the lead-in-phase of the study, wafarin was administered at a single 5 mg dose on Days 1-3 followed by a titration period on Days 4-14 to achieve a stable International Normalized Ratio (INR) of 1.5 –2. A loading dose of 25 mg dutasteride or placebo was administered on Day 15 followed by daily doses of 0.5 mg dutasteride or placebo on Days 16-35. The study was double blind.

Serial blood samples were collected over 24 hours for PK determination of S and R warfarin. However for PD determination, blood was collected daily (Days 1-35) for monitoring of prothrombin time (PT) as a PD biochemical marker.

From this study the following conclusions can be made:

1. In terms of PK parameters, for R-warfarin, but not for S-warfarin, the AUC and Cmax appear to be decreased by about 20% with dutasteride relative to placebo (**Tables 11 and 12 and Figures 17 and 18**)
2. No changes in PT nor INR values following all treatments (**Table 13 and Figures 19 and 20**)

**Table 11. Summary of (R)-Warfarin PK Parameters**

| Parameter | Warfarin + GI198745 | | Warfarin + Placebo | |
|---|---|---|---|---|
| | Day 14 (n=11) | Day 35 (n=11) | Day 14 (n=12) | Day 35 (n=12) |
| DN-$AUC_{24}$ (ng*h/mL) | | | | |
| Mean | 2415 | 2272 | 3075 | 2837 |
| SD | 642 | 670 | 670 | 571 |
| DN-$C_{max}$ (ng/mL) | | | | |
| Mean | 140 | 147 | 175 | 164 |
| SD | 28 | 38 | 27 | 26 |
| DN-$C_{min}$ (ng/mL) | | | | |
| Mean | 79.0 | 77.9 | 102 | 93.4 |
| SD | 25.3 | 27.4 | 23.9 | 20.5 |
| $t_{max}$ (h) | | | | |
| Median | 1.00 | 0.50 | 0.50 | 1.00 |
| Min/Max | | | | |
| $CL_{po}/F$ (L/h) | | | | |
| Mean | 0.436 | 0.467 | 0.340 | 0.370 |
| SD | 0.089 | 0.101 | 0.074 | 0.099 |

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Table 12. Summary of (S)-Warfarin PK Parameters

| | *Warfarin + GI198745* | | *Warfarin + Placebo* | |
|---|---|---|---|---|
| | Day 14 (n=11) | Day 35 (n=11) | Day 14 (n=12) | Day 35 (n=12) |
| DN-$AUC_{24}$ (ng*h/mL) | | | | |
| Mean | 1852 | 1831 | 1910 | 1797 |
| SD | 697 | 735 | 588 | 479 |
| DN-$C_{max}$ (ng/mL) | | | | |
| Mean | 117 | 128 | 126 | 120 |
| SD | 34 | 34 | 22 | 24 |
| DN-$C_{min}$ (ng/mL) | | | | |
| Mean | 56.6 | 60.5 | 58.2 | 53.2 |
| SD | 23.7 | 32.2 | 21.6 | 18.3 |
| $t_{max}$ (h) | | | | |
| Median | 1.00 | 0.50 | 0.50 | 1.00 |
| min/max | | | | |
| $CL_{po}/F$ (L/h) | | | | |
| Mean | 0.601 | 0.615 | 0.578 | 0.601 |
| SD | 0.186 | 0.205 | 0.205 | 0.188 |

Figure 17. Mean Dose-Normalized (R)-Warfarin Concentration-time Profiles on Day 35

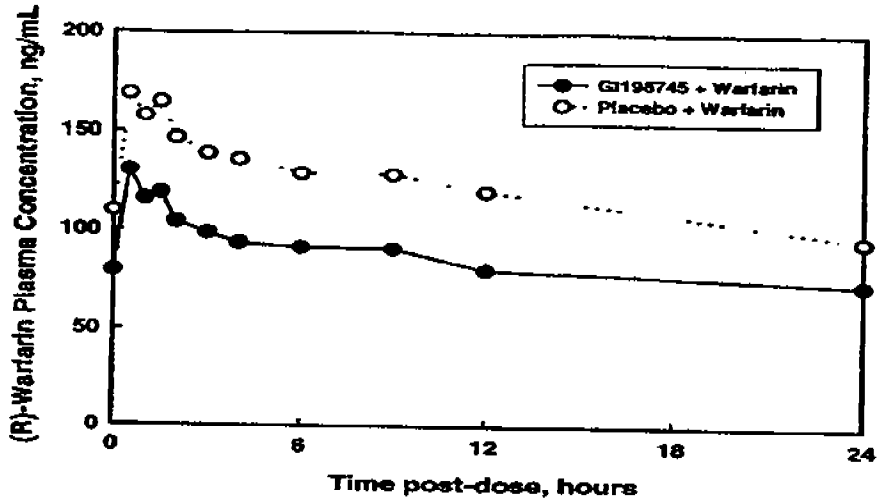

Figure 18. Mean Dose-Normalized (S)-Warfarin Concentration-time Profiles on Day 35

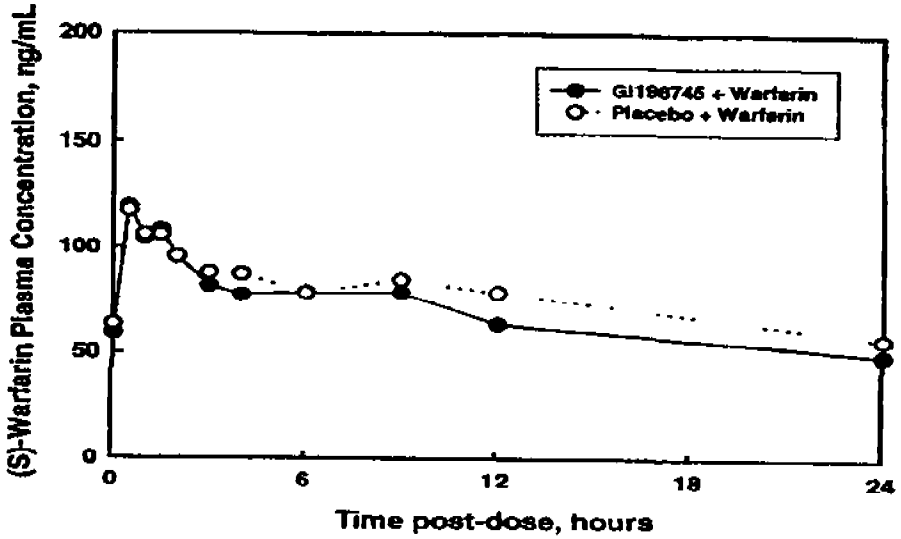


Table 13. Summary of Warfarin PD Parameters

| | Warfarin + GI198745 | | Warfarin + Placebo | |
|---|---|---|---|---|
| | Day 15 (n=11) | Day 35 (n=11) | Day 15 (n=12) | Day 35 (n=12) |
| PT (sec) | | | | |
| Mean | 16.7 | 15.6 | 16.8 | 14.8 |
| SD | 1.6 | 1.7 | 1.1 | 0.8 |
| INR | | | | |
| Mean | 1.6 | 1.4 | 1.6 | 1.2 |
| SD | 0.3 | 0.3 | 0.2 | 0.1 |

**2) Tamsulosin (FLOMAX) and Terazosin (HYTRIN)**

Study # ARIA1011 was conducted to evaluate the effect of tamsulosin and terazosin on the PK and PD (e.eg, DHT) of dutasteride in healthy subjects. This is not a placebo-controlled study as briefly described below:

**Tamsulosin group** (n=19): Received tamsulosin 0.4 mg dose daily for 14 days (Days 1-14) followed by a 7-days washout period (Days 15-21). After the washout period, subjects received a loading dose of 40 mg dose of dutasteride followed by 0.5 mg daily dose for 21 days (Days 22-42). Finally, tamsulosin was reintroduced while continuing dutasteride for the last 14 days (Day 43-56).

**Terazosin group** (n=19): Terazosin was titrated to 10 mg daily for 14 days (Days 1-14) followed by a 7-day washout period (Days 15-21). Subjects then received a 40 mg loading dose of dutasteride followed by a 0.5 mg daily for 21 days (Days 22-42). Finally, terazosin was added (titrated to 10 mg daily) while continuing dutasteride for the last 14 days (Days 43-56).

From both groups, PK Blood samples were collected pre-dose and over 24 hours on Days 14 and 56. For DHT and testosterone serum levels, blood was collected at pre-dose on Days 1 (baseline), 43, and 56. Subjects returned every 2 months until their dutasteride levels were below detection.

**Comments:**

1. The study lacks of placebo controlled-group.
2. Dutasteride did not show any significant effect on the Cmax and AUC of either tamsulosin or terazosin (**Table 14 and Figures 21 and 22**)
3. On Day 43 and 56 dutasteride produced approximately 95% reduction in DHT levels with no difference between tamsulosin and terazosin groups (**Table 15**).

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Table 14.

**Summary of Tamsulosin and Terazosin PK Parameters (source Table 8)**

| | Tamsulosin Drug Group (n=19) | | Terazosin Drug Group (n=19) | |
|---|---|---|---|---|
| | Day 14 Monotherapy | Day 56 Combination | Day 14 Monotherapy | Day 56 Combination |
| $AUC_{24}$ (ng*h /mL) | | | | |
| Mean | 206 | 215 | 2326 | 2419 |
| SD | 89 | 85 | 449 | 637 |
| $C_{max}$ (ng/mL) | | | | |
| Mean | 17.8 | 18.2 | 236 | 246 |
| SD | 7.4 | 6.9 | 48 | 72 |
| $\lambda_z$ ($h^{-1}$) | | | | |
| Mean | 0.075 | 0.079 | 0.080 | 0.075 |
| SD | 0.017 | 0.024 | 0.013 | 0.012 |
| $t_{max}$ (h) | | | | |
| Median | 6.00 | 6.00 | 1.00 | 1.00 |
| Range | | | | |

**Figure 21. Tamsulosin Concentration-Time Profiles (n=19)**
**(open circle tamsulosin alone and open square is tamsulosin with dutasteride)**

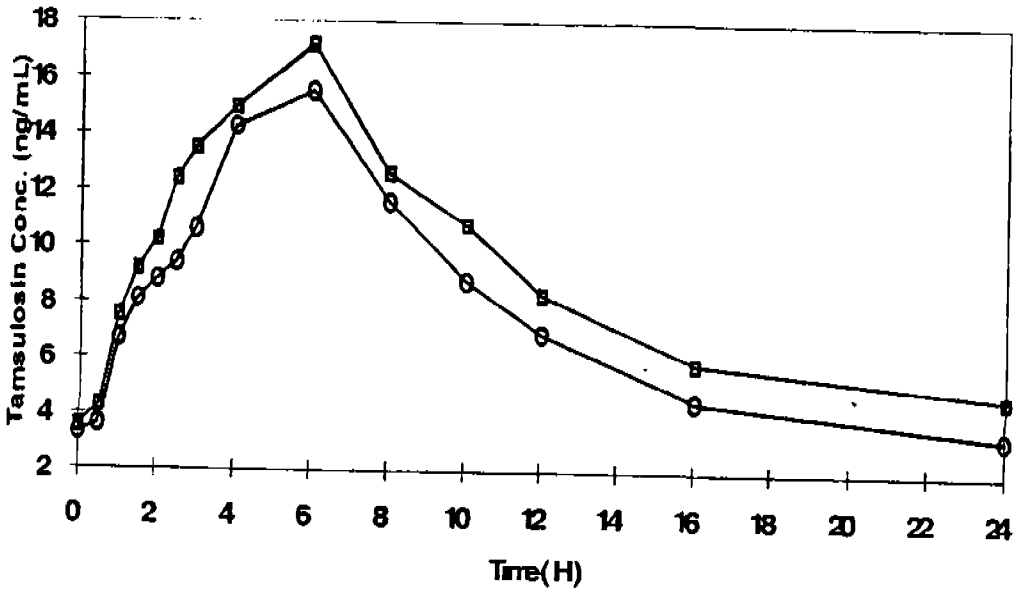

**Figure 22. Terazosin Concentration-Time Profiles (n=19)**
**(open circle terazosin alone and open square is terazosin with dutasteride)**

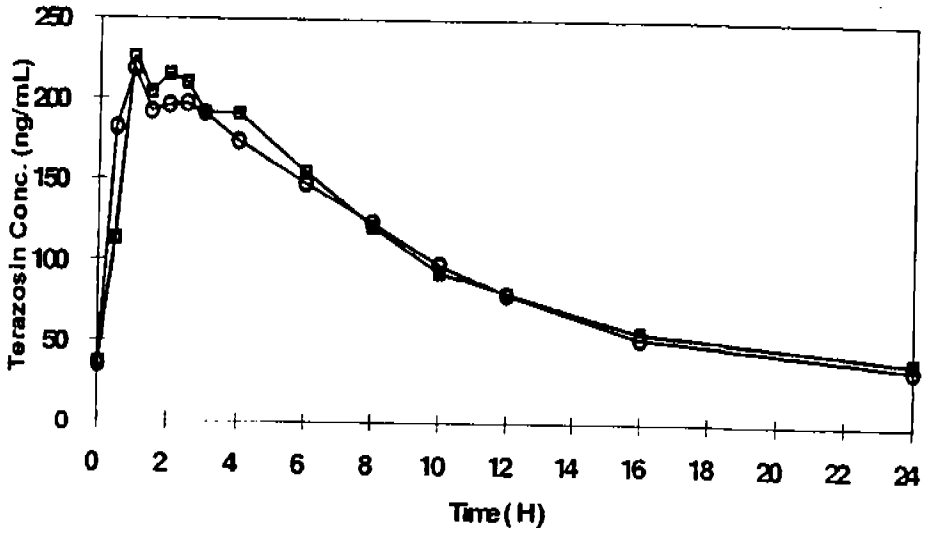


**Table 15.**

**Summary of DHT/T Median Percent Change from Baseline at End of GI198745 Treatment and at the End of Combination Treatments (source Tables 13 and 14)**

| | Tamsulosin group | | Terazosin group | |
|---|---|---|---|---|
| | DHT (N=19) | T (N=19) | DHT (N=19) | T (N=19) |
| Day 43 (end of GI198745) | | | | |
| Median | -94 | 10 | -95 | 22 |
| Range | | | | |
| Day 56 (end of combination) | | | | |
| Median | -93 | 21 | -94 | 37 |
| Range | | | | |

### ii) Is There Any Effect of Other Drugs on Dutasteride?

**Cholestyramine:**

This study was conducted to investigate the effect of cholestyramine on the PK of dutasteride (study # ARIA1010). Briefly, this was a single dose parallel study in 12 healthy subjects following overnight fast as described below:

Treatment 1 (n=12): dutasteride was administered at the same dose (5mg) alone.

Treatment 2 (n=12): dutasteride was administered as a single 5 mg dose followed 1 hour later with 12 gram cholestyramine.

Serial blood samples were collected over 24 hours after drug administration.

**Comments:**

1. Based on this study, it can be concluded that choestyramine had no significant effect on the PK of dutasteride (**Figures 23 and 24**).

2. This is a parallel single dose study. Therefore, the data should be interpreted with caution.

3. This data seems to be in conflict with the data obtained from *in vitro* experiment. The rational for the *in vitro* experiment was to investigate the binding of dutasteride to cholestyramine in case of the accidental ingestion of large dose of dutasteride. Thus, cholestyramine and/or charcoal can be used as antidote to remove unabsorbed dutasteride from the GI tract. The *in vitro* data showed that dutasteride was effectively bound to cholestyramine and charcoal. The *in vivo* data, however, did not show any effect of cholestyramine on the absorption of dutasteride. This raises the following questions about the following:

    - The validity of the *in vitro* experiment.
    - The validity of the *in vivo* study.

**Conclusions:**

The study is supportive, if the true objective of the human study is to investigate if cholestyramine and dutasteride can be concurrently administered together. However, the *in vivo* study failed to support the finding of the *in vitro* experiment. Therefore, cholestyramine cannot be used as antidote for accidental ingestion of large dose of dutasteride.