CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022460Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY ADDENDUM

NDA: 022460	Submission Dates: 3/20/2009, 4/14/2010, and 5/28/2010
Brand Name	Pending
Generic Name	Dutasteride and Tamsulosin hydrochloride (HCl)
Reviewer	Chongwoo Yu, Ph.D.
Team Leader	Myong Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Reproductive and Urologic Products
Sponsor	GlaxoSimthKline (GSK)
Relevant IND/NDA	IND 47,838 and NDA 021319
Submission Type	505(b)(2)
Formulation, Strength, Regimen	Oral capsules, combination of dutasteride 0.5 mg and tamsulosin HCl 0.4 mg, Once daily approximately 30 min after the same meal each day
Indication	Treatment of symptomatic benign prostatic hyperplasia (BPH) in men with enlarged prostate

The purpose of this addendum is to address the Clinical Pharmacology related labeling changes that the Sponsor has made according to the Division's recommendations sent to the Sponsor on May 24, 2010 via email by Project Manager, Olga Salis. Sponsor has submitted their proposed labeling edits on May 28, 2010 (NDA 022460, Document Number 24). Important changes include the following:

- **Highlights**:
  - CYP 3A4 inhibitors: Sponsor accepts the Division's revision of the DRUG INTERACTIONS section of the highlights as following - *CYP Inhibitors: TRADENAME is metabolized by both CYP3A4 and CYP2D6. Concomitant use with known inhibitors can cause a marked increase in plasma levels resulting in an increased rate of side effects. Use of TRADENAME with ketoconazole and paroxetine is not recommended. Caution should be exercised when used with less potent inhibitors, such as, but not limited to terbinafine and erythromycin. (5.2, 7.1, 12.3)*
  - Use in Specific Populations: Sponsor accepts the Division's recommendation of including the information that the drug was not studied in patients with end stage renal disease or severe hepatic impairment.
- **Full Prescribing Information**:

    - Dosage & Administration: Sponsor accepts to include the instruction not to take the drug with strong CYP 3A4 inhibitors. This was to be consistent with the currently approved Flomax® PLR labeling (NDA 020579, labeling approved on 12/22/2009).
- **Other edits:** Minor edits including deletion of unnecessary cross references (i.e., for when no additional information was in the referred section) and deleting the trade names of other drugs (i.e., Flomax®) were made.

The final agreed upon label between the Sponsor and the Division will be submitted as an agreement is reached on the final edits. There are no outstanding Clinical Pharmacology issues.

1.1 Recommendation

The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds NDA 022460 acceptable from a Clinical Pharmacology perspective.

1.2 Phase IV Commitments

None

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22460	ORIG-1	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLINE	DUTASTERIDE/ TAMSULOSIN HYDROCHLORIDE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHONGWOO YU
06/04/2010

MYONG JIN KIM
06/04/2010

OFFICE OF CLINICAL PHARMACOLOGY ADDENDUM

NDA: 22-460	Submission Date: 3/20/2009
Brand Name	Pending
Generic Name	Dutasteride and Tamsulosin hydrochloride (HCl)
Reviewer	Chongwoo Yu, Ph.D.
Team Leader	Myong Jin Kim, Pharm.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Reproductive and Urologic Products
Sponsor	GlaxoSimthKline (GSK)
Relevant IND/NDA	IND 47,838 and NDA 21-319
Submission Type	505(b)(2)
Formulation, Strength, Regimen	Oral capsules, combination of dutasteride 0.5 mg and tamsulosin HCl 0.4 mg, Once daily approximately 30 min after the same meal each day
Indication	Treatment of symptomatic benign prostatic hyperplasia (BPH) in men with enlarged prostate

The purpose of this addendum is to address the Division of Scientific Investigations (DSI) consult requested by the Office of Clinical Pharmacology (OCP) (signed off by Dr. Dennis Bashaw on May 19, 2009) on the clinical BE sites (Covance Research, Evansville, IN and Austin, TX) and the bioanalytical site (GlaxoSmithKline, Research Triangle Park, NC) for the pivotal BE study, ARI109882 (refer to original Clinical Pharmacology review of NDA 22-460, DARRTS, January 6, 2010).

As a result of the requested DSI inspection, Form 483s were issued to one of the clinical sites (Covance Research, Austin, TX) on July 21, 2009 and to the bioanalytical site (GlaxoSmithKline, Research Triangle Park, NC) on December 10, 2009. OCP received a copy of these Form 483s on January 7, 2010 via email from DSI reviewer, Dr. Sripal Mada. No Form 483 was issued to the other clinical site (Covance Research, Evansville, IN).

The Clinical and Clinical Pharmacology review teams are in agreement that the citations on the Form 483 issued to the clinical site (Covance Research, Austin, TX) are considered as relatively minor issues and that they would not have any impact on the end results of the study or the approvability of this NDA.

The Sponsor responded to the analytical Form 483 on January 8, 2010 and OCP received a copy of the Sponsor's response via email from the project manager, Olga Salis on January 11, 2010. Upon receipt of the DSI consult report (DARRTS, January 14, 2010),

there are no outstanding Clinical Pharmacology issues and the Division plans to address labeling at a later time.

1.1 Recommendation

The Division of Clinical Pharmacology 3, Office of Clinical Pharmacology finds NDA 22-460 acceptable from a Clinical Pharmacology perspective provided that a satisfactory agreement is reached regarding the labeling language.

1.2 Phase IV Commitments

None

1.3 DSI Consult Report

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 14, 2010

TO: Scott Monroe, M.D.
Director, Division of Reproductive and Urologic Products
Office of New Drugs (HFD-130)

FROM: Sripal R. Mada, Ph.D.
Martin K. Yau, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: Martin K. Yau, Ph.D. Martin K. Yau 1/14/2010
Acting Team Leader - Bioequivalence
GLP & Bioequivalence Investigations Branch
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDA 22-460, FLODART™ (Dutasteride 0.5 mg and Tamsulosin HCl 0.4 mg combination capsule) from GlaxoSmithKline

At the request of Division of Reproductive and Urologic Products (DRUP), the Division of Scientific Investigations (DSI) audited both the clinical and analytical portions of the following bioequivalence (BE) study:

Study # ARI109882: "An Open-Label, Randomized, Single Dose Three-Period Partial Crossover Study to Determine the Bioequivalence and Food Effect of a Combination Capsule Formulation of Dutasteride and Tamsulosin Hydrochloride (0.5 mg / 0.4 mg) Compared to Concomitant Dosing of AVODART® 0.5 mg and Flomax 0.4 mg Commercial Capsules in Healthy Male Subjects"

Study ARI109882 was conducted at two clinical facilities (Contract Research Organizations) in the US. The first facility was in Covance GFI Research at 800 St. Mary's Drive, Evansville, IN 47714, and the second facility in Covance Research at 313 E. Anderson Lane, Austin, TX 78752. The analytical portion of the study was conducted at GlaxoSmithKline, 3030 E. Cornwallis Road, Research Triangle Park, NC 27709.

Clinical Site 1: Covance GFI Research at 800 St. Mary's Drive, Evansville, IN 47714 (Evansville Facility)

Following inspection at the clinical site 1 (June 29 - July 01, 2009), No Form FDA-483 was issued.

Clinical Site 2: Covance Research at 313 E. Anderson Lane, Austin, TX 78752 (Austin Facility)

Following inspection at the clinical site 2 (July 13-21, 2009), a one-item Form FDA-483 was issued **(Attachment 1)**. The Covance's response (dated August 10, 2009) was received by DSI on August 20, 2009 **(Attachment 2)**. The Form FDA-483 observation **(in bold type)**, the firm's response, and our evaluations follow.

1. Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation. Specifically for protocol GSK ARI109882, study # 207897:

A. The randomization schedule for subject 206 is incorrect in that it documents treatment B (dutasteride 0.5 mg/tamsulosin 0.4 mg combination capsule) for dosing Period 2 on 08 Dec 2007 was given when in fact subject 206 was actually given treatment A (Flumax 0.4 mg and Avodart 0.5 mg individual capsules).

B. The source document for subject 211 documents a 6 hour supine BP of 125/74 mmHg on 10 Nov 2007, yet a BP of 128/74 mmHg was documented on the eCRF for 6 hours post dose reading.

C. The source document for subject 243 documents the 48 hour blood collection on 10 Dec 2007 at 0916. A 48 hours Post Dose time of 10:16 was reported on the eCRF on 10 Dec 2007.

D. The source document for subject 245 72 hours post dose on 5 Feb 2008 is missing from the subject file.

E. The source document for subject 246 72 hours post dose on 5 Feb 2008 is missing from the subject file.

F. Source document for subject 246 documents the 2 hour blood collection on 05 Jan 2008 at 1122. A 2 hours Post Dose time of 11:21 was documented on the eCRF on 5 Jan 2008.

Regarding Item 1A, Covance explained in their written response **(Attachment 2)** that the dose administrator (doser) inadvertently marked Treatment B on the source records. Correct dose was actually administered as reflected in the study protocol and report (i.e., no mistake in the study report). Covance also said that they provided evidence obtained from their pharmacy to the

FDA investigator during the inspection to support that this is a documentation error in the source records. The FDA investigator accepted Covance's explanation.

Covance also acknowledged the Form FDA-483 observations 1B, 1C and 1F. Covance said that they already informed GSK of these reporting errors. These errors are minor and those should not impact the study outcomes.

For items 1D and 1E of the Form FDA-483, Covance stated that the source documents were misfiled. Covance is committed to provide a copy of this source document to FDA upon retrieval.

Analytical site: GlaxoSmithKline, 3030 E. Cornwallis Road, Research Triangle Park, NC 27709 (GSK)

Following inspection of the analytical site (December 7-10, 2009), Form FDA-483 was issued **(Attachment 3)**. The GSK's response (dated January 08, 2010) was received by DSI on January 11, 2010 **(Attachment 4)**. The Form FDA-483 observation **(in bold type)**, GSK's written response, and our evaluations follow.

1. Audit trail feature in Analyst v.1.4.1 was disabled. Only PDF files of chromatograms and final run results were available; the electric data files were not archived and not stored in a secure environment.

As cited in the 483 observation above, the audit trail feature in Analyst v.1.4.1 was disabled and only PDF files of chromatograms and final run results were available. This is objectionable because any changes in the integration of chromatograms cannot be verified to assure that changes were not made to bias results of QCs, calibration standards, and/or subject samples. The available electronic data files were not reliable, as they were not archived and not stored in a secure environment.

During the inspection, GSK informed FDA investigators that all chromatograms within an analytical run were integrated using the same integration parameters, and GSK did not manually re-integrate any chromatograms from all the analytical runs (i.e., no samples including calibration standards, QCs, and subject samples were manually re-integrated). GSK also said their procedure allowed minor changes in integration parameters between runs to optimize integration, but the same parameters were used for all samples in the same run. To verify that information, GSK was asked by FDA investigator to list the

integration parameters used in all the dutasteride and tamsulosin analytical runs. For dutasteride, 81 out of 93 runs used the same integration parameters (i.e., global integration parameters); 12 runs used integration parameters slightly different from global integration parameter. For tamsulosin, 79 out of 94 runs used global integration parameters; 15 runs used integration parameters slightly different from the global integration parameters (see **Attachment 5**). For dutasteride and tamsulosin runs with integration parameters different from the global integration parameters (i.e., modified integration parameters), GSK was asked by the FDA investigators to reintegrate chromatograms in the entire runs using the global integration parameters. QCs results from these runs generated using modified integration parameters were compared to results generated using global integration parameters. Overall, DSI found that the QC results are similar regardless of whether global or modified integration parameters were used. Moreover, there was no change in run acceptance when modified integration parameters were used. Based on these findings, DSI is of the opinion that data were not biased by changing integration parameters. Source records in analytical runs were also checked during the inspection to confirm that no manual integration was conducted for all chromatograms generated in the study. No problem was noted.

In the written response, GSK said they have now changed their practices and have enabled the Analyst audit trail feature to prompt for reasons for changes during quantitation. They now obtain the PDF copy of the Analyst audit trail, and archived all PDF copies along with the proprietary Analyst files such that they can be made available during inspection.

Overall DSI considers that this Form FDA-483 observation has been resolved.

2. Failure to use suitable quality control samples (QCs) that are representative of the dutasteride concentrations in serum samples of study subjects. Specifically, QC concentrations used were 0.3, 3, 8, and 40 ng/mL, but >99% of dutasteride concentrations were < 3 ng/mL. The mean C_{max} values of Treatment A, B, C, and D determined in the study were all <2.1 ng/mL.

As cited in the above 483 observation, only two (0.3 ng/mL and 3 ng/mL) of the four dutasteride QC concentrations are representative of the dutasteride concentrations obtained in study subjects. Normally, three QC concentrations in duplicate (i.e., n=2 at each of three QC concentration representative of

low, mid, and high dutasteride concentration observed in study samples) should be used to monitor performance of each analytical run. However, upon review of all the QC results showed that almost all QCs at 0.3 and 3 ng/mL met the acceptance criteria (i.e. <15% deviation from the nominal value). In addition, in the Form FDA-483 response, GSK also reported that a high degree of accuracy of the QC data from 0.3 ng/mL (2.6% bias) to 3 ng/mL (0.9% bias) was observed using a linear regression equation. The result suggested that the response of the standard curve was linear over 0.3 and 3 ng/mL. Consequently, DSI is of the opinion that this Form FDA-483 observation should not significantly affect the study outcomes.

3. Failure to provide sufficient long term frozen storage stability data to assure sample integrity over the period when study serum samples were collected after first dosing at the clinical sites to the end of samples analysis.

GSK did not conduct any long term frozen storage stability experiment for FLODART™ (combination of dutasteride and tamsulosin). Instead, QC samples were prepared at GSK and stored with the subject samples in the same -30°C freezer. According to GSK, the QC samples were used as internal controls to support study sample integrity over the frozen storage period prior to sample analysis. However, during the inspection, DSI uncovered that the QC samples were not prepared at the same time when study samples were collected at the clinical sites, but were prepared later at GSK around the time when shipments of the study samples arrived. Consequently, frozen storage period of the QCs samples were not adequate to cover the period when study serum samples were collected after first dosing at the clinical sites to the end of sample analysis (about 125 days). Moreover, study samples were not stored in -30°C freezer but in -20°C freezer at the clinical site. However, this stability issue only affects sample integrity of only 71 samples. In light of small sample number, there should not be significant impact on the study outcome.

4. Failure to perform sufficient assessments of Incurred Sample Reproducibility (ISR). Only 4% of dutasteride/tamsulosin samples were re-analyzed for ISR.

The SOP for ISR in effect at the time was not adequate. However, GSK has now revised their SOP (becoming effective January 2010), requiring 10% (5% for >2000 samples) of total study samples excluding samples from control or placebo subjects. However, ISR

results (**Attachment 6**) from the 4% study samples indicated that significant ISR problem is unlikely.

5. Many study samples (>100) collected in this study were hemolyzed, but no experiment was conducted to investigate the effect of hemolysis on the accuracy of the UPLC-MS/MS method.

GSK acknowledged that the effect of hemolysis was not directly evaluated during the method validation for dutasteride and tamsulosin. GSK revised their SOP (becomes effective January 2010) to evaluate this effect in future studies. Following, a review of the GSK's response, we agrees that this observation should not have a significant impact on study outcomes.

6. No selectivity experiment on selected OTC drugs and concomitant medications was attempted (see Table 8, clinical pharmacology study report ARI109882), although SOP (# SOP-DMD-0007 v05) stated that these experiments should be conducted.

Per SOP at the time when the study was conducted (SOP-DMD-0007 v05, effective date October 15, 2007) selectivity experiment on selected OTC drugs and concomitant medications should be studied. Table 8 of clinical pharmacology study report ARI109882 reveals subjects were administered OTC drugs and other medications, but no experiment to evaluate assay interference was conducted. In their response, GSK only said that they will evaluate the OTC drugs and concomitant medications in future studies, and that based on molecular structures of OTC drugs and concomitant medications, assay interference is unlikely. During the inspection, DSI noticed no significant interference on analyte and internal standard peaks upon review of study chromatograms.

7. SOP (# SOP-DMD-0007 v05) allows calibration standards with concentrations greater than LLOQ to be acceptable even of deviations from nominal values are > 15% (i.e., accept deviations up to 20% instead of ≤ 15%).

Per GSK's SOP at the time when the study was conducted, the acceptance criterion for all the calibration standards was ±20%. However, FDA guidance for industry (Bioanalytical Method Validation), recommends that a calibration standard should not be accepted if the deviation is >15% from the nominal value (>20% deviation for LLOQ). In their response GSK reported that only 45 out of 2805 standards other than LLOQ had deviations >15% from the nominal values. Consequently, this finding should not have significant impact on the study outcomes.

8. No temperature monitoring procedure in effect during the study covering areas such as temperature monitoring, alarm checks and calibration for freezers used to store study samples received and analyzed. Specifically:

- **A. The firm does not conduct periodic alarm checks on freezers utilized to store study samples and QC samples to provide assurance that freezer set points for alarms continue to operate adequately.**
- **B. The firm does not perform preventive maintenance or calibration of the centrifuge utilized during the processing of study samples.**
- **C. SOP for freezer maintenance was not maintained during the study period.**

In their response, GSK has agreed to revise their current procedures to correct the findings cited specifically above in 8A, 8B, and 8C. During the inspection, continuous temperature records for the freezers were reviewed and no significant problem was noted.

9. Documentation was incomplete. For example:

- **A. No documentation of handling of stability samples (e.g., freeze-thaw, bench-top experiments).**
- **B. Failure to retain PDF files of original data (i.e., chromatograms, results) in a precision and accuracy validation run (Run G198745HUSEVALB001) that was re-injected.**
- **C. Pipetting error by Zymark Rapid Plate in Run # ARI109882HUSE053 was not documented in the source data.**

In their response, GSK stated that processes are now put in place to correct the documentation issues cited above. This observation is unlikely to have significant impact on the study outcome.

Conclusion:

Following evaluation of all Form FDA-483 items and written responses from GSK and Covance-Austin, DSI concludes that the inspectional findings should not have significant impacts on the outcomes of study ARI109882.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Sripal R. Mada, Ph.D.

Martin K. Yau, Ph.D.

Final Classifications:

Clinical

NAI - Covance Clinical Research, Evansville, IN
FEI: 3006697109

VAI - Covance Clinical Research, Austin, TX
FEI: 3006785106

Analytical

VAI - GlaxoSmithKline, Research Triangle Park, NC
FEI: 3006693646

cc:
DSI/GLPBB/Mada/Yau/Rivera-Lopez/CF
ODE3/DRUP/Bension/Kauls/Salis
OCP/DCP3/Bashaw/Kim/Yu
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Edit: MKY 01/12/2010
DSI: (b) (4) Q:\Bioequiv\EIRCover\22460gsk.dut.doc
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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22460	ORIG-1	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLINE	DUTASTERIDE/ TAMSULOSIN HYDROCHLORIDE

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/s/

CHONGWOO YU
01/15/2010

MYONG JIN KIM
01/15/2010

CLINICAL PHARMACOLOGY REVIEW

NDA:	22-460
Type/Category:	505(b)(2)/Original
Brand Name:	Pending
Generic Name:	Dutasteride and Tamsulosin hydrochloride (HCl)
Relevant IND/NDA:	IND 47,838 and NDA 21-319
Indication:	Treatment of symptomatic benign prostatic hyperplasia (BPH) in men with enlarged prostate
Dosage Form:	Combination capsule
Route of Administration:	Oral
Dosing Regimen and Strength:	Once daily approximately 30 min after the same meal each day, combination of dutasteride 0.5 mg and tamsulosin HCl 0.4 mg
Sponsor:	GlaxoSimthKline (GSK)
OCP Division:	Division of Clinical Pharmacology 3
OND Division:	Division of Reproductive and Urologic Products (DRUP)
Submission Date:	March 20, 2009
Reviewer:	Chongwoo Yu, Ph.D.
Team Leader:	Myong-Jin Kim, Pharm.D.

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY

DTC is an oral dosage form that combines dutasteride, a 5α-reductase inhibitor and the active ingredient in Avodart® (NDA 21-319, approved on November 20, 2001), and tamsulosin hydrochloride (HCl), an α-adrenergic blocker and the active ingredient in Flomax® (NDA 20-579, approved on April 15, 1997). GSK is the Sponsor for the Avodart® NDA while Boehringer Ingelheim Pharmaceuticals is the Sponsor for the Flomax® NDA. Astellas Pharma Inc. is the assignee of the sole Orange Book listed patent for Flomax® (tamsulosin HCl, U.S. Patent No. 4,703,063), which is set to expire on April 27, 2010. DTC will not be commercialized until after expiry of the Orange Book patent identified above and any applicable pediatric exclusivity for Flomax®.

The Sponsor submitted a 505(b)(2) application for DTC, a combination capsule that consists of dutasteride 0.5 mg and tamsulosin HCl 0.4 mg. The proposed indication is the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with enlarged prostate and it is to be given once daily approximately 30 min after the same meal each day. The Sponsor submitted the following studies to support the approval of DTC: a pivotal bioequivalence (BE) study ARI109882, and 4 supporting BE studies (ARI111402, ARI103880, 163/07, and 186/07). The efficacy and safety of dutasteride 0.5 mg co-administered with tamsulosin HCl 0.4 mg for the treatment of symptomatic BPH was previously demonstrated in a 2-year Phase 3 study (Study ARI40005) (NDA 21-319/S-014, approved on June 19, 2008). Therefore, the Sponsor conducted a pivotal BE study (ARI109882) between the DTC and co-administration of dutasteride and tamsulosin HCl to support the approval of DTC.

Division of Scientific Investigations (DSI) consult (signed off by Dr. Dennis Bashaw on May 19, 2009) on the clinical BE sites (Covance Research, Evansville, IN and Austin, TX) and the bioanalytical site (GlaxoSmithKline, Research Triangle Park, NC) was requested for the pivotal BE study, ARI109882 and is pending.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology III (OCP/DCP-III) has reviewed NDA 22-460 submitted on March 20, 2009. The overall Clinical Pharmacology information submitted to support this NDA is acceptable provided that a satisfactory agreement is reached regarding the labeling language and the DSI consult that is still pending turns out to have no approvability issues.

1.2 POSTMARKETING REQUIREMENTS / COMMITMENTS

None

1.3 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Bioequivalency Assessment of the Proposed DTC and the Co-administration of Avodart® and Tamsulosin HCl Capsules

BE of DTC and the concomitantly dosed monotherapies, Avodart® and Flomax® (used in the pivotal efficacy and safety study, ARI40005) was demonstrated in a single dose, randomized, three-period,

partial cross-over pivotal BE study, ARI109882 conducted under both fed and fasted state. Demonstrated BE from Study ARI109882 was used to bridge the efficacy and safety data from pivotal study, ARI40005 (that compares co-administration of dutasteride and tamsulosin to the monotherapies [i.e., co-administration of dutasteride and tamsulosin vs. dutasteride vs. tamsulosin]) to the combination capsule, DTC. In addition, BE for tamsulosin between the combination product, DTC (containing tamsulosin HCl pellet (b) (4)% w/w) and concomitant dosing of Avodart® and Flomax® monotherpies was demonstrated in a repeat dose, randomized, cross-over study (Study ARI111402). The results of the single and multiple dose BE studies are summarized below:

- Single Dose BE (Study ARI109882):
  - BE (C_{max} and AUC) of dutasteride was demonstrated between the combination product, DTC and concomitant dosing with dutasteride and tamsulosin HCl monotherapies under both fasted and fed state.
  - BE (C_{max} and AUC) of tamsulosin was demonstrated between the combination product, DTC and concomitant dosing with dutasteride and tamsulosin HCl monotherapies under both fasted and fed state.

- Multiple Dose BE (Study ARI111402): BE (C_{max} and AUC) of tamsulosin was demonstrated between combination capsule formulations containing either 10% ((b) (4)% w/w) or 15% ((b) (4)% w/w) enteric coated tamsulosin and the concomitant dosing of Avodart® 0.5 mg and Flomax® 0.4 mg monotherapies at steady-state under fasted state.

It was noted that the pivotal efficacy and safety study, ARI40005 used both the currently approved tamsulosin product, Flomax® 0.4 mg and a different formulation named Omnic 0.4 mg. The Omnic formulation contains the same active ingredient as Flomax® but has different inactive ingredients. A BE study (study ARI10021, submitted under NDA 21-319/S-014, approved on June 19, 2008) comparing Omnic 0.4 mg and Flomax® 0.4 mg under fasted state showed that they are BE (refer to Clinical Pharmacology Review by Dr. Doanh Tran, NDA 21-319/S-014, DARRTS, April 17, 2008).

Formulation for the Combination Capsule

Avodart® is an immediate release (IR) soft gelatin capsule and Flomax® is a hard gelatin capsule containing modified release (MR) pellets. The manufacture of dutasteride and tamsulosin HCl combination capsule (DTC) involves the over-encapsulation of two separate products (combining dutasteride 0.5 mg and tamsulosin HCl 0.4 mg) filled into a (b) (4) hard shell capsule. The drug substances, dutasteride and tamsulosin HCl, are the same active components used for commercial supply of Avodart® and generic tamsulosin HCl capsules ((b) (4) generic version sold in the European Union [EU] market). The strengths of each active component of DTC are identical to the commercially available monotherapies, Avodart® (dutasteride 0.5 mg) and Flomax® (tamsulosin HCl 0.4 mg).

Dosage Form Size

(b) (4). In the case of dutasteride, the soft gelatin capsule fill solution containing mono-di-glycerides of caprylic/capric acid (MDC) was (b) (4) In the case of tamsuloisn HCl, the concentration of the drug in the generic tamsulosin (b) (4)

(b) (4) These changes were supported by BE studies comparing the proposed product (after change) versus the corresponding commercial product (before change) as summarized below:

- Tamsulosin administered as a combination capsule (DTC) at steady state was BE (AUC and C_{max}) to tamsulosin co-administered as Flomax® with Avodart® (dutasteride) under fasted state (Study ARI111402).
- Dutasteride 0.5 mg administered as a single dose of a soft gelatin capsule containing (b) (4) mg soft gelatin capsule fill solution was BE (AUC and C_{max}) to when dutasteride was administered as a single dose of Avodart® (containing (b) (4) mg soft gelatin capsule fill solution) under fasted state (Study ARI103880).
- Tamsulosin 0.4 mg administered as a single dose of a tamsulosin HCl capsule containing MR pellets, (b) (4)% w/w (b) (4) was BE (AUC and C_{max}) to tamsulosin administered as a single dose of a Flomax 0.4 mg MR capsule (Boehringer Ingelheim Pharmaceuticals Inc., USA) under fed state (Study 163/07).
- Tamsulosin 0.4 mg administered as a single dose of tamsulosin HCl capsules containing MR pellets, (b) (4)% w/w (b) (4) was BE (AUC and C_{max}) to tamsulosin administered as a single dose of a Flomax 0.4 mg MR capsule (Boehringer Ingelheim Pharmaceuticals Inc., USA) under fed state (Study 186/07).

Food Effect

BE between DTC and concomitant dosing of Avodart® and Flomax® monotherapies under both fed and fasted state has been assessed (Study ARI109882). Individual components of DTC (dutasteride and tamsulosin HCl) are BE to co-administration of Avodart® and Flomax® under fed and fasted state. Food does not affect the PK of dutasteride following administration of DTC nor Avodart®. However, a mean 30% decrease in C_{max} was observed for both the tamsulosin component of DTC and Flomax® when administered with food. Because the prescribing information for Flomax® recommends administration approximately one-half hour following the same meal each day, the Sponsor proposes to have the same administration recommendation for DTC. This dosing recommendation is consistent with the manner in which the individual components were given in the pivotal efficacy and safety study, ARI40005.

ADME (Absorption, Distribution, Metabolism, and Excretion)

There are no additional Clinical Pharmacology studies submitted besides the five BE studies conducted to support the approval of DTC. Sponsor is relying on the information on the currently approved Avodart® (2008) and Flomax® (2008) package inserts. Section 12.3 *Pharmacokinetics* of the DTC package insert needs to be updated with the PK data obtained using DTC.

Drug-Drug Interactions

There are no drug interaction studies conducted using DTC. A PK study (Study ARI1011, submitted under NDA 21-319/S-014, approved on June 19, 2008) shows that co-administration of dutasteride did not significantly affect the PK of tamsulosin. In addition, a review of available data (published data on tamsulosin) suggests that tamsulosin co-administration is unlikely to significantly affect the PK of dutasteride. Dr. Doanh Tran's review (dated April 17, 2008) on Study ARI1011 and literature can be found in DARRTS under NDA 21-319/S-014. Information available on the package insert from individual components (Avodart® [2008] and Flomax® [2008]) is listed on the proposed DTC label.

Specific Population and Pediatric Waiver

There are no specific population studies conducted using DTC. Information available on the package insert from individual components (Avodart® [2008] and Flomax® [2008]) is listed on the proposed DTC label. The Sponsor has submitted a waiver request for pediatric studies with a justification that DTC will be ineffective or unsafe in the age group of 0 (birth) to 16 years old.

A full pediatric waiver was granted for the combination product, DTC by the Agency's pediatric review committee (PeRC) on September 23, 2009, as it was granted for the co-administration regimen in NDA 21-319/S014 earlier.

Bioanalytical Method Validation and DSI Consult

The concentrations of dutasteride in human serum were determined by validated, internal standard analytical methods consisting of protein precipitation followed by liquid chromatography coupled with tandem mass spectrometric (LC-MS/MS) detection (Studies ARI103880 and ARI109882). The concentrations of tamsulosin in human serum were determined by a validated, internal standard analytical method consisting of protein precipitation (Studies ARI109882 and ARI111402) or solvent extraction (Studies 163/07 and 186/07) followed by LC-MS/MS detection. Bioanalytical method validation reports submitted in this submission are found to be acceptable. DSI consult (signed off by Dr. Dennis Bashaw on May 19, 2009) on the clinical BE sites (Covance Research, Evansville, IN and Austin, TX) and the bioanalytical site (GlaxoSmithKline, Research Triangle Park, NC) was requested for the pivotal BE study, ARI109882 and is pending. An addendum to this review will be added when the DSI consult results become available.

2. QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What is dutasteride?

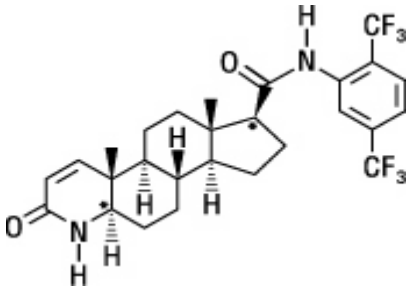
Dutasteride, a 5α-reductase inhibitor, is indicated for the treatment of symptomatic BPH in men with an enlarged prostate to:

- improve symptoms,
- reduce the risk of acute urinary retention, and
- reduce the risk of the need for BPH-related surgery.

Dutasteride inhibits the conversion of testosterone to dihydrotestosterone (DHT). DHT is the androgen primarily responsible for the initial development and subsequent enlargement of the prostate gland.

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

Dutasteride is a synthetic 4-azasteroid compound 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:

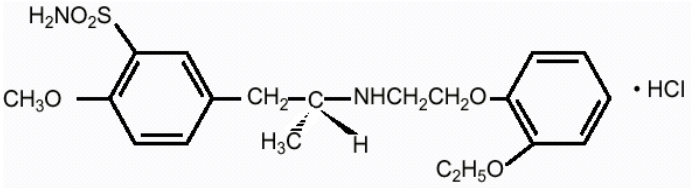


Dutasteride is a white to pale yellow powder with a melting point of 242° to 250°C. It is soluble in ethanol (44 mg/ml), methanol (64 mg/ml), and polyethylene glycol 400 (3 mg/ml), but it is insoluble in water.

2.1.2 What is tamsulosin?

Tamsulosin is an α_1 adrenoceptor blocker that exhibits selectivity for α_{1A} receptors in the human prostate. Tamsulosin is indicated for the treatment of the signs and symptoms of BPH.

Tamsulosin HCl is (-)-(*R*)-5-[2-[[2-(*o*-Ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide, monohydrochloride. Tamsulosin HCl is a white crystalline powder that melts with decomposition at approximately 230°C. It is sparingly soluble in water and methanol, slightly soluble in glacial acetic acid and ethanol, and practically insoluble in ether. The empirical formula of tamsulosin HCl is $C_{20}H_{28}N_2O_5S{\cdot}HCl$. The molecular weight of tamsulosin HCl is 444.98 g/mol. Its structural formula is:



2.1.3 What clinical data is submitted to support the approval of DTC?

The clinical data to support DTC include a pivotal BE study (ARI109882) that demonstrated BE between DTC and co-administration of dutasteride and tamsulosin capsules, and a pivotal efficacy and safety study (ARI40005) that compared co-administration of dutasteride and tamsulosin to the monotherapies. The data from Study ARI40005 were the subject of NDA 21-319 / S-014 which was approved on June 19, 2008. The demonstrated BE from Study ARI109882 is used to bridge the efficacy and safety data from ARI40005 to DTC. The biopharmaceutics package for this application consists of four single-dose BE studies and one steady-state tamsulosin BE study in healthy volunteers (Table 1). Study ARI109882 is the pivotal BE study which bridges DTC to Study ARI40005, the pivotal efficacy and safety study for co-administration of dutasteride and tamsulosin, and also provides data on food effect.

Table 1: Bioequivalence Studies

Study	Design	Enrolled/ Completed	BE Comparisons (Primary Objective)
Pivotal			
ARI109882	Open-label, randomized, single-dose, 3-period, 4-treatment partial block crossover	101/81	FLODART vs AVODART and Flomax under fasting and fed conditions
Supportive			
ARI111402	Open-label, randomized, repeat dose (7 days), 3-period crossover	24/23	Tamsulosin of FLODART vs Flomax (given with AVODART) – fasting conditions
ARI103880	Open-label, randomized, single-dose, 3-period crossover	37/37	Dutasteride capsules containing either (b) (4) (b) (4) (b) (4) vs AVODART Capsules (b) (4) - fasting conditions
163/07	Open-label, randomized, single-dose, laboratory-blinded, 2-period crossover	26/24	Tamsulosin modified-release (MR) Capsules containing MR pellets (b) (4) % w/w tamsulosin hydrochloride) (b) (4)) vs Flomax – fed conditions
186/07	Single-centre, randomized, single-dose, laboratory-blinded, 2-period, 2-sequence, crossover	26/25	Tamsulosin MR Capsules containing MR pellets ((b) (4) % w/w tamsulosin hydrochloride) ((b) (4)) vs Flomax – fed conditions

Please note that Flodart was the initially proposed trade name of DTC.

2.1.4 What are the expected benefits of DTC?

Use of DTC, a single capsule of dutasteride and tamsulosin combined, is expected to provide the following benefits while maintaining an acceptable and predictable tolerability profile:

- Ensure that symptomatic patients with enlarged prostates achieve the maximum clinical benefit possible through the complementary mechanisms of action of the two medications;
- Provide the rapid symptom improvement associated with tamsulosin;
- Maximize long-term symptomatic benefit best achieved with the combination;

- Provide the long-term reduction in acute urinary retention and BPH-related surgery unique to 5 alpha-reductase inhibitors;
- Reduce the pill burden necessary to achieve the above results.

2.2 General Clinical Pharmacology and Biopharmaceutics

2.2.1 What Clinical Pharmacology and Biopharmaceutics related information have been submitted to support this NDA supplement?

The original submission contained the following:

- Draft labeling in PLR format
- Information on the composition of drug products used in the clinical studies
- Full clinical study report of the 5 biopharmaceutical studies
- Bioanalytical study reports and method validation reports
- Request of waiver for pediatric studies

2.2.2 What are the dosing regimen and instructions?

DTC capsules are to be administered orally, once daily taken approximately 30 min after the same meal each day and are to be swallowed as whole.

2.2.3 What is the quantitative composition of the drug products used in the clinical trials of this supplement?

DTC, for oral administration, is a oblong, hard-shell capsule each containing one oblong, opaque, dull-yellow dutasteride soft gelatin capsule (0.5 mg dutasteride) and white to off-white tamsulosin HCl pellets (0.4 mg tamsulosin HCl). DTC is manufactured by encapsulation of two intermediate products (a dutasteride soft gelatin capsule and tamsulosin HCl pellets) filled into a (b) (4) hard shell capsule. The DTC hard-shell capsules, size 00, have a brown body and an orange cap imprinted with GS 7CZ in black ink.

(b) (4)

In the case of dutasteride, the soft gelatin capsule fill solution was (b) (4)

In the case of tamsulosin HCl, the concentration of the drug in the (b) (4) DTC is packed into opaque, white high density polyethylene (HDPE) bottles with polypropylene child-resistant closures with induction-seal liners.

It should be noted that the Sponsor has (b) (4) based on the purity of the batch of active substance. According the CMC reviewer, Dr. Yichun Sun, the correction factor calculation appears to be appropriate. The complete statements of the components and quantitative composition of dutasteride product intermediate and tamsulosin HCl product intermediate are given in Tables 2 and 3 below.

Table 2: Composition of Dutasteride Product Component, 0.5 mg Dutasteride

Component	Quantity (mg/capsule)	Function	Reference to Standard
Fill Solution			
Dutasteride [1]	0.50	Active	GlaxoSmithKline
Mono-di-glycerides of Caprylic/Capric Acid (MDC) [1]	(b) (4)		Supplier
Butylated Hydroxytoluene (BHT)			USNF
(b) (4)			-
Gelatin			USNF
Glycerin			USP
Titanium Dioxide			USP
Ferric Oxide, Yellow [2]			USNF
(b) (4)			USP
			-
			Ph.Eur.
			USNF

Note:
1. (b) (4)
2. Ferric Oxide is also referred to as Iron Oxide Yellow.
3. (b) (4)
4.

Table 3: Composition of Tamsulosin Product Component, 0.4 mg Tamsulosin HCl

Component	Quantity (mg/capsule)	Function	Reference to Standard
(b) (4)			
Tamsulosin Hydrochloride [1]	0.400	Active	Supplier
Microcrystalline Cellulose	(b) (4)		USNF
Methacrylic Acid Copolymer Dispersion [2]			USNF
Talc			USP
Triethyl Citrate			USNF
(b) (4)			USP
			-
Methacrylic Acid Copolymer Dispersion [2]			USNF
Talc			USP
Triethyl Citrate			USNF
(b) (4)			USP
			-
Total Unit Dose			-

Note:
(b) (4)

2.2.4 Is the combination capsule formulation adequately bridged with the co-administration of the two individual products?

In a single dose, randomized, three-period partial cross-over pivotal BE study (Study ARI109882), it was demonstrated that the individual components of DTC (dutasteride and tamsulosin HCl) are BE to co-administration of Avodart® and Flomax® under both fed and fasted state. Food does not affect the PK of dutasteride following administration of combination capsule, DTC nor Avodart®. However, a mean 30% decrease in tamsulosin C_{max} was observed following administration of combination capsule, DTC or Flomax® co-administered with Avodart® with a high fat meal and a mean 6-9% decrease on tamsulosin AUC was observed following administration of combination capsule, DTC or Flomax® co-administered with Avodart® with a high fat meal. Considering that there is a 30% decrease in tamsulosin AUC and 40-70% decrease in tamsulosin C_{max} following administration of Flomax® monotherapy with food, the extent of food effect has decreased approximately 20-30% for both AUC and C_{max}. This might be due to combining the two respective formulations of dutasteride and tamsulosin but the cause is inconclusive. Because the prescribing information for Flomax® recommends administration approximately one-half hour following the same meal each day, the Sponsor proposes to have the same administration recommendation for DTC. This dosing recommendation is consistent with the manner in which the individual components were given in the pivotal efficacy and safety study, ARI40005. The results of the statistical comparison of dutasteride and tamsulosin PK parameters are summarized in Tables 4 and 5.

Table 4: Statistical Assessment of Serum Dutasteride PK Parameters Following a Single Dose of DTC versus Co-administration of Dutasteride and Tamsulosin HCl (Study ARI109882)

Parameter	Comparison	Point Estimate	90% CI	%CVw[2]
AUC(0-t)[1]	Fed Combination:Fed Co-administration	0.97	(0.92, 1.03)	24.1
	Fed Co-administration:Fasted Co-administration	1.09	(1.01, 1.18)	
	Fasted Combination:Fasted Co-administration	1.01	(0.91, 1.12)	
	Fed Combination: Fasted Combination	1.05	(0.97, 1.13)	
C_{max}[1]	Fed Combination:Fed Co-administration	1.00	(0.94, 1.05)	23.4
	Fed Co-administration:Fasted Co-administration	1.01	(0.93, 1.09)	
	Fasted Combination:Fasted Co-administration	0.99	(0.89, 1.09)	
	Fed Combination: Fasted Combination	1.01	(0.94, 1.09)	

[1] Point estimate is the ratio of adjusted geometric means between regimens
[2] %CVw represents a pooled estimate of within-subject variability across regimens

Combination: dutasteride 0.5 mg and tamsulosin HCl 0.4 mg combination capsule (DTC)
Co-administration: Advodart® 0.5 mg + Flomax® 0.4 mg

Table 5: Statistical Assessment of Serum Tamsulosin PK Parameters Following a Single Dose of DTC versus Co-administration of Dutasteride and Tamsulosin HCl (Study ARI109882)

Parameter	Comparison	Point Estimate	90% CI	%CVw[2]
AUC(0-t)[1]	Fed Combination:Fed Co-administration	1.03	(0.97, 1.09)	22.0
	Fed Co-administration:Fasted Co-administration	0.91	(0.85, 0.98)	
	Fasted Combination:Fasted Co-administration	1.00	(0.91, 1.10)	
	Fed Combination: Fasted Combination	0.94	(0.87, 1.01)	
C_{max}[1]	Fed Combination:Fed Co-administration	1.08	(1.00, 1.15)	28.4
	Fed Co-administration:Fasted Co-administration	0.70	(0.64, 0.77)	
	Fasted Combination:Fasted Co-administration	1.07	(0.95, 1.21)	
	Fed Combination: Fasted Combination	0.70	(0.64, 0.77)	

[1] Point estimate is the ratio of adjusted geometric means between regimens
[2] %CVw represents a pooled estimate of within-subject variability across regimens

Combination: dutasteride 0.5 mg and tamsulosin HCl 0.4 mg combination capsule (DTC)
Co-administration: Advodart® 0.5 mg + Flomax® 0.4 mg

(b) (4) In the case of dutasteride, the soft gelatin capsule fill solution was (b) (4) In the case of tamsuloisn HCl, the concentration of the drug in the generic tamsulosin (b) (4) These changes were supported by BE studies on the proposed intermediate (after change, individual component of the combination capsule) versus the corresponding commercial product (before change) just as summarized below:

- Tamsulosin administered as a combination capsule (DTC) at steady state was BE (AUC and C_{max}) to tamsulosin co-administered as Flomax® with Avodart® (dutasteride) under fasted state (Study ARI111402).
- Dutasteride 0.5 mg administered as a single dose of a soft gelatin capsule containing (b) (4) mg soft gelatin capsule fill solution was BE (AUC and C_{max}) to when dutasteride was administered as a single dose of Avodart® (containing (b) (4) mg soft gelatin capsule fill solution) under fasted state (Study ARI103880).
- Tamsulosin 0.4 mg administered as a single dose of a tamsulosin HCl capsule containing MR pellets, (b) (4) % w/w ((b) (4)) was BE (AUC and C_{max}) to tamsulosin administered as a single dose of a Flomax 0.4 mg MR capsule (Boehringer Ingelheim Pharmaceuticals Inc., USA) under fed state (Study 163/07).
- Tamsulosin 0.4 mg administered as a single dose of tamsulosin HCl capsules containing MR pellets, (b) (4) % w/w ((b) (4)) was BE (AUC and C_{max}) to tamsulosin administered as a single dose of a Flomax 0.4 mg MR capsule (Boehringer Ingelheim Pharmaceuticals Inc., USA) under fed state (Study 186/07).

2.2.5 What are the PK parameters of tamsulosin and dutasteride when a single dose of DTC was administered under fed?

Single Dose PK

The PK parameters of dutasteride and tamsulosin observed in a single dose, randomized, three-period partial cross-over pivotal BE study (Study ARI109882) are summarized below:

Dutasteride PK Parameters

Following a single dose of DTC under fed state, dutasteride had a median T_{max} of 3 hr (range: 1-10 hr). A mean C_{max} value of 2.14 ng/ml was observed for dutasteride. Dutasteride had a mean AUC(0-t) value of 39.6 ng·hr/ml.

Table 6: Summary of Serum Dutasteride PK Parameters Following a Single Dose of DTC Under Fed State (Study ARI109882)

Parameter	N	Arithmetic Mean (SD)
AUC(0-t) (ng·hr/ml)	92	39.6 (23.1)
C_{max} (ng/ml)	92	2.14 (0.77)
T_{max} (hr)	92	3 (1, 10)[1]

[1] Median (range)

Sponsor did not characterize the multiple dose PK parameters of dutasteride following multiple dose administration of DTC. According to the current Avodart® label, the terminal half-life of dutasteride monotherapy is approximately 5 weeks at steady state. Due to the long half-life of dutasteride, serum concentrations remain detectable (greater than 0.1 ng/ml) for up to 4 to 6 months after discontinuation of treatment. In Study ARI103880, dutasteride administered as a combination capsule, DTC, containing (b) (4) mg (b) (4) in the soft gelatin capsule was BE to when dutasteride was administered as Avodart®. The Sponsor is relying on dutasteride's steady state PK information on the current Avodart® label.

Tamsulosin PK Parameters

Following a single dose of DTC under fed state, tamsulosin had a median T_{max} of 6 hr (range: 2-24 hr). A mean $t_{1/2}$ value of 13.5 hr, a mean C_{max} value of 11.3 hr, and a mean AUC(0-t) value of 187.2 ng·hr/ml for tamsulosin was observed.

Table 7: Summary of Serum Tamsulosin PK Parameters Following a Single Dose of DTC Under Fed State (Study ARI109882)

Parameter	N	Arithmetic Mean (SD)
AUC(0-t) (ng·hr/ml)	92	187.2 (95.7)
C_{max} (ng/ml)	92	11.3 (4.44)
T_{max} (hr)	92	6 (2, 24)[1]
$t_{½}$ (hr)	91	13.5 (3.92)

[1] Median (range)

Multiple Dose PK

The multiple dose PK parameters of tamsulosin were characterized following once daily oral administration of DTC under fasted state in an open-label, randomized, repeat dose, 3-period crossover study to determine the BE of 3 different formulations of tamsulosin at steady state in healthy male volunteers study (Study ARI111402) are summarized below:

Table 7: Summary of Serum Tamsulosin PK Parameters Following Multiple Doses of DTC under Fasted State (Study ARI111402)

Parameter	N	Day 1 Arithmetic Mean (SD)	Day 7 Arithmetic Mean (SD)
AUC(0-24) (ng·hr/ml)	23	138.7 (33.0)	188.9 (56.2)
C_{max} (ng/ml)	23	14.4 (3.3)	17.2 (4.2)
C_{min} (ng/ml)	23	NC	3.11 (1.59)
T_{max} (hr)	23	5 (3, 7)[1]	5 (3, 7)[1]
$t_{½}$ (hr)	23	NC	13.9 (2.67)

[1] Median (range)
NC: Not calculated

2.2.6 What is the Sponsor's justification of the pediatric waiver request and is it acceptable?

The current DTC (dutasteride and tamsulosin HCl combination capsule) is for the treatment of BPH in men with an enlarged prostate. BPH is a disease of aging men and has no pediatric correlate. Neither dutasteride nor tamsulosin, in concomitant use or as a combination product has been investigated in the pediatric population. Dutasteride is contraindicated in children. A full pediatric waiver was requested by the Sponsor and was granted for the combination product, DTC by the Agency's pediatric review committee (PeRC) on September 23, 2009.

2.2.7 Did the Sponsor use validated bioanalytical methods to generate the study data?

Yes. The bioanalytical methods involved LC-MS/MS detection. Details of the bioanalytical method used in each study are summarized below.

For Studies ARI103880 and ARI109882, the concentrations of dutasteride in human serum were determined by validated, internal standard added analytical methods consisting of protein precipitation followed by LC-MS/MS detection. The analytical methods were selective for dutasteride and were linear over the dynamic range of 0.1-50 ng/ml, with a lower limit of quantification (LLOQ) of 0.1 ng/ml. Precision of the assay, as determined by coefficients of variation, was ≤ 14.7 % and accuracy (% bias) within ± 13.6 % at all concentrations within the dynamic range.

For Studies ARI109882 and ARI111402, the concentrations of tamsulosin in human serum were determined by a validated, internal standard added analytical method consisting of protein precipitation followed by LC-MS/MS detection. The analytical method was selective for tamsulosin and was linear over the dynamic range of 0.05-50 ng/ml, with a LLOQ of 0.05 ng/ml. Precision of the assay, as determined by coefficients of variation, was δ10.4 % and accuracy (% bias) within ± 14.7 % at all concentrations within the dynamic range.

For Studies 163/07 and 186/07 performed by (b) (4), the concentrations of tamsulosin in human plasma were determined by a validated, internal standard added analytical method consisting of solvent extraction followed by LC-MS/MS detection. The analytical method was selective for tamsulosin and was linear over the dynamic range of 0.2-30 ng/ml, with a LLOQ of 0.2 ng/ml. Precision of the assay, as determined by coefficients of variation, was ≤ 11.1 % and accuracy (% bias) within ± 3.3 % at all concentrations within the dynamic range.

The bioanalytical methods had preset acceptance criteria established. All acceptance criteria were in compliance with the *Bioanalytical Method Validation Guidance* and were met.

DSI consult (signed off by Dr. Dennis Bashaw on May 19, 2009) on the clinical BE sites (Covance Research, Evansville, IN and Austin, TX) and the bioanalytical site (GlaxoSmithKline, Research Triangle Park, NC) was requested for the pivotal BE study, ARI109882 and is pending. An addendum to this review will be added when the DSI consult results become available.

Appendix

A.1. Individual Study Review

A.1.1. Study ARI109882 (Pivotal BE Study)

An Open-Label, Randomized, Single Dose, Three-Period Partial Crossover Study to Determine the Bioequivalence and Food Effect of a Combination Capsule Formulation of Dutasteride and Tamsulosin Hydrochloride (0.5 mg/0.4 mg) Compared to Concomitant Dosing of Avodart® 0.5 mg and Flomax® 0.4 mg Commercial Capsules in Healthy Male Subjects

Protocol No:	ARI109882
Phase:	1
Principal Investigator:	Ronald Kimberlin, M.D. and David Carter, M.D.
Clinical Study Center:	Covance Research, Evansville, IN
Clinical Study Dates:	October 18, 2007 - February 22, 2008
Analytical Study Facility:	GlaxoSmithKline, Research Triangle Park, NC
Analytical Study Dates:	December 15, 2006 - June 18, 2007

OBJECTIVE

The primary objective of the study was to:

1. To investigate the BE of a combination capsule formulation of dutasteride 0.5 mg / tamsulosin HCl 0.4 mg relative to concomitant dosing of Avodart® 0.5 mg and Flomax® 0.4 mg under fed state.
2. To investigate the BE of a combination capsule formulation of dutasteride 0.5 mg / tamsulosin HCl 0.4 mg relative to concomitant dosing of Avodart® 0.5 mg and Flomax® 0.4 mg under fasted state.
3. To assess the effect of a high fat meal on the PK of a combination capsule formulation of dutasteride 0.5 mg / tamsulosin HCl 0.4 mg.

The secondary objective of the study was to assess the safety and tolerability of dosing with the combination capsule formulation of dutasteride 0.5 mg / tamsulosin HCl 0.4 mg.

STUDY RATIONALE

To support the product label for the dutasteride and tamsulosin HCl combination capsule, this study evaluated the BE of the combination product to concomitant dosing with separate capsules of dutasteride and tamsulosin HCl commercial formulations. In this study, subjects were dosed under fed and fasted state. Although dutasteride can be dosed under fed or fasted state, tamsulosin is to be dosed approximately 30 min after a meal. Therefore, the combination product was dosed under fed state, which requires that BE of the combination product compared to the individual components is demonstrated under fed state. A fasted arm was included to satisfy the Health Canada requirement that BE also needs to be demonstrated under fasted state. This study also evaluated the effect of food (high fat meal state vs. fasted state) on the absorption of dutasteride and tamsulosin HCl when given in a combination capsule formulation.

STUDY ENDPOINTS

The primary endpoint of the study was:

- Fed BE endpoints: For tamsulosin, the primary endpoints were AUC(0-24), AUC(0-∞) [defaulting to AUC(0-t) if AUC(0-∞) cannot be consistently determined], and C_{max} under fed state. For dutasteride, the primary endpoints were AUC(0-24), AUC(0-72), and C_{max} under fed state.
- Fasted BE endpoints: For tamsulosin, the primary endpoints were AUC(0-24), AUC(0-∞) [defaulting to AUC(0-t) if AUC(0-∞) cannot be consistently determined], and C_{max} under fasted state. For dutasteride, the primary endpoints were AUC(0-24), AUC(0-72), and C_{max} in the fasted state.

Secondary endpoints were:

- The secondary PK endpoints were $t_{1/2}$, t_{max} and λ for both tamsulosin and dutasteride, and C_{min} for tamsulosin only, as data permitted.
- Safety and tolerability of all treatments as assessed by blood pressure and pulse rate measurements, adverse events (AEs) and clinical laboratory safety tests.

STUDY DESIGN, TREATMENT, AND SUBJECTS

This was a multi-center, open-label, single dose, randomized, 3-way partial crossover design study in healthy adult males. Each subject participated in 3 sessions and received 3 of the 4 treatment regimens listed in Table A-1-1. Subjects were randomized to one of the following sequences: ABC, ACB, BAC, BCA, CAB, CBA, ABD, ADB, BAD, BDA, DAB, or DBA. Dosing was separated by approximately a 28-day washout period. The doses were as follows:

Table A-1-1: Study Medication Dosing Treatments

Regimen	Description
A	Flomax 0.4 mg (sustained release capsule commercially available in United States) and AVODART 0.5 mg in a fed state (Reference)
B	Dutasteride and Tamsulosin HCl Combination Capsules, 0.5 mg dutasteride, 0.4 mg tamsulosin hydrochloride in a fed state (Test)
C	Flomax 0.4 mg (sustained release capsule commercially available in United States) and AVODART 0.5 mg in a fasted state (Reference)
D	Dutasteride and Tamsulosin HCl Combination Capsules, 0.5 mg dutasteride, 0.4 mg tamsulosin hydrochloride in a fasted state (Test)

Subjects in the fed groups (Regimen A and Regimen B) were dosed approximately 30 min after the start of the meal. Each subject received the dose at approximately the same time in each session. Medication was swallowed, without chewing, with 240 ml of water at room temperature.

In each session, subjects were admitted to the clinical research unit (CRU) the evening prior to dosing (Day -1) and remained as inpatients until approximately 48 hr after dosing. The subjects returned to the CRU for an outpatient visit at approximately 72 hr post-dose. Upon completion of the last dosing session, subjects were contacted via telephone within approximately 10-14 days for a follow-up inquiry (or visit at the discretion of the investigator) and were subsequently discharged from the study. The total study duration was approximately 4 months.

The patient inclusion criteria included the following:

- Healthy subjects defined as individuals who were free from clinically significant illness or disease as determined by the investigator based on their medical history, physical examination, laboratory studies, electrocardiograms (ECGs), and other tests.
- Males between 18 - 45 yrs of age, inclusive.
- Weight range 55 - 95 kg (inclusive) and body mass index 19 - 30 kg/m^2 (inclusive).

- Willing and able to give written informed consent, willing to participate for the full duration of the study, and able to understand and follow instructions related to study procedures.

A subject was not eligible for inclusion in this study if any of the following criteria applied:

- Slow metabolizer for CYP2D6 as determined by screening PGx analysis. The Sponsor has not provided detail information on the screening PGx nor the definition of slow CYP2D6 metabolizers applied in this study.
- Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements within 7 days (or 14 days if the drug is a potential enzyme inducer, such as St. John's Wort) or 5 half-lives (whichever was longer) prior to the first dose of study medication, unless in the opinion of the investigator and sponsor the medication did not interfere with the study procedures or compromise subject safety.
- History of regular alcohol consumption exceeding 14 drinks/week for men (1 drink = 5 ounces of wine or 12 ounces of beer or 1.5 ounces of hard liquor) within 6 months of screening. Subjects were able and willing to abstain from beverages and foods containing alcohol 24 hr prior to and during the dosing day.
- A positive urine drug or alcohol (breath test or urine) screen result at screening or check-in. A minimum list of drugs that were screened for included amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines.
- The subject received an investigational drug or participated in any other research trial within 30 days or 5 half-lives, or twice the duration of the biological effect of any drug (whichever was longer) prior to the first dose of current study medication or anytime during the study.
- Subjects who consumed the following foods or drinks within 7 days prior to the first dose of study medication or at any time during the clinical phase of the study: grapefruit juice; red wine; grapefruit or cruciferous vegetables (watercress, broccoli, cabbage, Brussels sprouts).
- QTc ≥ 450 msec at screening.

A total of 101 male subjects with a mean age of 29.5 yrs were enrolled in the study. 81 subjects completed the study as planned. The most common reasons for withdrawal were withdrawn consent and protocol deviations.

Table A-1-2: Summary of Subject Disposition and Demographic Characteristics

Number of subjects planned, n:	98
Number of subjects randomized, n:	101
Number of subjects completed as planned, n (%):	81 (80)
Number of subjects withdrawn (any reason), n (%):	20 (20)
Withdrew consent	7 (7)
Protocol deviation	7 (7)
Adverse event	4 (4)
Investigator discretion (missed 72 hour post-dose visit in Periods 1 and 2)	1 (1)
Lost to follow-up	1 (1)
Number of subjects included in safety population, n (%):	101 (100)
Number of subjects included in PK population, n (%):	101 (100)
Age in Years, Mean (Range)	29.5 (19-45)
Sex, n (%)	
Female:	0
Male:	101 (100)
BMI (kg/m²), Mean (Range)	25.6 (19-30)
Height (cm), Mean (Range)	176.2 (164-191)
Weight (kg), Mean (Range)	79.4 (59.0-106.4)
Ethnicity, n (%)	
Hispanic or Latino:	10 (10)
Not Hispanic or Latino:	91 (90)
Race, n (%)	
African American/African Heritage	22 (22)
White – White/Caucasian/European Heritage	78 (77)
White – Mixed Race	1 (1)

FORMULATION

Dutasteride and tamsulosin HCl combination capsules (DTC) were supplied by GlaxoSmithKline as hard gelatin capsules with an orange cap and brown body, each containing 0.5 mg dutasteride (GI198745) and 0.4 mg tamsulosin HCl. The capsules were imprinted with GS 7CZ in black ink on the cap. Dutasteride and tamsulosin HCl combination capsules were supplied as 30 capsules in a white 100 cc HDPE bottle with a 33-400 child resistant closure and a single clinical label.

Avodart® was supplied by GlaxoSmithKline as oblong, dull yellow, soft gelatin capsules containing 0.5 mg dutasteride (GI198745). These capsules were identical in formulation to the commercially available Avodart® except they were plain. They were not branded with the red ink commercial print. Avodart® capsules were supplied as 100 capsules in a white 120 cc HDPE bottle with a 38-400 child resistant closure and a single clinical label.

Flomax® was supplied by GlaxoSmithKline as the commercially available product. Flomax® capsules were elongated hard gelatin capsules with an olive green cap and orange body, each containing 0.4 mg tamsulosin HCl. The capsules were imprinted on one side with Flomax® 0.4 mg and on the other side with BI 58 in black ink. Flomax® capsules were supplied as 100 capsules in their white commercial bottle with commercial label.

Table A-1-3: Identity of Investigational Product(s)

Drug	Dose/Form/Route	Frequency/Duration	Batch or Lot Number
Flomax	0.4 mg / sustained release capsule / oral	Single dose	Lot # G0700308
AVODART	0.5 mg/ capsule / oral	Single dose	Batch # E09094
Dutasteride and Tamsulosin Hydrochloride Combination Capsule	0.5 mg dutasteride, 0.4 mg tamsulosin HCl / capsules / oral	Single dose	Batch # 705002-91294

PHARMACOKINETIC EVALUATION

Blood sampling

In each session, blood samples (approximately 2 ml each) for analysis of dutasteride and tamsulosin concentrations were collected via an IV cannula at pre-dose and at the following time points following dosing: 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, and 24 hrs. Venipuncture was used to collect samples at 36, 48 and 72 hrs post-dose.

Concomitant Therapy

Use of drugs, including herbal/dietary supplements and vitamins, was prohibited within 7 days (or 14 days if the drug was a potential enzyme inducer, such as St. John's Wort) or 5 half-lives (whichever was longer) prior to the first dose of study medication, unless in the opinion of the investigator and sponsor the medication would not interfere with the study procedures or compromise subject safety. The investigator was informed by a subject as soon as possible about any medication taken from the time of screening until the end of the clinical phase of the study (final laboratory sample) and these were fully documented in the subject's CRF. All concomitant medications taken during the study were recorded in the CRF. The minimum requirement was that drug name and the dates of administration were recorded. Acetaminophen at doses of ≤ 2 grams/day was permitted.

Bioanalytical method
Serum dutasteride (GI198745) and tamsulosin (GI138525) concentrations were determined by Worldwide Bioanalysis, Drug Metabolism and Pharmacokinetics, GlaxoSmithKline, Research Triangle Park, NC, USA. Human serum samples were analyzed for dutasteride and tamsulosin concentrations using a validated bioanalytical method.

Dutasteride and tamsulosin were extracted from human serum by protein precipitation. Extracts were analyzed by high-performance LC-MS/MS detection. The assay was validated over the dutasteride concentration range 0.1 to 50 ng/ml and over the tamsulosin concentration range 0.05 to 50 ng/ml in human serum. Quality controls (QC) were prepared and analyzed with each batch of samples against separately prepared calibration standards to assess the day-to-day performance of the assay. For the analysis to be acceptable, no more than one third of the quality control results were to deviate from the nominal concentration by more than 15%, with at least one quality control result acceptable at each concentration. QC results from this study met these acceptance criteria. All acceptance criteria were in compliance with the *Bioanalytical Method Validation Guidance* and were met.

Safety Assessments
Clinical laboratory assessments such as clinical chemistry (albumin, ALT, alkaline phosphatase, AST, BUN, calcium, chloride, creatinine, GGT, glucose [fasting], potassium, sodium, total bilirubin, total CO_2), hematology (CBC with RBC indices and WBC differential, platelet count), urinalysis (specific gravity, pH, glucose, protein, blood, ketones, microscopic examination [if dipstick is positive]), and other tests (HIV antibody, Hepatitis B, Hepatitis C, urine drug screen, alcohol screen) were performed. In addition, physical examinations, vital signs (e.g., blood pressure and heart rate) readings were performed at prespecified time points indicated in the protocol. Supine 12-lead ECGs were taken at screening only.

DATA ANALYSIS
Pharmacokinetic Analysis
Following $\log_e$-transformation, $\log_e$-transformed values of PK parameters were analyzed by analysis of variance (ANOVA) using mixed effects model, fitting the fixed effects for treatment sequence, session, and regimen and subject within sequence as a random effect. For each endpoint, results from these analyses were exponentiated back to obtain point and 90% CI estimates of the test-to-reference ratios of geometric least-squares (GLS) means (B:A in fed state and D:C in fasted state). BE was demonstrated if the 90% confidence intervals (CIs) for the ratios of AUC [AUC(0-∞) for tamsulosin and AUC(0-t) for dutasteride] and C_{max} were completely contained within the range 0.8000 to 1.2500.

To assess the effect of food on the combination capsule formulation, similar analyses were performed to obtain the point estimate (PE) and CI for the comparison of B (fed):D (fasted).

T_{max} was analyzed nonparametrically using the Wilcoxon Matched Pairs Method [B-A in fed state, B (fed)-D (fasted)] and Mann-Whitney Method (D-C in fasted state) to compute the PE and 90% CI for the median difference for each comparison of interest.

Safety Evaluations and Adverse Events
No formal statistical analyses of the safety data were performed. Safety data, including AEs, vital signs, clinical laboratory data and ECG data were listed and summarized. Any clinically significant abnormalities were described.

PHARMACOKINETIC RESULTS

Dutasteride PK Parameters

Following a single dose of DTC under fed state, dutasteride had a median T_{max} of 3 hr (range: 1-10 hrs. A mean C_{max} value of 2.14 ng/ml was observed for dutasteride. Dutasteride had a mean AUC(0-t) value of 39.6 ng·hr/ml.

Table A-1-4: Summary of Serum Dutasteride PK Parameters Following a Single Dose of DTC Under Fed State (Study ARI109882)

Parameter	N	Arithmetic Mean (SD)
AUC(0-t) (ng·hr/ml)	92	39.6 (23.1)
C_{max} (ng/ml)	92	2.14 (0.77)
T_{max} (hr)	92	3.00 (1.00, 10.00)[1]

[1] Median (range)

Sponsor did not characterize the multiple dose PK parameters of dutasteride following multiple dose administration of DTC. According to the current Avodart® label, the terminal half-life of dutasteride monotherapy is approximately 5 weeks at steady state. Due to the long half-life of dutasteride, serum concentrations remain detectable (greater than 0.1 ng/ml) for up to 4 to 6 months after discontinuation of treatment. In Study ARI103880, dutasteride administered as a combination capsule, DTC, containing (b) (4) mg (b) (4) in the soft gelatin capsule was BE to when dutasteride was administered as Avodart®. The Sponsor is relying on dutasteride's steady state PK information on the current Avodart® label.

Tamsulosin PK Parameters

Following a single dose of DTC under fed state, tamsulosin had a median T_{max} of 6 hr (range: 2-24 hr). A mean $t_{1/2}$ value of 13.5 hr, a mean C_{max} value of 11.3 hr, and a mean AUC(0-t) value of 187.2 ng·hr/ml for tamsulosin was observed.

Table A-1-5: Summary of Serum Tamsulosin PK Parameters Following a Single Dose of DTC Under Fed State (Study ARI109882)

Parameter	N	Arithmetic Mean (SD)
AUC(0-t) (ng·hr/ml)	92	187.2 (95.7)
C_{max} (ng/ml)	92	11.3 (4.44)
T_{max} (hr)	92	6.00 (2.00, 24.00)[1]
$t_{½}$ (hr)	91	13.5 (3.92)

[1] Median (range)

STATSTICAL ANALYSIS

A total of 101 subjects were enrolled to the study, with 81 completers and 20 subjects prematurely withdrawn from the study. Per protocol, subjects who provided PK parameter data were included in PK parameter population.

Statistical Analysis of Dutasteride PK Parameters

Dutasteride C_{max} and AUC values were similar between the fasted or fed state, whether administered alone or in combination with 0.4 mg tamsulosin HCl. Dutasteride C_{max} and AUC(0-t) point estimates

(PE) were within 9% of unity, and the 90% confidence intervals (CI) for each treatment comparison were entirely contained within the equivalence interval of 80-125%. It was noted that dutasteride mean t_{max} was observed 1 hr later in the fed (3.6 hr) compared to fasted (2.5 hr) state. The results of the statistical comparison of dutasteride PK parameters are summarized in Table A-1-6.

Table A-1-6: Statistical Assessment of Serum Dutasteride PK Parameters Following a Single Dose of DTC (Study ARI109882)

Parameter	Comparison	Point Estimate	90% CI	%CVw[2]
AUC(0-t)[1]	Fed Combination:Fed Co-administration	0.97	(0.92, 1.03)	24.1
	Fed Co-administration:Fasted Co-administration	1.09	(1.01, 1.18)	
	Fasted Combination:Fasted Co-administration	1.01	(0.91, 1.12)	
	Fed Combination: Fasted Combination	1.05	(0.97, 1.13)	
C_{max}[1]	Fed Combination:Fed Co-administration	1.00	(0.94, 1.05)	23.4
	Fed Co-administration:Fasted Co-administration	1.01	(0.93, 1.09)	
	Fasted Combination:Fasted Co-administration	0.99	(0.89, 1.09)	
	Fed Combination: Fasted Combination	1.01	(0.94, 1.09)	

[1] Point estimate is the ratio of adjusted geometric means between regimens
[2] %CVw represents a pooled estimate of within-subject variability across regimens

Combination: dutasteride 0.5 mg and tamsulosin HCl 0.4 mg combination capsule
Co-administration: Advodart® 0.5 mg + Flomax® 0.4 mg

Statistical Analysis of Tamsulosin PK Parameters

For tamsulosin, C_{max} values under fed state were found to be 30% less than those under fasted state. The magnitude of the food effect was similar in both the test and reference dosage forms. The 90% CIs associated with tamsulosin C_{max} and AUC values were entirely contained within the 80-125% interval for all regimen comparisons, except where fed state C_{max} values were compared to fasted state C_{max} values. The results of the statistical comparison of tamsulosin PK parameters are summarized in Table A-1-7.

Table A-1-7: Statistical Assessment of Serum Tamsulosin PK Parameters Following a Single Dose of DTC (Study ARI109882)

Parameter	Comparison	Point Estimate	90% CI	%CVw[2]
AUC(0-t)[1]	Fed Combination:Fed Co-administration	1.03	(0.97, 1.09)	22.0
	Fed Co-administration:Fasted Co-administration	0.91	(0.85, 0.98)	
	Fasted Combination:Fasted Co-administration	1.00	(0.91, 1.10)	
	Fed Combination: Fasted Combination	0.94	(0.87, 1.01)	
C_{max}[1]	Fed Combination:Fed Co-administration	1.08	(1.00, 1.15)	28.4
	Fed Co-administration:Fasted Co-administration	0.70	(0.64, 0.77)	
	Fasted Combination:Fasted Co-administration	1.07	(0.95, 1.21)	
	Fed Combination: Fasted Combination	0.70	(0.64, 0.77)	

[1] Point estimate is the ratio of adjusted geometric means between regimens
[2] %CVw represents a pooled estimate of within-subject variability across regimens

Combination: dutasteride 0.5 mg and tamsulosin HCl 0.4 mg combination capsule
Co-administration: Advodart® 0.5 mg + Flomax® 0.4 mg

Discussion

BE of dutasteride was demonstrated under both fasted and fed state between the combination product, DTC (dutasteride 0.5 mg / tamsulosin HCl 0.4 mg) and concomitant dosing of the commercial formulations of dutasteride (Avodart® 0.5 mg) and tamsulosin (Flomax® 0.4 mg) monotherapies. For tamsulosin, BE was demonstrated between concomitant dosing of monotherapies and the combination product, DTC under both fasted and fed states. Food does not affect the PK of dutasteride following administration of combination capsule, DTC nor Avodart®. However, a mean 30% decrease in tamsulosin C_{max} was observed following administration of combination capsule, DTC or Flomax® co-administered with Avodart® with a high fat meal and a mean 6-9% decrease on tamsulosin AUC was observed following administration of combination capsule, DTC or Flomax® co-administered with Avodart® with a high fat meal. Considering that there is a 30% decrease in tamsulosin AUC and 40-70% decrease in tamsulosin C_{max} following administration of Flomax® monotherapy with food, the extent of food effect has decreased approximately 20-30% for both AUC and C_{max}. This might be due to combining the two respective formulations of dutasteride and tamsulosin but the cause is inconclusive. Because the prescribing information for Flomax® recommends administration approximately one-half hour following the same meal each day, the Sponsor proposes to have the same administration recommendation for DTC. This dosing recommendation is consistent with the manner in which the individual components were given in the pivotal efficacy and safety study, ARI40005.

SAFETY RESULTS

Headache and dizziness were the most commonly reported AEs, consistent with the labeled safety profile of tamsulosin. All AEs were considered mild or moderate in nature, and all but 1 AE resolved. There were 2 subjects with AEs related to changes in clinical laboratory values and one subject with an AE related to a change in vital signs. There were no deaths or serious AEs (SAES) reported during this study.

CONCLUSION

- BE of dutasteride was demonstrated between the combination product, DTC and concomitant dosing with dutasteride and tamsulosin HCl monotherapies under fasted or fed state.
- BE of tamsulosin was demonstrated between the combination product, DTC and concomitant dosing with dutasteride and tamsulosin HCl monotherapies under fasted or fed state.
- Food does not affect the PK of dutasteride following administration of combination capsule, DTC nor Avodart®. However, a mean 30% decrease in tamsulosin C_{max} was observed following administration of combination capsule, DTC or Flomax® co-administered with Avodart® with a high fat meal and a mean 6-9% decrease on tamsulosin AUC was observed following administration of combination capsule, DTC or Flomax® co-administered with Avodart® with a high fat meal. This might be due to combining the two respective formulations of dutasteride and tamsulosin but the cause is inconclusive.
- Administration of the dutasteride and tamsulosin HCl combination capsule, DTC to healthy adult male volunteers was generally well tolerated under the conditions of this study. No new safety issues were identified; the most commonly reported AEs were headache and dizziness, which is consistent with the tamsulosin product label.

A.1.2. Study ARI111402

An Open-label, Randomized, Repeat Dose, 3 Period Crossover Study to Determine the Bioequivalence of 3 Different Formulations of Tamsulosin at Steady State in Healthy Male Volunteers

Protocol No:	ARI111402
Phase:	1
Principal Investigator:	Christian Lates, M.D. and Robert Blum, Pharm.D.
Clinical Study Center:	Buffalo Clinical Research Center, Buffalo, NY
Clinical Study Dates:	February 26, 2008 - April 23, 2008
Analytical Study Facility:	GlaxoSmithKline, Research Triangle Park, NC

OBJECTIVE

The primary objective of the study was to:

1. To investigate the BE of tamsulosin at steady state of a combination capsule formulation of dutasteride 0.5 mg / 10% enteric coated tamsulosin HCl 0.4 mg ([(b) (4)]% w/w, DTC) relative to concomitant dosing of Avodart® 0.5 mg and Flomax® 0.4 mg under fasting conditions.
2. To investigate the BE of tamsulosin at steady state of a combination capsule formulation of dutasteride 0.5 mg / 15% enteric coated tamsulosin HCl 0.4 mg [(b) (4)]% w/w) relative to concomitant dosing of Avodart® 0.5 mg and Flomax® 0.4 mg under fasting conditions.

The secondary objective of the study was to assess the safety and tolerability of dosing with the combination capsule formulation of dutasteride 0.5 mg / 10% enteric coated tamsulosin HCl 0.4 mg ([(b) (4)]% w/w), the combination capsule formulation of dutasteride 0.5 mg / 15% enteric coated tamsulosin HCl 0.4 mg ([(b) (4)]% w/w), and concomitant dosing of Avodart® 0.5 mg and Flomax® 0.4 mg.

STUDY RATIONALE

This study was conducted to establish BE of the 10% enteric coated tamsulosin in the combination product and the 15% enteric coated tamsulosin in the modified combination product relative to concomitant dosing with separate capsules of dutasteride and tamsulosin commercial formulations at steady state, with respect to tamsulosin. There is concern that tamsulosin may accumulate after repeat dosing, therefore, this study established BE at steady state of tamsulosin only. The results of this study was used as a basis of selecting the combination product formulation that contains 10% enteric coated ([(b) (4)]% w/w) tamsulosin for further development.

STUDY ENDPOINTS

The primary endpoint of the study was:

- AUC (0-24) and C_{max} of tamsulosin in the combination capsule formulation of dutasteride 0.5 mg / 10% enteric coated tamsulosin HCl 0.4 mg after a single dose and at steady state.
- AUC (0-24) and C_{max} of tamsulosin in the combination capsule formulation of dutasteride 0.5 mg / 15% enteric coated tamsulosin HCl 0.4 mg after a single dose and at steady state.
- AUC (0-24) and C_{max} of tamsulosin in concomitant dosing of Avodart® 0.5 mg and Flomax® 0.4 mg.

Secondary endpoints were:

- C(tau) (defined as the concentration at 24 hr after the Day 7 dose), $t_{1/2}$, T_{max}, λ, C_{min}, and fluctuation [(C_{max} - C_{min})/(AUC(0-24)/24)] of tamsulosin, as data permit.
- Safety and tolerability of all treatments as assessed by blood pressure and pulse rate measurements, AEs and clinical laboratory safety tests.

STUDY DESIGN, TREATMENT, AND SUBJECTS

This was an open-label, randomized, repeat dose, 3 period crossover study in healthy males. Each subject was to receive one of the three treatment regimens in each dosing session. There was an approximately 5-7 day washout between dosing of each session. Subjects were to participate in 3 dosing sessions. In order to minimize the potential impact of genetic variability to the PK of tamsulosin, poor CYP 2D6 metabolizers were excluded from this study.

Eligible subjects were admitted to the research unit the evening prior to dosing (Day -1) and remained in the unit until approximately 48 hr after dosing on Day 7. The subjects returned to the research unit for an outpatient visit at approximately 72 hr post-dose Day 7 after each treatment session. On days when full PK sampling took place (Days 1 and 7) subjects were fasted for 10 hr prior to drug administration and for 4 hr after. There was a washout period of approximately 5-7 days after the last dose in each treatment session. Subjects returned to the research unit 10 days after the last dose for follow-up and were subsequently discharged from the study. The total duration of each subject's participation from screening to follow-up was approximately 9 weeks.

Subjects were be assigned to ABC, ACB, BAC, BCA, CAB, or CBA in accordance with the randomization schedule generated by Discovery Biometrics, prior to the start of the study, using validated internal software (RandAll).

Table A-2-1: Identity of Investigational Products

Treatment	Drug	Dose/Form/Route	Frequency /Duration	Lot or Batch Number
A	Dutasteride and Tamsulosin Hydrochloride (10%) Combination Capsule	0.5 mg dutasteride, 0.4 mg tamsulosin HCl / capsules / oral	Once daily / 7 days	Batch # 705002-91294
B	Dutasteride and Tamsulosin Hydrochloride (15%) Combination Capsule	0.5 mg dutasteride, 0.4 mg tamsulosin HCl / capsules / oral	Once daily / 7 days	Batch # 710001-102133
C	Flomax	0.4 mg tamsulosin/ sustained release capsule / oral	Once daily / 7 days with AVODART	Lot # L0700337
	AVODART (GI198745)	0.5 mg dutasteride/ capsule / oral	Once daily / 7 days with Flomax	Batch # E09094

A subject was eligible for inclusion in this study only if all of the following criteria apply:

- Healthy as determined by a responsible physician, based on a medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring. A subject with a clinical abnormality or laboratory parameters outside the reference range for the population being studied may be included only if the Investigator and the GSK Medical Monitor agree that

the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures. Subjects with orthostasis at screening should be excluded from enrollment.
- Males between 18 and 45 years of age (inclusive).
- Male subjects agreed to use one of the contraception methods listed in the protocol. This criterion was followed from the time of the first dose of study medication until follow-up from the study.
- Body weight ≥ 55 kg and BMI within the range 19.0 – 30.0 kg/m2 (inclusive).
- Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form.
- QTcB or QTcF < 450 msec.
- Subjects agreed not to donate blood and blood products for 6 months after the last dose of study medication.

A subject was not eligible for inclusion in this study if any of the following criteria applied:
- The subject had a positive pre-study drug/alcohol screen. A minimum list of drugs that will be screened for include amphetamines, barbiturates, cocaine, opiates, cannabinoids, and benzodiazepines.
- Slow metabolizer for CYP2D6 as determined by screening PGx analysis. The Sponsor did not provide detail information on the screening PGx nor the definition of slow CYP2D6 metabolizers applied in this study.
- A positive pre-study Hepatitis B surface antigen or positive Hepatitis C antibody result within 3 months of screening.
- A positive test for HIV antibody.
- History of regular alcohol consumption within 6 months of the study defined as: An average weekly intake of > 14 drinks/week. One drink is equivalent to: 12 g alcohol = 5 ounces (150 ml) of wine or 12 ounces (360 ml) of beer or 1.5 ounces (45 ml) of 80 proof distilled spirits.
- The subject participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).
- Exposure to more than four new chemical entities within 12 months prior to the first dosing day.
- Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements (including St John's Wort) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication and until collection of the final PK sample from the study, unless in the opinion of the Investigator and GSK Medical Monitor the medication will not interfere with the study procedures or compromise subject safety.
- History of sensitivity to any of the study medications, or components thereof, including sulfonamides, or a history of drug or other allergy that, in the opinion of the investigator or GSK Medical Monitor, contraindicates their participation.
- History of postural hypotension, dizziness, poor hydration, vertigo, vaso-vagal reactions or any other signs and symptoms of orthostasis, which in the opinion of the investigator could be exacerbated by tamsulosin and result in putting the subject at risk of injury.
- Orthostatic hypotension at screening, defined as a reduction in systolic blood pressure of 20 mmHg or more and/or a reduction in diastolic blood pressure of 10 mmHg or more for standing vs. supine measurements.
- Where participation in the study would result in donation of blood or blood products in excess of 500 ml within a 56 day period.

- Unwillingness or inability to follow the procedures outlined in the protocol.
- History of sensitivity to heparin or heparin-induced thrombocytopenia.
- Consumption of red wine, seville oranges, grapefruit, grapefruit juice or cruciferous vegetables (watercress, broccoli, cabbage, Brussels sprouts) from 7 days prior to the first dose of study medication and until collection of the final PK sample in the study

A total of 24 subjects enrolled in the study and 23 completed the study. One subject was withdrawn from the study due to an SAE of epididymitis, which was deemed by the Investigator to be not related to study medication.

Table A-2-2: Summary of Subject Disposition and Demographic Characteristics

Number of Subjects	
Number of subjects planned, N:	24
Number of subjects randomized, N:	24
Number of subjects included in All subjects (safety) population, n (%):	24 (100)
Number of subjects included in PK population, n (%):	24 (100)
Number of subjects completed as planned, n (%):	23 (96)
Number of subjects withdrawn (any reason), n (%):	1 (4)
Reasons for subject withdrawal, n (%)	
Serious Adverse Event	1 (4)
Demographics	
Age in Years, Mean (Range)	24 (19-45)
Sex, n (%)	
Female:	0
Male:	24 (100)
BMI, Mean (Range)	26.0 (21.8-29.5)
Height, Mean (Range)	177 (165-185)
Weight, Mean (Range)	81.4 (65.3-95)
Ethnicity, n (%)	
Hispanic or Latino:	2 (8)
Not Hispanic or Latino:	22 (92)
Race, n (%)	
African American/African Heritage	11 (46)
Asian – South East Asian Heritage	2 (8)
White – White/Caucasian/European Heritage	10 (42)
Mixed Race	1 (4)

FORMULATION

Avodart® was supplied by GSK as oblong, dull yellow, soft gelatin capsules containing 0.5 mg dutasteride (GI198745). These capsules were identical in formulation to the commercially available Avodart® except they were plain. They were not branded with the red ink commercial print. Avodart® capsules were supplied as 100 capsules in a white 120cc HDPE bottle with a 38-400 child resistant closure and a single clinical label. Flomax® was supplied by GSK as the commercially available product. Flomax® capsules were elongated hard gelatin capsules with an olive green cap and orange body, each containing 0.4 mg tamsulosin HCl. The capsules were imprinted on one side with Flomax® 0.4 mg and on the other side with BI 58 in black ink. Flomax® capsules were supplied as 100 capsules in their white commercial bottle with commercial label.

Dutasteride and tamsulosin HCl combination capsules (10% and 15%) were supplied by GSK as hard gelatin capsules with an orange cap and brown body, each containing 0.5 mg dutasteride (GI198745) and 0.4 mg tamsulosin HCl. The capsules were imprinted with GS 7CZ in black ink on the cap. Each formulation looked identical. Dutasteride and tamsulosin HCl combination capsules (10% and 15%) were supplied as 30 capsules in a white 100 cc HDPE bottle with a 33-400 child resistant closure and a single clinical label.

PHARMACOKINETIC EVALUATION

Blood sampling

In each session, blood samples (approximately 2 ml each) for analysis of tamsulosin concentrations were collected on Day 1 at pre-dose and at the following time points: 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, and 16 hr post-dose. Pre-dose samples were collected on Days 2-6. On Day 7, samples were collected at pre-dose and the following time points: 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, and 72 hr post-dose. Samples were collected into empty red top tubes without anticoagulant and allowed to clot at room temperature for no longer than 30 min. The samples were stored frozen at or below -20ºC until shipped on dry ice to the Department of Worldwide Bioanalysis, DMPK, GSK, US for analysis.

Concomitant Therapy

Subjects were to abstain from taking any vitamins, herbal, and dietary supplements within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication until the collection of the final PK sample from the study, unless in the opinion of the Investigator and Sponsor the medication would not interfere with the study.
Acetaminophen, at doses of ≤ 2 grams/day was permitted. Other concomitant medication could be considered on a case by case basis by the GSK Medical Monitor.

Bioanalytical method

Serum tamsulosin (GI138525) concentrations were determined by Worldwide Bioanalysis, Drug Metabolism and Pharmacokinetics, GSK, Research Triangle Park, NC, USA. Human serum samples were analysed for tamsulosin concentrations using a validated bioanalytical method. Tamsulosin was extracted from human serum by protein precipitation. Extracts were analyzed by high-performance LC-MS/MS detection. The assay was validated and linear over the tamsulosin concentration range of 0.05-50 ng/ml in human serum.

QCs were prepared and analyzed with each batch of samples against separately prepared calibration standards to assess the day-to-day performance of the assay. For the analysis to be acceptable, no more than one third of the quality control results were to deviate from the nominal concentration by more than 15%, with at least one QC result acceptable at each concentration. Precision of the assay, as determined by coefficients of variation, was ≤ 10.4 % and accuracy (% bias) within ± 14.7 % at all concentrations within the linear range. QC results from this study met these acceptance criteria. All acceptance criteria were in compliance with the *Bioanalytical Method Validation Guidance* and were met.

Safety Assessments

Clinical laboratory assessments such as clinical chemistry (albumin, ALT, alkaline phosphatase, AST, BUN, calcium, chloride, creatinine, GGT, glucose [fasting], potassium, sodium, total and direct bilirubin, total CO_2, total protein [screening]), hematology (CBC with RBC indices and WBC differential, platelet count), urinalysis (specific gravity, pH, glucose, protein, blood, ketones, microscopic examination [if dipstick is positive]), and other tests (HIV antibody, Hepatitis B, Hepatitis C, urine drug screen, alcohol screen) were performed. In addition, physical examinations, vital signs (e.g., blood pressure, heart rate, and orthostatic vital signs) readings were performed at prespecified time points indicated in the protocol. Supine 12-lead ECGs were taken at screening only.

DATA ANALYSIS

Pharmacokinetic Analysis

PK analyses were conducted by Covance Laboratories Inc, Madison, WI, USA, under the direction of Clinical Pharmacokinetics/Modeling and Simulation, CPDM, GSK. The statistical analyses of PK data were the responsibility of Discovery Biometrics (DB), GSK.

PK analyses of serum tamsulosin concentration-time data were conducted using non-compartmental Model 200 (for extravascular administration) of WinNonlin Professional Edition version 5.2 (Pharsight Corporation, Mountain View, CA) according to the Sponsor's guidance described on non-compartmental analysis of PK data. Actual elapsed time from dosing was used to estimate all individual serum PK parameters for evaluable subjects. Values for the following PK parameters were estimated following administration of single and multiple doses of tamsulosin, as appropriate.

- The maximum observed serum concentration (C_{max}), the first time to reach C_{max} (T_{max}), and the trough concentrations (C_T) were the actual observed values.
- Where possible, the terminal serum elimination rate-constant (λ_z) was estimated from log-linear regression analysis of the terminal phase of the serum concentration-time profile. The number of points included in the terminal phase was determined by visual inspection of the semi-log plots of the serum concentration-time profiles. The associated apparent terminal elimination half-life ($t_{1/2}$) was calculated as $\ln 2/\lambda_z$.
- Fluctuation (FL) of tamsulosin was calculated [$(C_{max} - C_{min})/(AUC(0\text{-}24)/24)$].
- The area under the serum concentration-time curve from time zero to 24 hr post-dose [AUC(0-24)] were calculated by a combination of linear and logarithmic trapezoidal methods. The linear trapezoidal method was used for all incremental trapezoids arising from increasing concentrations and the logarithmic trapezoidal method was used for those arising from decreasing concentrations.

Serum tamsulosin PK parameter estimates were listed by subject and treatment and study day. Individual serum tamsulosin parameter estimates were plotted by treatment on linear scales. Serum tamsulosin PK parameter values were summarized by treatment and study day.

PHARMACOKINETIC RESULTS

The PK parameters of tamsulosin were characterized following once daily oral administration under fasted state in an open-label, randomized, repeat dose, 3-period crossover study to determine the BE of 3 different formulations of tamsulosin at steady state in healthy male volunteers study (Study ARI111402) are summarized below:

Table A-2-4: Summary of Serum Tamsulosin PK Parameters Following Multiple Doses of DTC under Fasted State (Study ARI111402)

Parameter	N	Day 1 Arithmetic Mean (SD)	Day 7 Arithmetic Mean (SD)
AUC(0-24) (ng·hr/ml)	23	138.7 (33.0)	188.9 (56.2)
C_{max} (ng/ml)	23	14.4 (3.3)	17.2 (4.2)
C_{min} (ng/ml)	23	NC	3.11 (1.59)
T_{max} (hr)	23	5 (3, 7)[1]	5 (3, 7)[1]
$t_{½}$ (hr)	23	NC	13.9 (2.67)

[1] Median (range)
NC: Not calculated

STATSTICAL ANALYSIS

Comparing regimen A with regimen C, the point estimates of AUC(0-24) and C_{max} were contained within the 80-125% interval, indicating no significant differences between regimen A and regimen C. Similarly, the point estimates of AUC(0-24) and C_{max} were contained within the 80-125% interval, indicating no significant difference between regimen B and regimen C. The 90% CIs for the T_{max} point estimates include zero, indicating no significant differences were observed between regimens A and B versus regimen C. Low to moderate within-subject variability was observed in these PK parameters.

Table A-2-5: Summary of Results of Statistical Analysis of Tamsulosin Bioequivalence at Steady-State

Parameter	Comparison	Least Square Geometric Mean		Point Estimate of Ratio	90% CI	CVw[3] (%)	CVb[4] (%)
		Test	Reference				
AUC(0-24)-ss[1] (ng*hr/ML)	A : C	182.52	179.89	1.01	(0.93,1.11)	17.8	33.0
	B : C	167.60	179.89	0.93	(0.85,1.02)		
Cmax-ss[1] (ng/ML)	A : C	16.74	17.01	0.98	(0.91,1.06)	14.8	27.0
	B : C	15.55	17.01	0.91	(0.85,0.98)		
Cmin-ss[1] (ng/ML)	A : C	2.83	2.74	1.03	(0.90,1.19)	27.7	55.5
	B : C	2.86	2.74	1.04	(0.91,1.20)		
Cτ[1] (ng/ML)	A : C	3.16	2.93	1.08	(0.95,1.23)	26.8	56.2
	B : C	3.05	2.93	1.04	(0.91,1.18)		
1/2[1] (hr)	A : C	13.69	13.85	0.99	(0.94,1.04)	11.2	20.7
	B : C	14.13	13.85	1.02	(0.97,1.08)		
Fluctuation[1] (%)	A : C	179.11	188.32	0.95	(0.90,1.01)	12.3	26.4
	B : C	177.96	188.32	0.94	(0.89,1.00)		
tmax[2] (hr)	A - C	5.00	5.00	0.00	(-0.50,0.50)		-
	B - C	5.00	5.00	0.01	(0.00,0.50)		

Source data: Pharmacokinetic Table 10.7 and Table 10.9

1. Point estimate is the ratio of adjusted geometric means between regimens
2. Point estimate represents the estimated median difference between regimens
3. CVw% represents a pooled estimate of within-subject variability across regimens
4. CVb% represents a pooled estimate of between-subject variability across regimens

Regimens:
A 0.5 mg dutasteride, 10% enteric coated 0.4 mg tamsulosin hydrochloride
B 0.5 mg dutasteride, 15% enteric coated 0.4 mg tamsulosin hydrochloride
C Flomax 0.4 mg and AVODART 0.5 mg

The point estimates of slope (versus day) and corresponding 90% CIs for tamsulosin C_τ values in regimens A, B, and C were 100% (96%, 104%), 96% (92%, 100%), and 98% (93%, 104%) respectively. The 90% CIs were all within (91%, 110%), indicating that the steady state was achieved for all regimens.

Table A-2-6: Tamsulosin at Steady-State Assessment

Parameter	Regimen	Point Estimate of Slope	90% CI	CVw%
Cτ (ng/mL)	A	1.00	(0.96, 1.04)	12.7
	B	0.96	(0.92, 1.00)	16.8
	C	0.98	(0.93, 1.04)	22.0

Source Data: Pharmacokinetic Table 10.5

Regimen:
A 0.5 mg dutasteride, 10% enteric coated 0.4 mg tamsulosin hydrochloride
B 0.5 mg dutasteride, 15% enteric coated 0.4 mg tamsulosin hydrochloride
C Flomax 0.4 mg and AVODART 0.5 mg

Discussion

This study demonstrated BE of tamsulosin at steady state in each of the combination capsule formulations of dutasteride 0.5 mg/enteric coated tamsulosin 0.4 mg (10% and 15%) compared to concomitant dosing of Avodart® 0.5 mg and Flomax® 0.4 mg.

SAFETY RESULTS

There was one SAE which led to withdrawal from the study. Subject 122 (randomized to treatment sequence BAC) was withdrawn from the study after dosing in Session 1 due to an SAE of hospitalization for epididymitis which was not considered to be related to study drug by the investigator.

The most commonly reported AEs in any regimen (>10%) were headache, dizziness and nasal congestion. A slightly higher proportion of AEs were seen with Regimen A (dutasteride and tamsulosin HCl (10%) combination capsule) than with either Regimens B or C. All AEs were considered by the investigator to be mild or moderate in intensity and were consistent with the expected side effects of tamsulosin (Flomax® package insert, 2008).

Table A-2-3: Summary of Drug-related Adverse Events

	Number of Subjects with Drug-Related AEs (%)			
	Regimen A (n=23)	Regimen B (n=24)	Regimen C (n=23)	Total (n=24)
Subjects with any AE	7 (30)	4 (17)	5 (22)	12 (50)
System Organ Class Preferred Term				
Dizziness	1 (4)	1 (4)	3 (13)	5 (21)
Headache	3 (13)	2 (8)	0	4 (17)
Dizziness postural	2 (9)	1 (4)	0	3 (13)
Abnormal dreams	0	1 (4)	2 (9)	3 (13)
Abdominal pain upper	1 (4)	0	0	1 (4)
Nasal congestion	1 (4)	0	0	1 (4)

Source Data: Safety Table 11.03
Regimen A: 0.5 mg dutasteride, 10% enteric coated 0.4 mg tamsulosin hydrochloride
Regimen B: 0.5 mg dutasteride, 15% enteric coated 0.4 mg tamsulosin hydrochloride
Regimen C: Flomax 0.4 mg and AVODART 0.5 mg

CONCLUSION

- The tamsulosin component of the combination capsule formulations of dutasteride 0.5 mg and either 10% ([(b) (4)]% w/w tamsulosin) or 15% ([(b) (4)]% w/w tamsulosin) enteric coated tamsulosin HCl 0.4 mg are BE to the concomitant dosing of Avodart® 0.5 mg and Flomax® 0.4 mg monotherapies at steady-state under fasted state.
- While both the 10% enteric coated ([(b) (4)]% w/w) and 15% enteric coated ([(b) (4)]% w/w) tamsulosin pellets were found to be BE with Flomax®, the 10% enteric coated ([(b) (4)]% w/w) tamsulosin pellet more closely matched the formulation of the generic tamsulosin capsule product ([(b) (4)]% w/w) and [(b) (4)]
- Administration of the combination capsule formulations of dutasteride 0.5 mg/tamsulosin HCl 0.4 mg to healthy adult male volunteers was generally well tolerated under the conditions of this study.

A.1.3. Study ARI103880

An Open Label, Single Dose, Randomized, Three Period Crossover Study to Investigate the Relative Bioavailability of 0.5mg of Dutasteride from Soft Gelatin Capsules containing [(b) (4)] mg of [(b) (4)]l[1] (Avodart® - reference) vs. Soft Gelatin Capsules containing [(b) (4)]mg and [(b) (4)] mg of [(b) (4)][1] in Healthy Male Volunteers.

Protocol No:	ARI103880
Phase:	1
Principal Investigator:	Robert Blum, Pharm.D.
Clinical Study Center:	Buffalo Clinical Research Center, Buffalo, NY
Clinical Study Dates:	March 30, 2005 - July 5, 2005
Analytical Study Facility:	GlaxoSmithKline, Research Triangle Park, NC

[1] [(b) (4)]).

OBJECTIVE

The primary objective was to assess the relative bioavailability of 0.5 mg dutasteride when dosed from a capsule formulation containing [(b) (4)] mg and [(b) (4)] mg of [(b) (4)] as compared with the currently marketed 0.5 mg soft gelatin capsule Avodart® ([(b) (4)]mg [(b) (4)]). The secondary objective was to further assess the safety and tolerability of different formulations of dutasteride.

STUDY DESIGN

This study was a single-dose, open label, randomized, 3 period crossover design. The study was performed in healthy male subjects in the fasted state. Blood samples for PK assessments were taken from each subject at the following times: pre-dose (time 0) and at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, and 72 hrs post-dose. Formulation A was Avodart® (containing [(b) (4)] mg [(b) (4)]) as the reference, Formulation B was dutasteride soft gelatin capsule containing [(b) (4)] mg [(b) (4)] and Formulation C was dutasteride soft gelatin capsule containing [(b) (4)] mg [(b) (4)].

RESULTS

There were 37 subjects enrolled in the study. The subjects mean age (range) was 30 (19-48) years and the mean weight (range) was 82.7 (57-106) kg. The subjects races were African American (16 %), Asian (8 %), white (70 %) with 5 % not classified. The number of subjects included in the PK analysis and safety analysis were 35, 34, and 35 for Formulation A, Formulation B, and Formulation C, respectively. The PK parameters for the 3 formulations are summarized in Table A-3-1.

Table A-3-1: Geometric Means (%CV) of Dutasteride PK Parameters

Formulation	N	AUC(0-t)[1] (ng.hr/mL)	Cmax (ng/mL)	Tmax (hr)[2]
A	35	26.3 (95)	2.48 (46)	1.00 (1.00-6.00)
B	34	23.5 (113)	2.18 (43)	2.00 (1.00-4.00)
C	35	24.3 (96)	2.15 (47)	2.00 (1.00-4.00)

Source Data: Study ARI103880 Table 11 and Table 12

AUC(0-t) defined as from time zero to last time-point of 72 hours

Median (range)

A :AVODART (containing [(b) (4)] mg [(b) (4)])

B :Dutasteride Soft Gelatin Capsule containing [(b) (4)] mg [(b) (4)]

C Dutasteride Soft Gelatin Capsule containing [(b) (4)] mg [(b) (4)]

A summary of the statistical results comparing the test and reference dutasteride formulations is shown in Table A-3-2.

Table A-3-2: Summary of Statistical Analysis of Dutasteride PK Parameters

Parameter	Comparison Test vs. Reference	Geometric LS Means		LS Means Ratio	90 % CI
		Test	Reference		
Cmax	B :A	2.19	2.44	0.90	(0.81, 0.99)
	C : A	2.13	2.44	0.87	(0.79, 0.96)
AUC(0-t)[1]	B:A	24.08	25.38	0.95	(0.88, 1.03)
	C : A	23.56	25.38	0.93	(0.86, 1.00)

Source Data: Study ARI103880 Table 13

1. AUC(0-t) defined as from time zero to last time-point of 72 hours

A :AVODART (containing (b) (4) mg (b) (4))

B :Dutasteride Soft Gelatin Capsule containing (b) (4) mg (b) (4)

C Dutasteride Soft Gelatin Capsule containing (b) (4) mg (b) (4)

The 90 % CIs for both dutasteride AUC and C_{max} ratios for Formulation B relative to Formulation A were within the equivalence interval of 80-125%. Thus, Formulation B was shown to be BE to the marketed dutasteride formulation. For Formulation C, the 90 % CIs for the dutasteride AUC ratio was within the equivalence interval of 80-125%; however, the 90 % CI for C_{max} was not completely contained with the equivalence range. Therefore, Formulation C was not shown to be BE to the marketed dutasteride formulation. The study medication was generally well tolerated. One subject withdrew from the study due to nausea determined not being related to study drug by the investigator. Blood pressure increase and tachycardia were reported as mild, drug-related AEs for one subject during Period 2 and Period 3. Headache was also reported as a drug-related AE. The only abnormal ECG reported was categorized as "abnormal - not clinically significant" by the investigator.

CONCLUSIONS

- Dutasteride soft gelatin capsules containing (b) (4) mg (b) (4) were BE to the reference formulation (Avodart®).
- Dutasteride soft gelatin capsules containing (b) (4) mg and (b) (4) mg (b) (4) had 95 % and 93 % bioavailability, respectively, relative to Avodart® with regard to the extent of dutasteride absorption, with 90% CIs falling within the 80-125% range.
- Dutasteride soft gelatin capsules containing (b) (4) mg and (b) (4) mg (b) (4) had C_{max} values that were 10 % and 13 % less than Avodart®. Only dutasteride soft gelatin capsules containing (b) (4) mg (b) (4) had 90% CIs falling within the 80-125% range in terms of C_{max}.
- The amount of vehicle (b) (4) in this study had a limited impact on the extent of dutasteride absorption but did appear to have an effect on the rate of dutasteride absorption, as the formulations with lower amounts of (b) (4) appear to have lower mean C_{max} values.
- Study medication was generally well tolerated.
- Based on the study results, the Sponsor selected Formulation B (b) (4) mg (b) (4)) for further development.

A.1.4. Study 163/07

Randomized, Two-period, Cross-over, Bioequivalence Study Comparing Tamsulosin 0.4 mg MR capsules ((b) (4)) to Flomax® 0.4 mg MR capsules (Boehringer Ingelheim Pharmaceuticals, Inc., USA) in Healthy Volunteers under Fed Condition.

Protocol No:	163/07
Phase:	1
Principal Investigator:	Jifi Grim, M.D., Ph.D.
Clinical Study Center:	Quinta-Analytica, Praha, Czech Republic
Date of Clinical Report:	September 26, 2007
Analytical Study Facility:	(b) (4)
Analytical Study Dates:	September 6, 2007 - September 11, 2007

OBJECTIVE

The study was designed to compare the relative bioavailability (rate and extent of absorption) of Tamsulosin HCl capsules ((b) (4)) to Flomax® (Boehringer Ingelheim Pharmaceuticals, Inc., USA) in healthy volunteers under fed state and to assess the BE of these products based on confidence acceptance intervals of 80% to 125% for ln-transformed AUC(0-t), AUC(0-∞) and C_{max} of tamsulosin.

STUDY DESIGN

The study was an open-label, laboratory-blinded, randomized, single dose, two-period, cross-over BE study in 26 healthy male adult subjects under fed state. A 14 day washout period between drug administrations was performed. The test product was tamsulosin HCl capsule containing MR pellets (tamsulosin HCl pellets, (b) (4) % w/w) and the reference product was Flomax®. A standard FDA high-fat breakfast was served 30 min before drug administration. The whole breakfast was consumed in 30 min or less. The drug was administered 30 min after the start of the meal. Blood collections for PK parameter estimation were made prior to dosing (time 0) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 24, 32, 48, and 72 hr post-dose. The AE and clinically significant deviations from laboratory tests, physical examinations, and vital signs were reported for the evaluation of safety.

RESULTS

Of the 26 subjects enrolled, 24 subjects completed the study. The mean (range) age was 28.7 (19-47) years, the mean (range) weight was 79.3 (60.0- 94.2) kg and the mean (range) BMI was 24.2 (19.8-26.8) kg/m^2. The PK parameters for comparative BE evaluation are summarized in Table A-4-1.

Table A-4-1: Geometric Means of Tamsulosin PK Parameters for BE Evaluation

Parameter		GEOMETRIC LEAST SQUARES MEANS		RATIO T/R (%)	90% CONFIDENCE LIMITS (%)	
		Test[1]	Reference[2]		Lower	Upper
AUC(0-t) (ng•h/mL)[3]	24	144.89	146.90	98.63	93.11	104.47
AUC(0-∞) (ng•h/mL)	24	153.93	156.04	98.65	93.32	104.29
Cmax (ng/ mL)	24	9.50	9.17	103.56	95.65	112.13

Source Data: Study 163/07 Table 3

1. Test Tamsulosin hydrochloride 0.4 mg capsule
2. Reference- Flomax 0.4 mg capsule
3. AUC to the last measurable tamsulosin concentration

The results confirm that the 90% CIs for the test ((b) (4)) to reference (Flomax®) ratios of the geometric least squares means for AUC(0-t), AUC(0-∞) and C_{max} for tamsulosin were within the BE acceptance range of 80 to 125%. One subject reported a mild AE of weakness 5 hr after taking tamsulosin HCl capsule that lasted for 11 min. One subject was diagnosed with moderate virosis more than 24 hr after taking Flomax® that was deemed not to be related to the study medication by the clinical study investigators. The subject was healthy at the time of the follow-up examination. No SAEs were reported.

CONCLUSIONS

- The test formulation, tamsulosin HCl 0.4 mg capsule containing MR pellets ((b) (4)% w/w) ((b) (4)), is BE to the reference formulation, Flomax® 0.4 mg MR capsules (Boehringer Ingelheim Pharmaceuticals, Inc., USA), under fed state.
- Tamsulosin HCl capsule and Flomax® were well tolerated in this study.

A.1.5. Study 186/07

Single Dose Crossover Comparative Bioavailability Study of Tamsulosin 0.4 mg Modified-Release Capsules in Healthy Male Volunteers / Fed State

Protocol No: 186/07
Phase: 1
Principal Investigator: Eric Sicard, M.D.
Clinical Study Center: Algorithme Pharma Inc., Laval, Quebec, Canada
Clinical Study Dates: November 19, 2007 - December 6, 2007
Analytical Study Facility: (b) (4)
Analytical Study Dates: December 10, 2007 - December 14, 2007

OBJECTIVE

To evaluate and compare the relative bioavailability and therefore the BE of two different formulations of tamsulosin after a single oral dose administration under fed state.

STUDY DESIGN

The study was a single-center, randomized, single dose, laboratory blinded, 2-period, 2-sequence, cross-over design in healthy males. Each treatment period was separated by a wash out period of at least 7 days. The test product was tamsulosin HCl capsule containing MR pellets ((b) (4) % w/w tamsulosin HCl, (b) (4)) and the reference product was Flomax®. In each study period subjects received a FDA standardized high-fat, high-calorie breakfast 30 min before drug administration. Blood samples were collected for PK parameter estimation prior to (time 0) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 24, 36, 48, and 72 hr after drug administration. Safety was evaluated through the assessment of AEs and laboratory tests.

RESULTS

Of the 26 healthy male subjects who were included in the study, 25 completed the crossover design and received a single oral dose of the assigned formulation on Day 1 and Day 8. All subjects were white. The mean (range) age of the subjects was 35 (21-53) years, the mean weight (range) was 76.6 (56.5-99.8) kg and the mean BMI (range) was 24.7 (19.5-29.8) kg/m^2. The PK parameters for comparative BE evaluation are summarized in Table A-5-1.

Table A-5-1: Geometric Means of Tamsulosin PK Parameters for BE Evaluation

Parameter	N	GEOMETRIC LEAST SQUARES MEANS		RATIO T/R (%)	90% CONFIDENCE LIMITS (%)	
		Test[1]	Reference[2]		Lower	Upper
AUC(0-t) (ng•h/mL)[3]	24	176.15	178.35	98.76	93.47	104.36
AUC(0-∞) (ng•h/mL)	24	184.07	186.04	98.94	93.60	104.59
Cmax (ng/ mL)	24	9.28	8.87	104.63	98.84	110.76

Source Data Study 186-07 Table 15
1. Test Tamsulosin hydrochloride 0.4 mg capsule
2. Reference- Flomax 0.4 mg capsule
3. AUC to the last measurable tamsulosin concentration

The results confirm that the 90% CIs for test to reference ratios of the geometric least squares means for AUC(0-t), AUC(0-∞) and C_{max} for tamsulosin were within the BE acceptance range of 80-125%.

Seven (7) of the 26 subjects experienced AEs during the study. Nine AEs (9 different types) were reported after the single dose administration of the test product and 9 AEs (7 different types) were reported after the single dose administration of the reference product. Three AEs associated with post-study laboratory test results were imputed to both formulations. Five AEs (alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine increased, nasal dryness, and testicular pain) that were possibly related to the study drugs were unexpected. No deaths or SAEs were recorded in this study.

CONCLUSIONS

- The test formulation, tamsulosin HCl 0.4 mg capsule containing MR pellets ([(b) (4)]% w/w) ([(b) (4)]), is BE to the reference formulation, Flomax® 0.4 mg MR capsules (Boehringer Ingelheim Pharmaceuticals, Inc., USA) under fed state.
- The study drugs were generally well tolerated.

A.2. Clinical Pharmacology Filing Memo

Office of Clinical Pharmacology *New Drug Application Filing and Review Form*			
General Information About the Submission			
	Information		Information
NDA Number	22-460	**Brand Name**	Flodart
OCP Division	DCP3	**Generic Name**	Dutasteride 0.5 mg and tamsulosin 0.4 mg
Medical Division	DRUP	**Drug Class**	5α-reductase inhibitor (dutasteride) and α-adrenergic blocker (tamsulosin)
OCP Reviewer	Chongwoo Yu, Ph.D	**Indication(s)**	Treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate
OCP Team Leader	Myong Jin Kim, Pharm. D.	**Dosage Form**	Combination IR soft gelatin Capsule
Secondary Reviewer	Myong Jin Kim, Pharm. D.	**Dosing Regimen**	One capsule daily approximately 30 min after the same meal each day
Date of Submission	March 20, 2009	**Route of Administration**	Oral
Estimated Due Date of OCP Review	November 20, 2009	**Sponsor**	GlaxoSmithKline (GSK)
PDUFA Due Date	January 20, 2010	**Priority Classification**	Standard
Division Due Date	December 27, 2009		

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary				
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				

ethnicity:				
gender:				
pediatrics:	NA			Pediatric waiver request
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 1:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X	1		ARI40005
Population Analyses -				
PK:				
PD:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	X	5		ARI109882, ARI111402, ARI103880, 163/07, 186/07
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Immunogenicity profile				
Literature References	X	20		
Total Number of Studies		26		

Other comments

	Comments
QBR questions (key issues to be considered)	1. Acceptability of the pivotal BE study. 2. Acceptability of the pediatric waiver request 3. Sufficient bioanalytical assay validation information including DSI inspection report?
Other comments or information not included above	1. Need to request a consult to DSI for inspection of sites where the pivotal BE study was conducted. DSI consult on the clinical BE sites (Covance Research, Evansville, IN and Austin, TX) and the bioanalytical site (GlaxoSmithKline, Research Triangle Park, NC) was requested for the pivotal BE study, ARI109882 and was signed off by Dr. Dennis Bashaw on May 19, 2009.

Filing Memo

Clinical Pharmacology Review

NDA: 22-460
Compound: Flodart (dutasteride and tamsulosin) capsules
Sponsor: GlaxoSmithKline (GSK)

Date: 4/28/2009
Reviewer: Chongwoo Yu, Ph.D.

Introduction:
Flodart is an oral dosage form that combines dutasteride, a 5α-reductase inhibitor and the active ingredient in Avodart (NDA 21-319, approved on November 20, 2001), and tamsulosin, an α-adrenergic blocker and the active ingredient in Flomax (NDA 20-579, approved on April 15, 1997). GSK is the Sponsor of the Advodart NDA while Boehringer Ingelheim Pharmaceuticals is the Sponsor for the Flomax NDA. Astellas Pharma Inc. is the assignee of the sole Orange Book listed patent for Flomax (tamsulosin hydrochloride, U.S. Patent No. 4,703,063), which is set to expire on October 27, 2009. Flodart will not be commercialized until after expiry of the Orange Book patient identified above and any applicable pediatric exclusivity for Flomax.

This NDA has been submitted as a 505(b)(2) application since the Sponsor is relying on publicly available data for tamsulosin. On June 19, 2008, dutasteride (Avodart) co-administered with tamsulosin was approved to treat symptomatic BPH in men with enlarged prostate. The clinical data supporting that indication (2-year data from Study ARI40005 in NDA 21-319/S-014), along with additional safety data from Study ARI40005 in this application will be relied on to support the safety and efficacy of Flodart. In addition, this marketing application includes 1 pivotal (Study ARI109882) and 4 supporting biopharmaceutics studies for establishing the bioequivalence (BE) of dutasteride and tamsulosin administered separately (co-administration) as in Study ARI40005 and together (combination) in Flodart. The BE assessment from Study ARI109882 is used to bridge the efficacy and safety data from Study ARI40005 to Flodart. A total of 3,511 patients and 141 healthy volunteers have received co-administered dutasteride and tamsulosin. A total of 119 healthy volunteers have been exposed to Flodart.

Drug Substance and Product Formulation:
Avodart is an immediate release soft gelatin capsule and Flomax is a hard gelatin capsule containing modified release pellets. The manufacture of dutasteride and tamsulosin hydrochloride combination capsule (Flodart) involves the over-encapsulation of two separate intermediate products (containing a dutasteride product intermediate (0.5 mg dutasteride) and a tamsulosin hydrochloride product intermediate (0.4 mg tamsulosin hydrochloride)). The drug substances, dutasteride and tamsulosin hydrochloride, are the same active components used for commercial supply of Avodart and generic tamsulosin hydrochloride capsules (b) (4), generic version sold in the EU market). The strengths of each active component of Flodart are identical to the commercially available monotherapies Avodart, 0.5 mg dutasteride and Flomax, 0.4 mg tamsulosin hydrochloride. The proposed sites of manufacture and manufacturing processes for the drug substances to be used in Flodart are the same as those currently utilized for the commercial products, Avodart and generic tamsulosin hydrochloride capsules (b) (4) The excipients used to produce dutasteride and tamsulosin hydrochloride product intermediates are identical to those used for commercial Avodart and the generic tamsulosin hydrochloride capsule pellets (b) (4).

(b) (4)

BE of Flodart and the concomitantly dosed Avodart and Flomax (used in the pivotal efficacy and safety study ARI40005) was assessed in a single dose, randomized, three-period, partial cross-over pivotal BE study, ARI109882. It was noted that the pivotal efficacy and safety study ARI40005 used both the currently approved tamsulosin product Flomax 0.4 mg and a

different formulation named Omnic 0.4 mg. The Omnic formulation contains the same active ingredient as Flomax but has different inactive ingredients. DSI consult on the clinical BE sites (Covance Research, Evansville, IN and Austin, TX) and the bioanalytical site (GlaxoSmithKline, Research Triangle Park, NC) was requested for the pivotal BE study, ARI109882 and was signed off by Dr. Dennis Bashaw on May 19, 2009. A BE study (study ARI10021, submitted under NDA 21-319/S-014, approved on June 19, 2008) comparing Omnic 0.4 mg and Flomax 0.4 mg under fasting condition showed that they are BE (a review on this study can be found in Dr. Donny Tran's review dated April 17, 2008 under NDA 21-319/S-014 available in DFS). In addition, BE for tamsulosin was assessed in a repeat dose, randomized, three-period, cross-over study (Study ARI111402) between the Flodart containing either the tamsulosin hydrochloride pellet, (b) (4)% w/w (elected as tamsulosin hydrochloride product intermediate) or tamsulosin hydrochloride pellet, (b) (4)% w/w and Avodart and Flomax co-administered.

Bioavailability and ADME (Absorption, Distribution, Metabolism, and Excretion):

There are no clinical pharmacology studies conducted using Flodart. Sponsor is relying on the information on the currently approved Avodart (2008) and Flomax (2008) package inserts.

Drug-Drug Interactions:

There are no drug interaction studies conducted using Flodart. A PK study (Study ARI1011, submitted under NDA 21-319/S-014, approved on June 19, 2008) shows that co-administration of dutasteride did not significantly affect the PK of tamsulosin. In addition, a review of available data (published data on tamsulosin suggests that tamsulosin co-administration is unlikely to significantly affect the PK of dutasteride. Dr. Donny Tran's review (dated April 17, 2008) on Study ARI1011 and literature can be found in DFS under NDA 21-319/S-014. Information available on the package insert from individual components (Avodart (2008) and Flomax (2008)) is listed on the proposed Flodart label.

Specific Population and Pediatric Waiver:

There are no specific population studies conducted using Flodart. Information available on the package insert from individual components (Avodart (2008) and Flomax (2008)) is listed on the proposed Flodart label. The Sponsor has submitted a waiver for pediatric studies with a justification that Flodart will be ineffective or unsafe in the age group of 0 (birth) to 16 years old.

Bioanalytical Method validation:

The concentrations of dutasteride in human serum were determined by validated, internal standard analytical methods consisting of protein precipitation followed by liquid chromatography coupled with tandem mass spectrometric detection (Studies ARI103880 and ARI109882). The concentrations of tamsulosin in human serum were determined by a validated, internal standard analytical method consisting of protein precipitation (Studies ARI109882 and ARI111402) or solvent extraction (Studies 163/07 and 186/07) followed by liquid chromatography coupled with tandem mass spectrometric detection. Bioanalytical method validation reports are submitted for review.

Food Effect:

BE between Flodart and co-administered Avodart and Flomax under both fed and fasting conditions has been assessed (Study ARI109882). According to the Sponsor, administration with food does not affect the dutasteride component of Flodart nor Avodart. However, a mean 30% decrease in C_{max} was observed for both the tamsulosin component of Flodart and Flomax when administered with food. Because the prescribing information for Flomax recommends administration approximately one-half hour following the same meal each day, the Sponsor proposes to have the same administration recommendation for Flodart. This dosing recommendation is consistent with the manner in which the individual components were given in the pivotal efficacy and safety study ARI40005.

Recommendation:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Clinical Pharmacology section for NDA 22-460 is fileable.

Comments for the Sponsor:

None.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22460	ORIG-1	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLINE	DUTASTERIDE/ TAMSULOSIN HYDROCHLORIDE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHONGWOO YU
01/06/2010

MYONG JIN KIM
01/06/2010

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 22-460 (N00)	**Reviewer:** Sandra Suarez Sharp, Ph.D	
Division:	DRUP		
Sponsor:	GSK	**Team Leader:** Angelica Dorantes, Ph.D .	
Trade Name:	Flodart™ Capsules	**Supervisor:** Patrick J. Marroum, Ph.D	
Generic Name:	Dutasteride and Tamsulosin Hydrochloride Capsules	**Date Assigned:**	NA
Indication:	Benign prostatic hyperplasia (BPH)	**Date of Review:**	Nov 30, 2009
Formulation/ Strength	Capsule containing one capsule of dutasteride in solution (0.4) and tamsulosin 0.5 mg as modified release pellets		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission date	**CDER Stamp/Received Date**	**Date of informal/Formal Consult**	**DUE DATE**
Nov 24, 2009	Nov 24, 2009	NA	NA
Type of Submission:	Response to FDA Request/Comment: CMC - CMC Development Information on the Release of Dutasteride from Dutasteride and Tamsulosin Hydrochloride Combination Capsules (DTC).		
Type of Consult:	Dissolution method and specifications		

REVIEW SUMMARY:

Flodart™ consists of hard-shell capsules containing one capsule of Dutasteride Product Intermediate (0.5 mg of dutasteride in solution) and (b) (4) mg of Tamsulosin Hydrochloride Product Intermediate (0.4 mg of tamsulosin as modified release pellets). Flodart™ is being proposed for the treatment of symptomatic benign prostatic hyperplasia (BPH). The proposed dosage regimen is one capsule once a day taken approximately 30 minutes after the same meal each day.

Reference is made to the ONDQA/Biopharmaceutics review for this submission rendered in DARRTS on Oct 8, 2009. Reference is also made to the comments sent to sponsor on November 18, 2009 as follows:

- On October 2, 2009, you provided requested information regarding the dissolution method development for the tamsulosin component of the combination product. These data included the evaluation of the effect of dissolution media, pH, and paddle speed. It was shown that there was no difference in the dissolution profile as a function of paddle speed (e.g. (b) (4) rpm); therefore, we recommend that you use the lower paddle speed (e.g 50 rpm) instead.
- Based on the mean tamsulosin hydrochloride dissolution profiles from combination capsule batches used in BE Studies (Batch 705002), primary stability testing (Batches

94705001 and 705004-91294) and at registration (Batch 806001), the following acceptance criteria for the dissolution test of the tamsulosin component are recommended:

Drug Name	Dosage Form	USP Apparatus	Speed (rpms)	Medium	Volume (mL)	Acceptance Criteria
Flodart (tamsulosin component)	Capsule (tamsulosin part: ER pellets)	II (Paddle)	**50**	Acid Stage (0-2 hrs): 0.1 N HCl Buffer stage: Add 250 mL of 0.2 M Sodium Phosphate Tribasic, Dodecahydrate pH 6.8	750 1000	**Acid Stage:** Not greater than (b)(4)% dissolved in 2 hours **Buffer Stage:** Timepoint Acceptance Criteria 3 hrs (b)(4)% 6 hrs: (b)(4)%

- Based on the data provided the following acceptance criterion for the dissolution test of the dutasteride component is recommended:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Acceptance Criterion
Flodart (dutasteride component)	Capsule (soft gelatin)	II (Paddle)	75	**Tier I(non-enzymatic):** 900 mL of 1%w/v cetyltrimethylammonium bromide (CTAB) in 0.1 N HCl **Tier II (enzymatic)** 900 mL of 1% w/v CTAB in 0.1 N HCl with 0.16% w/v pepsin	900	Q = (b)(4)% in 45 minutes

A telecom was held with the sponsor on November 19, 2009 on the dissolution methods and specifications for Dutasteride and Tamsulosin Hydrochloride in DTC and the following agreements were reached:

- The sponsor agreed on changing the paddle speed to 50 rpm for the tamsulosin component.
- The sponsor mentioned that the proposed acceptance criteria of (b)(4) at 3 hrs time-point is supported by a bioequivalence study in which a batch that meets this specification was bioequivalent to the bio-batch. The Agency committed to verify this claim.
- The sponsor agreed on the Agency's proposed acceptance criterion of (b)(4)% at 6 hrs.
- The sponsor committed to send additional information to support their proposed acceptance criteria for the dutasteride component (Q = (b)(4)% in 60 minutes).

On November 24, 2009 the following information was received from GSK that supports the proposed acceptance criterion of Q = (b)(4)% in 60 minutes for the dutasteride component:

(b) (4)

(b) (4)

RECOMMENDATION:

The ONDQA/Biopharmaceutics team has reviewed the dissolution information for Dutasteride and Tamsulosin Hydrochloride Capsules submitted to NDA 22-460 (S0016) on November 24, 2009. We found the rationale to support the dutasteride's proposed dissolution specifications acceptable. The upper bound of the dissolution specification for the tamsulosin component is not acceptable. The following comments should be conveyed to the sponsor:

1. The data submitted to NDA 22-460 on November 24, 2009 regarding the dissolution method and specification for **the dutasteride component** of your DCT product support your proposed dissolution **acceptance criterion of Q = (b) (4) % in 60 minutes**.
2. We have reviewed the bioequivalence studies conducted with DTC Batch 705002-91294 and the similar DTC product Batch 710001-102133 as well as the dissolution profiles data for these batches. Your proposed lower limit of the specification for the **tamsulosin hydrochloride** component is supported given that the mean dissolution profile for bath 710001-102133 was (b) (4)%. However, your proposed upper limit of (b) (4)% at 6 hours is **NOT** justified based on a mean

dissolution profile of (b)(4)% for batch 705002-91294. We recommend that the upper bound be set as (b)(4)%.

3. In summary, the following method and acceptance criteria for Dutasteride and Tamsulosin Hydrochloride Capsules have been agreed upon or recommended by the Agency:

Drug Name	Dosage Form	USP Apparatus	Speed (rpms)	Medium	Volume (mL)	Acceptance Criteria
Flodart (tamsulosin component)	Capsule (tamsulosin part: ER pellets)	II (Paddle)	**50**	Acid Stage (0-2 hrs): 0.1 N HCl Buffer stage: Add 250 mL of 0.2 M Sodium Phosphate Tribasic, Dodecahydrate pH 6.8	750 1000	**Acid Stage:** Not greater than (b)(4)% dissolved in 2 hours **Buffer Stage:** Timepoint Acceptance Criteria 3 hrs: (b)(4)% 6 hrs: (b)(4)%

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Acceptance Criterion
Flodart (dutasteride component)	Capsule (soft gelatin)	II (Paddle)	75	**Tier I(non-enzymatic):** 900 mL of 1%w/v cetyltrimethylammonium bromide (CTAB) in 0.1 N HCl **Tier II (enzymatic)** 900 mL of 1% w/v CTAB in 0.1 N HCl with 0.16% w/v pepsin	900	Q = (b)(4)% in 60 minutes

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Patrick J. Marroum, Ph. D.
Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

cc: JDavis, Adorantes, DChristner, YSun

Appendix

Table 1. Tamsulosin Hydrochloride Pharmacokinetic Results for Study ARI111402: Dutasteride and Tamsulosin Hydrochloride Combination Capsules ([(b) (4)]% w/w pellets Batch 705002-91294; [(b) (4)]% w/w pellets Batch 710001-102133) Versus Co-administered FLOMAX® and AVODART®

Treatment Comparison	Parameter	Geometric LS Means		T/R Ratio [1] (%)	90% Confidence Interval Range (%)
		Test (T)	Reference (R)		
Batch 705002-91294 Dutasteride and Tamsulosin Hydrochloride Combination Capsule ([(b) (4)]% w/w pellets) versus FLOMAX® and AVODART® co-administered	**Fasted**				
	$AUC_{(0-24h)}$ (ng h/mL)	182.5	179.9	101	93 - 111
	Cmax (ng/mL)	16.7	17.0	98	91 – 106
Batch 710001-102133 Dutasteride and Tamsulosin Hydrochloride Combination Capsule ([(b) (4)]% w/w pellets) versus FLOMAX® and AVODART® co-administered	**Fasted**				
	$AUC_{(0-24h)}$ (ng h/mL)	167.6	179.9	93	85 - 102
	Cmax (ng/mL)	15.6	17.0	91	85 - 98

Note:
1. Point estimate is the ratio of adjusted geometric means between regimens.

Table 2. Tamsulosin Hydrochloride Pharmacokinetic Results for Study ARI109882: Dutasteride and Tamsulosin Hydrochloride Combination Capsules (Batch 705002-91294) Versus **Co-administered FLOMAX® and AVODART®**

Treatment Comparison	Parameter	Geometric LS Means		T/R Ratio[1] (%)	90% Confidence Interval Range (%)
		Test (T)	Reference (R)		
Dutasteride and Tamsulosin Hydrochloride Combination Capsule versus FLOMAX® and AVODART® co-administered	**Fed**				
	$AUC_{(0-t)}$ (ng h/mL)	170.5	165.8	103	97 – 109
	$AUC_{(0-\infty)}$ (ng h/mL)	178.6	171.9	104	98 - 110
	Cmax (ng/mL)	10.6	9.85	108	100 - 115
	Fasted				
	$AUC_{(0-t)}$ (ng h/mL)	181.4	181.2	100	91 - 110
	$AUC_{(0-\infty)}$ (ng h/mL)	186.6	185.6	101	92 – 110
	Cmax (ng/mL)	15.1	14.1	107	95 - 121

Table 3. Dutasteride and Tamsulosin Hydrochloride Combination Capsules Dissolution (% Tamsulosin HCl Released) Batch 705002-91294 (BE Study ARI109882)

Sample	Sampling point (hours)				
	2	3	4	5	7
1	1	59	75	86	98
2	1	54	70	81	95
3	2	59	75	86	99
4	2	59	75	86	98
5	2	55	71	81	95
6	3	65	81	91	102
7	2	60	76	87	100
8	2	56	72	83	96
9	2	56	72	83	96
10	1	55	71	82	96
11	2	57	73	85	97
12	1	58	74	85	97
Mean	**2**	**58**	**74**	**85**	**97**
% RSD	-	**5.2**	**4.1**	**3.4**	**2.2**
Range	**1 - 3**	**54 - 65**	**70 - 81**	**81 - 91**	**95 - 102**

Table 4. Batch Analysis for Dutasteride and Tamsulosin HCl Combination Capsules with Tamsulosin HCl Pellets (b) (4)% w/w
Batch 710001-102133 used in Support of Clinical Studies

Batch Number	710001-102133
Description	A brown and orange capsule imprinted with GS 7CZ in black ink
(b) (4)	

Note:
1. Drug-related impurities content includes (b) (4) (b) (4)
2. (b) (4)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22460	QUALITY-1	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLINE	DUTASTERIDE/ TAMSULOSIN HYDROCHLORIDE

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/s/

SANDRA SUAREZ
12/05/2009

PATRICK J MARROUM
12/07/2009

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 22-460 (N00)	**Reviewer:** Sandra Suarez Sharp, Ph.D	
Division:	DRUP		
Sponsor:	GSK	**Team Leader:** Angelica Dorantes, Ph.D .	
Trade Name:	Flodart™ Capsules	**Supervisor:** Patrick J. Marroum, Ph.D	
Generic Name:	Dutasteride and Tamsulosin Hydrochloride Capsules	**Date Assigned:**	Sep 14, 2009
Indication:	Benign prostatic hyperplasia (BPH)	**Date of Review:**	Oct 6, 2009
Formulation/ Strength	Capsule containing one capsule of dutasteride in solution (0.4) and tamsulosin 0.5 mg as modified release pellets		
Route of Administration	Oral		

SUBMISSIONS REVIEWED IN THIS DOCUMENT			
Submission date	**CDER Stamp/Received Date**	**Date of informal/Formal Consult**	**DUE DATE**
March 20, 2009	March 20, 2009	Sep 14, 2009	Oct 7, 2009
Type of Submission:	CMC prior approval supplement		
Type of Consult:	Dissolution method and specifications		

REVIEW SUMMARY:

Flodart™ consists of hard-shell capsules containing one capsule of Dutasteride Product Intermediate (0.5 mg of dutasteride in solution) and (b) (4) mg of Tamsulosin Hydrochloride Product Intermediate (0.4 mg of tamsulosin as modified release pellets). Flodart™ is being proposed for the treatment of symptomatic benign prostatic hyperplasia (BPH). The proposed dosage regimen is one capsule once a day taken approximately 30 minutes after the same meal each day. As monotherapy, dutasteride (AVODART) is approved by the Agency for the treatment of symptomatic BPH. Tamsulosin (FLOMAX) is also approved by the Agency as monotherapy for the treatment of the signs and symptoms of BPH.

This review summarizes the dissolution method and specifications being proposed for Flodart™. The dissolution profile of the dutasteride component of the combination capsule is affected by a cross-linking effect upon stability testing. In vivo BE studies demonstrated that the cross-linking effect does not alter the BA of dutasteride from AVODART. To address cross-linking, the dutasteride dissolution method for Flodart™, like the AVODART dissolution method, is a two-tiered procedure involving non-enzymatic (Tier 1) and enzymatic (Tier 2) media. Since the dutasteride is fully dissolved in the fill solution of the formulation, a single point dissolution specification of Q= (b) (4)% is appropriate. The sponsor's proposed dissolution method and specifications for the dutasteride component are as follows:

Dutasteride and Tamsulosin Hydrochloride Combination Capsule (Flodart)
Dutasteride Dissolution Method

(b) (4)

[redacted]

(b) (4). Therefore, the sponsor will be recommended to use the lowest paddle speed tested (e.g. 50 rpm) as part of the tamsulosin dissolution method.

RECOMMENDATION:
The proposed dissolution methods for the two components of Flodart™ capsules (dutasteride and tamsulosin) are acceptable from Biopharmaceutics standpoint provided that the sponsor agrees with the following recommendations:

Dutasteride
Recommended Dissolution Specifications: Q= (b) (4)% in 45 min

Tamsulosin
Recommended Paddle Speed: 50 rpm
Recommended Dissolution Specifications:

- **Acid Stage:** Not greater than (b) (4)% dissolved in 2 hours

- **Buffer Stage:**
  3 hrs: (b) (4)%
  6 hrs: (b) (4)%

Sandra Suarez Sharp, Ph. D.
Biopharmaceutics Reviewer
Office of New Drugs Quality Assessment

Patrick J. Marroum, Ph. D.
Biopharmaceutics Supervisor
Office of New Drugs Quality Assessment

cc: JDavis, Adorantes, DChristner

INTRODUCTION

Flodart™ capsules contain dutasteride (0.5 mg) and tamsulosin hydrochloride (0.4 mg) a competitive inhibitor of type 1 and type 2 5α-reductase and a 1A adrenoceptor antagonistis, respectively intended to treat symptomatic benign prostatic hyperplasia (BPH). This indication is consistent with the currently approved indication for dutasteride (AVODART) co-administered with tamsulosin. As monotherapy, dutasteride is indicated for the treatment of symptomatic BPH in men with an enlarged prostate to improve symptoms, and reduce the risks of AUR and need for BPH-related surgery. Tamsulosin is indicated for the treatment of the signs and symptoms of BPH. Dutasteride, as AVODART, was approved by the Agency on Nov 2001 (NDA 21-319) and tamsulosin, as FLOMAX, was approved on April 15, 1997 (NDA 20-579).

AVODART's Background

AVODART is an immediate release soft gelatin capsule. The solubility of dutasteride is low. Following the administration of a single dutasteride 0.5 mg dose, formulated in a soft gelatin capsule (AVODART), the time to peak serum concentrations (Tmax) occurs within 2 to 3 hours. The absolute bioavailability of dutasteride 0.5mg soft gelatin capsules is approximately 60% (range 40% to 94%). Food has no significant impact on the absorption of dutasteride.

AVODART's Dissolution Method

The dissolution of the dutasteride capsule is impacted by the occurrence of cross-linking in the soft gelatin shell. Gelatin cross linking for this type of formulation is documented in the literature[1,2] and it has commonly been observed for AVODART during stability

[1] Meyer, MC et. al. The effect of gelatin cross-linking on the BE of hard and soft gelatin acetaminophen capsules. Pharm. Res. 2000; 17(8): 962-6.

studies. According to the sponsor, the cross-linking phenomenon may be promoted by elevated temperatures (i.e., storage at 30°C and 40°C), UV light and/or the presence of trace impurities such as aldehydes. To address cross-linking, the dutasteride dissolution is a two-tiered procedure involving non-enzymatic (Tier 1) and enzymatic (Tier 2) media. There was no effect of capsule cross-linking on *in vivo* performance[1].

The approved in vitro dissolution[3,4,5] method and specification are follows:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Recommended Sampling Times (min)	Specification (Q)
Dutasteride	Capsule (soft gelatin)	II (Paddle)	50	**Tier I:** Dissolution Medium: 0.1 N HCI with 2% (w/v) sodium dodecyl sulfate (SDS) (900 mL) **Tier II:** Dissolution Medium: 0.1 N HCI with pepsin (1.6 g/L, label activity 1:3,000) (450 mL) for the first 25 minutes, followed by addition of 0.1 N HCI with SDS (4% w/v) (450 mL) for the remainder of the dissolution test.	900	15, 30, 45 and 60	(b) (4) in 45 minutes

Flomax's Background

Flomax is a hard gelatin capsule containing modified release pellets. Absorption of tamsulosin hydrochloride is essentially complete (>90%) following oral administration under fasting conditions. Tamsulosin exhibits linear kinetics following single and multiple dosing, with achievement of steady-state concentrations by the fifth day of once-daily dosing. The time to maximum concentration (Tmax) of tamsulosin is four to five hours following administration while fasted and six to seven hours when administered with food. Taking tamsulosin hydrochloride capsules (Flomax) under fasted conditions results in a 30% increase in bioavailability (AUC) and 40% to 70% increase in peak concentrations (Cmax) compared to fed conditions. Both Omnic and Flomax are modified-release formulations intended to slow the absorption of tamsulosin and avoid vasodilatory side effects (e.g., dizziness, orthostatic hypotension). In order to retain the controlled-release characteristics of tamsulosin HCl capsules, it is recommended to be taken approximately one-half hour following the same meal each day.

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[2] Digenis, GA et al. Cross-linking of gelatin capsules and its relevance to their in vitro-in vivo performance. J. Pharm. Sci.;1994; 83(7):915-21

[3] Clinical pharmacology review for NDA 21-319 DFS'ed by Dr. Al Habet on 10/22/01

[4] Chemistry review for NDA 21-319 DFS'ed by Dr. Salemme on 07/10/01

[5] FDA dissolution method online (last updated 01/26/06)

Flomax's Dissolution Method[6]

The approved in vitro dissolution method and specification are follows:

Drug Name	Dosage Form	USP Apparatus	Speed (rpm)	Medium	Volume (mL)	Recommended Sampling Times (min)	Acceptance criteria
Tamsulosin HCl	Capsule	II (Paddle)	100	➢ 0-2 hours: 0.003% polysorbate 80, pH 1.2 ➢ 2-8 hours: phosphate buffer, pH 7.2	500	1, 2, 3, 6, 8, and 10 hrs	2 hr: 13 –34%; 3 hr: 47– 68%; 8 hr: ≥ 80%

FLODART'S FORMULATION AND DISSOLUTION METHOD

Dutasteride and Tamsulosin Hydrochloride Combination Capsules for oral administration are orange/brown, oblong, hard-shell capsules ((b) (4) , size 00) containing one oblong, opaque, dull-yellow Dutasteride Product Intermediate (0.5 mg) and (b) (4) mg of white to off-white Tamsulosin Hydrochloride Product Intermediate (0.4 mg) (Table 1).

The manufacture of Flodart™ involves the over-encapsulation of two separate intermediate products: a dutasteride soft gelatin capsule (Table 2) based upon the AVODART formulation and tamsulosin hydrochloride pellets (Table 3) based upon those used in the commercial generic Tamsulosin Hydrochloride Capsule ((b) (4)). Both intermediate products are filled into a (b) (4) hard-shell capsule to deliver the 0.5 and 0.4 mg doses of dutasteride and tamsulosin HCl, respectively.

Table 1. Composition of Dutasteride and Tamsulosin Hydrochloride Combination Capsules, 0.5 mg Dutasteride and 0.4 mg Tamsulosin hydrochloride

Component	Quantity (per capsule)	Function	Reference to Standard
Dutasteride Product Intermediate	1 each	Active	GlaxoSmithKline
Tamsulosin Hydrochloride Product Intermediate [1]	(b) (4) mg	Active	GlaxoSmithKline
Pre-printed (b) (4) Hard-Shell Capsule	1 each	Capsule Shell	Supplier

[6] FDA dissolution method online (last updated 01/26/06)

Table 2. Composition of the Dutasteride Product Intermediate, 0.5 mg Dutasteride

Component	Quantity (mg/capsule)	Function
Fill Solution		
Dutasteride	0.50	Active
Mono-di-glycerides of Caprylic/Capric Acid (MDC)		
Butylated Hydroxytoluene (BHT)		
(b) (4)		
Gelatin		
Glycerin		
Titanium Dioxide		
Ferric Oxide, Yellow		
(b) (4)		

Table 3. Composition of the Tamsulosin HCl Product Intermediate, 0.4 mg Tamsulosin Hydrochloride

Component	Quantity (mg/capsule)	Function	Reference to Standard
(b) (4)			
Tamsulosin Hydrochloride [1]	0.400	Active	Supplier
Microcrystalline Cellulose	(b) (4)		USNF
Methacrylic Acid Copolymer Dispersion [2]			USNF
Talc			USP
Triethyl Citrate			USNF
(b) (4)			USP
			-
Methacrylic Acid Copolymer Dispersion [2]			USNF
Talc			USP
Triethyl Citrate			USNF
(b) (4)			USP
			-
			-

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22460	ORIG-1	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLINE	DUTASTERIDE/ TAMSULOSIN HYDROCHLORIDE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SANDRA SUAREZ
10/07/2009

PATRICK J MARROUM
10/08/2009

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**22-460**	**Brand Name**	**Flodart**
OCP Division	**DCP3**	**Generic Name**	**Dutasteride 0.5 mg and tamsulosin 0.4 mg**
Medical Division	**DRUP**	**Drug Class**	**5α-reductase inhibitor (dutasteride) and α-adrenergic blocker (tamsulosin)**
OCP Reviewer	**Chongwoo Yu, Ph.D**	**Indication(s)**	**Treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate**
OCP Team Leader	**Myong Jin Kim, Pharm. D.**	**Dosage Form**	**Combination IR soft gelatin Capsule**
Secondary Reviewer	**Myong Jin Kim, Pharm. D.**	**Dosing Regimen**	**One capsule daily approximately 30 min after the same meal each day**
Date of Submission	**March 20, 2009**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**November 20, 2009**	**Sponsor**	**GlaxoSmithKline (GSK)**
PDUFA Due Date	**January 20, 2010**	**Priority Classification**	**Standard**
Division Due Date	**December 27, 2009**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary				
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				

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ethnicity:				
gender:				
pediatrics:	NA			Pediatric waiver request
geriatrics:				
renal impairment:				
hepa ic impairment:				
PD:				
Phase 1:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X	1		ARI40005
Population Analyses -				
PK:				
PD:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
tradi ional design; single / multi dose:	X	5		ARI109882, ARI111402, ARI103880, 163/07, 186/07
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Immunogenicity profile				
Literature References	X	20		
Total Number of Studies		26		

Other comments

	Comments
QBR questions (key issues to be considered)	1. Acceptability of the pivotal BE study. 2. Acceptability of the pediatric waiver request 3. Sufficient bioanalytical assay validation information including DSI inspection report?
Other comments or information not included above	1. Need to request a consult to DSI for inspection of sites where the pivotal BE study was conducted. DSI consult on the clinical BE sites (Covance Research, Evansville, IN and Austin, TX) and the bioanalytical site (GlaxoSmithKline, Research Triangle Park, NC) was requested for the pivotal BE study, ARI109882 and was signed off by Dr. Dennis Bashaw on May 19, 2009.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			
2	Has the applicant provided metabolism and drug-drug interaction information?		x		Cross referencing other applications
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?		x		Cross referencing other applications
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?		x		Cross referencing other applications
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			x	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?		x		Cross referencing other applications
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?		x		Cross referencing other applications
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		x		Cross referencing other applications
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		x		Cross referencing other applications
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	Pediatric waiver submitted
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	Pediatric waiver submitted
17	Is there adequate information on the pharmacokinetics and exposure-	x			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
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	response in the clinical pharmacology section of the label?				
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		x		

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? ___Yes___

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

- *None*

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- *None*

Chongwoo Yu 4/30/2009

Reviewing Clinical Pharmacologist Date

Myong Jin Kim 4/30/2009

Team Leader/Supervisor Date

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Filing Memo

Clinical Pharmacology Review

NDA: 22-460
Compound: Flodart (dutasteride and tamsulosin) capsules
Sponsor: GlaxoSmithKline (GSK)

Date: 4/28/2009
Reviewer: Chongwoo Yu, Ph.D.

Introduction:
Flodart is an oral dosage form that combines dutasteride, a 5α-reductase inhibitor and the active ingredient in Avodart (NDA 21-319, approved on November 20, 2001), and tamsulosin, an α-adrenergic blocker and the active ingredient in Flomax (NDA 20-579, approved on April 15, 1997). GSK is the Sponsor of the Advodart NDA while Boehringer Ingelheim Pharmaceuticals is the Sponsor for the Flomax NDA. Astellas Pharma Inc. is the assignee of the sole Orange Book listed patent for Flomax (tamsulosin hydrochloride, U.S. Patent No. 4,703,063), which is set to expire on October 27, 2009. Flodart will not be commercialized until after expiry of the Orange Book patient identified above and any applicable pediatric exclusivity for Flomax.

This NDA has been submitted as a 505(b)(2) application since the Sponsor is relying on publicly available data for tamsulosin. On June 19, 2008, dutasteride (Avodart) co-administered with tamsulosin was approved to treat symptomatic BPH in men with enlarged prostate. The clinical data supporting that indication (2-year data from Study ARI40005 in NDA 21-319/S-014), along with additional safety data from Study ARI40005 in this application will be relied on to support the safety and efficacy of Flodart. In addition, this marketing application includes 1 pivotal (Study ARI109882) and 4 supporting biopharmaceutics studies for establishing the bioequivalence (BE) of dutasteride and tamsulosin administered separately (co-administration) as in Study ARI40005 and together (combination) in Flodart. The BE assessment from Study ARI109882 is used to bridge the efficacy and safety data from Study ARI40005 to Flodart. A total of 3,511 patients and 141 healthy volunteers have received co-administered dutasteride and tamsulosin. A total of 119 healthy volunteers have been exposed to Flodart.

Drug Substance and Product Formulation:
Avodart is an immediate release soft gelatin capsule and Flomax is a hard gelatin capsule containing modified release pellets. The manufacture of dutasteride and tamsulosin hydrochloride combination capsule (Flodart) involves the over-encapsulation of two separate intermediate products (containing a dutasteride product intermediate (0.5 mg dutasteride) and a tamsulosin hydrochloride product intermediate (0.4 mg tamsulosin hydrochloride)). The drug substances, dutasteride and tamsulosin hydrochloride, are the same active components used for commercial supply of Avodart and generic tamsulosin hydrochloride capsules (b) (4), generic version sold in the EU market). The strengths of each active component of Flodart are identical to the commercially available monotherapies Avodart, 0.5 mg dutasteride and Flomax, 0.4 mg tamsulosin hydrochloride. The proposed sites of manufacture and manufacturing processes for the drug substances to be used in Flodart are the same as those currently utilized for the commercial products, Avodart and generic tamsulosin hydrochloride capsules ((b) (4)). The excipients used to produce dutasteride and tamsulosin hydrochloride product intermediates are identical to those used for commercial Avodart and the generic tamsulosin hydrochloride capsule pellets ((b) (4)).

(b) (4) Each formulation change was supported by BE studies on the proposed intermediate versus the corresponding commercial product. In the case of dutasteride, the soft gelatin capsule fill solution was (b) (4) (Study ARI103880). In the case of tamsulosin hydrochloride, the concentration of the drug in the (b) (4)

BE of Flodart and the concomitantly dosed Avodart and Flomax (used in the pivotal efficacy and safety study ARI40005) was assessed in a single dose, randomized, three-period, partial cross-over pivotal BE study, ARI109882. It was noted that

the pivotal efficacy and safety study ARI40005 used both the currently approved tamsulosin product Flomax 0.4 mg and a different formulation named Omnic 0.4 mg. The Omnic formulation contains the same active ingredient as Flomax but has different inactive ingredients. DSI consult on the clinical BE sites (Covance Research, Evansville, IN and Austin, TX) and the bioanalytical site (GlaxoSmithKline, Research Triangle Park, NC) was requested for the pivotal BE study, ARI109882 and was signed off by Dr. Dennis Bashaw on May 19, 2009. A BE study (study ARI10021, submitted under NDA 21-319/S-014, approved on June 19, 2008) comparing Omnic 0.4 mg and Flomax 0.4 mg under fasting condition showed that they are BE (a review on this study can be found in Dr. Donny Tran's review dated April 17, 2008 under NDA 21-319/S-014 available in DFS). In addition, BE for tamsulosin was assessed in a repeat dose, randomized, three-period, cross-over study (Study ARI111402) between the Flodart containing either the tamsulosin hydrochloride pellet, (b) (4) (elected as tamsulosin hydrochloride product intermediate) or tamsulosin hydrochloride pellet, (b) (4) w/w and Avodart and Flomax co-administered.

Bioavailability and ADME (Absorption, Distribution, Metabolism, and Excretion):

There are no clinical pharmacology studies conducted using Flodart. Sponsor is relying on the information on the currently approved Avodart (2008) and Flomax (2008) package inserts.

Drug-Drug Interactions:

There are no drug interaction studies conducted using Flodart. A PK study (Study ARI1011, submitted under NDA 21-319/S-014, approved on June 19, 2008) shows that co-administration of dutasteride did not significantly affect the PK of tamsulosin. In addition, a review of available data (published data on tamsulosin suggests that tamsulosin co-administration is unlikely to significantly affect the PK of dutasteride. Dr. Donny Tran's review (dated April 17, 2008) on Study ARI1011 and literature can be found in DFS under NDA 21-319/S-014. Information available on the package insert from individual components (Avodart (2008) and Flomax (2008)) is listed on the proposed Flodart label.

Specific Population and Pediatric Waiver:

There are no specific population studies conducted using Flodart. Information available on the package insert from individual components (Avodart (2008) and Flomax (2008)) is listed on the proposed Flodart label. The Sponsor has submitted a waiver for pediatric studies with a justification that Flodart will be ineffective or unsafe in the age group of 0 (birth) to 16 years old.

Bioanalytical Method validation:

The concentrations of dutasteride in human serum were determined by validated, internal standard analytical methods consisting of protein precipitation followed by liquid chromatography coupled with tandem mass spectrometric detection (Studies ARI103880 and ARI109882). The concentrations of tamsulosin in human serum were determined by a validated, internal standard analytical method consisting of protein precipitation (Studies ARI109882 and ARI111402) or solvent extraction (Studies 163/07 and 186/07) followed by liquid chromatography coupled with tandem mass spectrometric detection. Bioanalytical method validation reports are submitted for review.

Food Effect:

BE between Flodart and co-administered Avodart and Flomax under both fed and fasting conditions has been assessed (Study ARI109882). According to the Sponsor, administration with food does not affect the dutasteride component of Flodart nor Avodart. However, a mean 30% decrease in C_{max} was observed for both the tamsulosin component of Flodart and Flomax when administered with food. Because the prescribing information for Flomax recommends administration approximately one-half hour following the same meal each day, the Sponsor proposes to have the same administration recommendation for Flodart. This dosing recommendation is consistent with the manner in which the individual components were given in the pivotal efficacy and safety study ARI40005.

Recommendation:

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 finds that the Clinical Pharmacology section for NDA 22-460 is fileable.

Comments for the Sponsor:

None.

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/s/

Chongwoo Yu
6/3/2009 07:12:52 AM
BIOPHARMACEUTICS

Myong-Jin Kim
6/3/2009 07:34:59 AM
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