# TITLE PAGE

**Division:** Worldwide Development
**Information Type:** Protocol Amendment

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| **Title:** | A randomized, double-blind, parallel group study to compare the efficacy and safety of combination treatment with dutasteride (0.5mg) and tamsulosin (0.2mg) with tamsulosin (0.2mg) monotherapy, administered once daily for 2 years, on the improvement of symptoms and health outcomes in men with moderate to severe benign prostatic hyperplasia |

**Compound Number:** GI198745

**Effective Date:** 08-JUL-2014

**Protocol Amendment Number:** 4

**Subject:** Infection, Quality of Life

**Author:** PPD

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**Revision Chronology:**

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| RM2010/00134/00 | 2010-SEP-30 | Original |
| RM2010/00134/01 | 2012-FEB-23 | Amendment No.: 01 |

- Change in the storage conditions for study drug, Section 5.3
- Addition of text on serum PSA measure at one additional visit, Section 7.3.4.2
- Addition of text on sexually related AE follow up, Section 6.3
- Addition of text on three supplementary efficacy measures, Section 7.2.1.2, Section 7.2.2.4, Section 7.4.2.2 and Section 9.3.6.1
- Correction of text on vital sign measures to include measures at Visit 3 and Visit 5, Section 7.3.3
- Correction of the treatment assignment language, Section 5.4.
- Clarification on study treatment discontinuation and study discontinuation, Section 4.2.1, Section 6.3, Section 7.4.4 and Section 7.2.2.5
- Clarification of data collected for partner pregnancies, Section 7.4.3.1 and Section 7.4.3.2.
- Clarification on the collection of Questionnaires in Appendix 2, Section 7.5.3.1
- Correction to T &E table, Section 7
- Clarification of language on protocol waivers, Section 3
- Clarification of language in PGx Section 2.3, Section 7.6 and Appendix 1
- Administrative change to correct

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| | | spelling errors and re-wording to provide clarification and consistency<br>• Removal of details which will be documented in the Study Procedures Manual.<br>• Addition of text on an optional SMS reminder service Section 7.2.3<br>• Addition of text to allow unscheduled visits when medically necessary Section 7 |
| RM2010/00134/02 | 2013-SEP-25 | Amendment No.: 02<br>• Addition of a PPK substudy for subjects of Chinese origin, living in China (only) Section 2.4, Section 7.7, Section 9.3.10 and Appendix 7.<br>• Addition of suicidality assessments, at pre-screening (V1a), and at 6, 12 and 24 months on treatment. Section 7.3.1, Section 7.3.9, Section 7.4.6, and Section 9.3.7.2.1.<br>• Addition of information on QTc events, liver events and partner pregnancy. Section 7.4.3, Section 7.4.4 and Section 7.4.5.<br>• Clarification on the information collected at baseline and at the pre-screening (V1a) and screening (V1b) visits. Protocol Summary.<br>• Update to Sponsor Signatory, Medical Monitoring Contact Information and List of Authors. Sponsor Information Page.<br>• Clarification that the study will be posted to clinical trial registries Section 10.1.<br>• Clarification of condom use for study subjects with female partners of childbearing potential. |

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| | | Section 4.1.2 and Section 7.4.5.<br>• Clarification on the use of PDE-5 inhibitors. Section 4.1.3 and Section 6.2.<br>• Update to T & E table to show new assessments for suicidality (all subjects) and PPK (Chinese subjects only). Section 7<br>• Additional information on definition of SAEs for cardiovascular events and death. Section 7.4.2<br>• Clarification on the wording for BPH related quality of life<br>• The details of the uroflow meter will be included in the study procedures manual.<br>• Administrative changes to correct spelling errors and re-wording to provide clarification and consistency |
| RM2010/00134/03 | 2013-NOV-12 | Amendment No.: 03<br>• Removed the exclusion criteria for subjects previously treated with PDE-5 inhibitors in Section 4.1.3.<br>• Other minor typographical changes. |
| RM2010/00134/04 | 2014-JUL-03 | Amendment No.: 4<br>• Correction of SAE fax number and e-mail address<br>• Insertion of details of secondary medical monitor<br>• Allowance of automated prostate volume calculator for TRUS measurements<br>• Restriction of selective beta 3 - adrenoreceptor agonist for over-active bladder syndrome (e.g. mirabegron)<br>• Restriction of ginseng for treatment of BPH or sexual |

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| | | dysfunction<br>• To correct that the C-SSRS questionnaire will be administered by a trained rater<br>• To correct that a Hepatitis RNA test will be used to confirm a Hepatitis C antibody positive result rather than a Hepatitis RIBA immunoblot assay<br>• Insertion of text for sentinel adverse event monitoring<br>• Administrative changes to provide consistency<br>• Removal of transition zone volume measurement<br>• Revision of text concerning provision of rhythm strip for ECG monitoring |
| RM2010/00134/05 | 2014-JUL-08 | Amendment No.: 4 (Republished)<br>• Compound number confirmation |

| Sponsor Signatory: | Signature: | Date: |
| --- | --- | --- |
| Mair Jenkins<br>Director Clinical<br>Development<br>Emerging Markets R and D | PPD | 8 July 14 |

# SPONSOR INFORMATION PAGE

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In some countries, the clinical trial sponsor may be the local GlaxoSmithKline affiliate company (or designee). Where applicable, the details of the Sponsor and contact person will be provided to the relevant regulatory authority as part of the clinical trial submission.

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Regulatory Agency Identifying Number(s): IND 47,838

# INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number ARI114265

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name: _____

_____ _____

Investigator Signature Date

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| 5 ARI | 5 Alpha-Reductase Inhibitor |
| AE | Adverse Event |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| AUR | Acute Urinary Retention |
| BHS | BPH-related Health Status |
| BII | BPH Impact Index |
| BPH | Benign Prostatic Hyperplasia |
| CIB | Clinical Investigator Brochure |
| CNS | Central Nervous System |
| CS | Clinically significant |
| C-SSRS | Columbia Suicide Severity Rating Scale |
| DHT | Dihydrotestosterone |
| DRE | Digital Rectal Examination |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GCSP | Global Clinical Safety Pharmacovigilance |
| GSK | GlaxoSmithKline |
| HBsAG | Hepatitis B Antigen |
| HGPIN | High grade prostatic intraepithelial neoplasia |
| HIFU | High Intensity Focused Ultrasound |
| IEC | Independent Ethics Committee |
| IND | Investigational New Drug |
| INR | International Nationalized Ratio |
| IPSS | International Prostate Symptom Score |
| IRB | Institutional Review Board |
| ITT | Intent-to-treat |
| IVRS | Interactive Voice Response System |
| LOCF | Last observation carried forward |
| LUTS | Lower urinary tract symptoms |
| MSDS | Material Safety Data Sheet |
| NCS | Not clinically significant |
| ODT | Oral Disintegrating tablet |
| PAS-SFI | Problem Assessment Scale Sexual Function Inventory |
| PDE-5 | Phosphodiesterase-5 |
| PGx | Pharmacogenetic |
| PPK | Population pharmacokinetics |
| PPSM | Patient Perception of Study Medication |
| PSA | Prostate Specific Antigen |
| PSRAE | Possible Suicidality Related Adverse Event form |
| Qmax | Maximum (peak) urinary flow rate |
| RAMOS | Registration and medication ordering system |

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|---|---|
| RAP | Reporting and Analysis Plan |
| RBC | Red Blood Cell |
| RTP | Research Triangle Park |
| SAE | Serious Adverse Event |
| SCA | Standard clarification agreement |
| SD | Standard deviation |
| SPM | Study Procedure manual |
| TRUS | Transrectal ultrasound |
| TUMT | Transurethral Microwave Thermotherapy |
| TUNA | Transurethral Needle Ablation |
| TURP | Transurethral resection of the prostate |
| USA | United States of America |
| UTI | Urinary Tract Infection |
| WBC | White Blood Cells |

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# PROTOCOL SUMMARY

## Rationale

GlaxoSmithKline plans to develop a Fixed Dose Combination (FDC) containing 0.5mg of dutasteride and 0.2mg of tamsulosin hydrochloride (hereafter referred to as tamsulosin) for the treatment of moderate to severe lower urinary track symptoms associated with Benign Prostatic Hypertrophy (BPH) in Asian men.

GSK conducted a 4 year study; Combination of Dutasteride and Tamsulosin (CombAT) in which dutasteride 0.5mg and tamsulosin 0.4mg were co-administered once daily for 4years, and compared to dutasteride 0.5mg and tamsulosin 0.4mg, administered as monotherapies. The study demonstrated that the co-administration of dutasteride and tamsulosin provided superior symptom improvement compared to each of the monotherapies alone. This symptom improvement was seen after 2 and 4 years of treatment. The 2 year pre-planned analysis of the CombAT data supported the approval of co-administration in the USA and Europe in 2008. The 2 year symptom data also supported the approval of an NDA and MAA for a single combination capsule in the USA and Europe in 2010.

To support the development of an FDC in the Asia Pacific region, GSK will conduct a study similar to CombAT using dutasteride 0.5mg co-administered with the approved and widely used 0.2mg dose of tamsulosin. The reason tamsulosin 0.2mg is the proposed dose for this study is the data from the tamsulosin PK studies showed that in Japanese subjects taking tamsulosin 0.4mg, the Cmax was higher compared with Caucasian subjects taking the same dose. The lower dose of tamsulosin is preferred in Asia, considering a key complication associated with the higher dose, postural hypotension.

The Japanese phase III dutasteride study (ARI105326) was a clinical study that allowed subjects to take tamsulosin 0.2mg for 52 weeks. In this study, subjects who were taking tamsulosin 0.2mg prior to the study start were instructed to continue taking tamsulosin 0.2mg concomitantly with dutasteride throughout the trial. The data from this subgroup and the dutasteride monotherapy group demonstrated superior symptom improvement compared to placebo and tamsulosin monotherapy. These results suggest that there is symptom improvement with the co-administration of tamsulosin at a lower dose.

The study will be conducted solely in Asian men from the Asia Pacific region.

## Objective(s)

The primary objective of the study is to assess the efficacy of combination treatment with dutasteride 0.5mg and tamsulosin 0.2mg once daily in providing superior symptomatic improvement in subjects with BPH compared with once daily tamsulosin 0.2mg monotherapy after 2 years of treatment.

The secondary objective is to assess efficacy and safety of combination treatment with dutasteride 0.5mg and tamsulosin 0.2mg including the clinical outcomes of AUR or BPH-related prostatic surgery compared with tamsulosin 0.2mg monotherapy after 2 years of treatment.

## Study Design

This is a multicentre, randomized, double-blind, parallel group study. The aim of the study is to investigate whether combination therapy with dutasteride and tamsulosin is more effective than tamsulosin monotherapy for the improvement of symptoms and health outcomes in a population at increased risk of BPH clinical progression including older men (≥50yrs), with moderate-severe symptoms of BPH, enlarged prostates (≥30cc) and PSA≥1.5ng/mL.

Eligible subjects will receive placebo tamsulosin and placebo dutasteride for four weeks. Following the four-week, single-blind, placebo, run-in period, each subject will be randomized to one of the following two treatment groups, according to a pre-determined randomisation schedule (1:1 ratio) for the double-blind phase of the study:

- Dutasteride 0.5mg once daily + tamsulosin 0.2mg once daily
- Dutasteride placebo once daily + tamsulosin 0.2mg once daily

Subjects will self-administer the study medication once daily for up to 104 weeks (2 years). Subjects will return to the clinic at 13 week intervals post-randomisation during the 2 year treatment period (i.e. at 13, 26, 39, 52, 65, 78, 91, and 104 weeks).

Approximately 586 men with symptomatic BPH will be randomized.

## Study Assessments

The primary efficacy endpoint of this study is change in IPSS from baseline at Year 2.

The secondary efficacy endpoints of this study are:

- Percent change in prostate volume from baseline
- Proportion of subjects with IPSS improvement.
- Change in Qmax from baseline and proportion of subjects with Qmax improvement from baseline.
- Time to event / proportion of subjects with AUR or BPH related prostatic surgery.
- Health Outcome Measures:
    - Change from baseline in BPH-related Health Status (Q8 of IPSS),
    - Change from baseline in BPH Impact Index (BII), and
    - Change from baseline in Problem Assessment Scale of the Sexual Function Inventory (PAS-SFI).

The planned assessments for all study participants include prostate volume by TRUS at screening (V1b) and annually thereafter for up to 2 years. Additionally, IPSS, BPH-related health status Q8 of IPSS, BPH Impact Index (BII) will be administered at pre-screening (V1a), baseline and every 13 weeks thereafter. The PAS-SFI will be administered at screening (V1b), baseline and annually thereafter. Peak urinary flow

(Qmax), and post void residual volume (PVR) will be measured at pre-screening (V1a), screening (V1b, if necessary), baseline and every 26 weeks thereafter. A physical examination with a qualitative breast examination, will be conducted at screening (V1b) and every 26 weeks thereafter. Measures of the total PSA will be conducted at pre-screening (V1a), 6 months, 52 weeks and every 52 weeks thereafter.

# 1. INTRODUCTION

## 1.1. Background

Benign prostatic hyperplasia (BPH) is a chronic and progressive disease. It is the most common benign neoplasm in the aging male population, with pathological changes found in 88% of men in their ninth decade and symptoms reported in nearly 50% of men aged ≥50 years in the general population [Napalkov, 1995]. The known proximal cause of BPH is age-related prostate growth that is stimulated primarily by the presence of dihydrotestosterone (DHT). DHT is formed when testosterone is reduced through the activity of the 5α-reductase enzymes type 1 and type 2, although type 2 is considered primarily responsible for this conversion in benign prostate tissue. Prostatic growth may lead to urethral obstruction that causes lower urinary tract symptoms (LUTS) such as weak or intermittent flow, urgency, frequency, nocturia and incontinence, which interfere with normal activities. The potentially progressive nature of the disease has been associated with an increased risk of acute urinary retention (AUR) and the need for surgery [Oelke, 2011].

The aim of BPH therapy is to improve symptoms and quality of life of patients, and to prevent or reduce the risk of BPH-related complications such as urinary retention or upper urinary tract dilatation [AUA, 2010; Oelke, 2011]. Commonly used and recommended treatment options include pharmacotherapeutic agents such as alpha blockers and 5α-reductase inhibitors (5ARIs), and surgical intervention in appropriate cases. With the more frequent use of pharmacotherapeutic agents, the rate of surgery for BPH has declined in recent years [Napalkov, 1995; Roehrborn, 2002]. However, a single pharmacotherapeutic agent may not be completely effective for patients with moderate-to-severe symptoms or patients at increased risk of disease progression. The combination of two compounds with different and complementary mechanisms of action provides additional benefits in disease management compared to either monotherapy alone. In November 2003, GSK initiated a multinational study over a 4-year treatment period (CombAT, ARI40005) to evaluate the efficacy and safety of co-administration of the two drugs (dutasteride 0.5 mg/ tamsulosin 0.4mg versus dutasteride 0.5mg and tamsulosin 0.4mg monotherapy).

Study ARI40005 considered the results from previous studies that explored the benefits of the combination of a single type 2 5ARI, finasteride, with different alpha blockers in BPH symptoms and outcomes in an average BPH population. The inclusion criteria for ARI40005 were designed to select men at increased risk for BPH progression, and included a requirement for baseline PV ≥30 mL, serum PSA levels ≥1.5 ng/mL, and an International Prostate Symptom Score [IPSS] ≥12 points. Efficacy measures included the combined endpoint of time to acute urinary retention (AUR) or BPH-related surgery after 4 years of treatment and symptom improvement after 2 and 4 years of treatment. Results of a planned Year 2 analysis demonstrated the efficacy and safety of co-administration, [Roehrborn, 2008]. Results of the planned Year 4 analyses for CombAT were published [Roehrborn, 2010]. The study demonstrated that in men with moderate to severe lower urinary tract symptoms (LUTS) and prostate enlargement (30 cc or greater), combination therapy with dutasteride (0.5mg) and tamsulosin (0.4mg) once daily provided a significantly greater degree of symptomatic benefit than either tamsulosin (0.4mg) or

dutasteride (0.5mg) monotherapy at the end of 2 and 4 years of treatment. In addition, at 4 years, dutasteride and tamsulosin in combination significantly reduced the risk of AUR and BPH related surgery compared to tamsulosin monotherapy. The data from the 4 year treatment study supports the long term use of dutasteride 0.5mg and tamsulosin 0.4mg co-administered in men with moderate to severe lower urinary track symptoms due to BPH and prostate enlargement.

In the overall CombAT population [4844 subjects], the observed safety and tolerability profile of combination therapy was generally consistent with the known safety profiles for the individual monotherapies. There was an observed imbalance in cardiac failure events [14 subjects (0.9%) in the combination group, 4 subjects (0.2 %) in the dutasteride group, and 10 subjects (0.6%) in the tamsulosin monotherapy group]. There was a higher incidence of ejaculation disorders [172 subjects (10.7 %) in the combination group compared to the individual monotherapies, 40 subjects (2.5%) in the dutasteride monotherapy group and 59 subjects (3.7%) in the tamsulosin monotherapy group]. No cardiac failure events were reported in the Asian subpopulation (a total of 325 subjects or 7% of the total population enrolled in the study).

The Japanese phase III study (ARI105326) suggests the benefits of co-administration of dutasteride in patients already receiving tamsulosin [Tsukamoto, 2009]. For this study, it was decided to include patients who had started tamsulosin before the start of the study and still had moderate to severe symptoms and an enlarged prostate. Stratified randomization of these patients and patients without any concurrent BPH medication was carried out to compare dutasteride and placebo.

Changes from baseline in the IPSS, peak urinary flow rate, and prostate volume were compared between the dutasteride group and the placebo group at Week 52. The dutasteride group, with regard to the whole group as well as to the subgroup receiving tamsulosin at baseline, showed superior improvement as compared to the placebo group. In the tamsulosin treated subgroup, the treatment difference in mean change from baseline in IPSS, which was the primary endpoint, was -1.7 between the dutasteride group (add-on to tamsulosin) and placebo group (tamsulosin monotherapy). This was comparable to the treatment difference of -1.6 between the whole dutasteride group and the placebo group, which suggests symptom improvement through the combination therapy to patients who have moderate or severe symptoms and an enlarged prostate with tamsulosin therapy.

In study ARI105326, the incidence of adverse events in the dutasteride group with and without the use of tamsulosin were comparable. The incidence of adverse events considered to be drug related was slightly higher in the dutasteride group without tamsulosin, however, no clear difference due to tamsulosin was confirmed with regard to each individual adverse event.

Approval of the co-administration therapy for the treatment of BPH was obtained in Europe and USA in 2008. In another study (ARI109882), bioequivalence between a newly developed fixed-dose combination (dutasteride 0.5mg / tamsulosin hydrochloride 0.4mg) and the co-administration therapy was demonstrated, and the fixed dose combination product was approved in Europe in March 2010 and in the US June 2010.

Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on the study treatments is provided in the approved label and in the clinical investigator brochure (CIB).

## 1.2. Study Rationale

GlaxoSmithKline plans to develop a Fixed Dose Combination (FDC) containing 0.5mg of dutasteride and 0.2mg of tamsulosin for the treatment of moderate to severe lower urinary track symptoms associated with Benign Prostatic Hypertrophy (BPH) in Asian men.

GSK conducted a 4 year study; Combination of Dutasteride and Tamsulosin (CombAT) in which dutasteride 0.5mg and tamsulosin 0.4mg were co-administered once daily for 4 years, and compared to dutasteride 0.5mg and tamsulosin 0.4mg monotherapy. This study demonstrated that the co-administration of dutasteride and tamsulosin provided superior symptom improvement compared to the monotherapies alone. This was seen after 2 and 4 years of treatment. The 2 year preplanned data CombAT supported the approval of co-administration in the USA and Europe in 2008. The 2 year symptom data also supported the approval of the NDA and MAA for a single combination product in the USA and Europe in 2010.

To support the development of an FDC in the Asia Pacific region, GSK will conduct a study similar to CombAT using dutasteride 0.5mg co-administered with the approved and widely used the 0.2mg dose of tamsulosin. Tamsulosin PK data showed that in Japanese subjects taking tamsulosin 0.4mg, the Cmax was higher compared to Caucasian subjects taking the same dose. The lower dose of tamsulosin is preferred in Asia, considering a key complication associated with the higher dose; postural hypotension.

The Japanese phase III dutasteride study (ARI105326) was a clinical study that allowed subjects to take tamsulosin 0.2mg for 52 weeks. In this study subjects who were taking tamsulosin 0.2mg prior to the study start were instructed to continue taking tamsulosin 0.2mg concomitantly with dutasteride throughout the trial. The data from this subgroup and the dutasteride monotherapy group demonstrated superior symptom improvement compared to placebo and tamsulosin monotherapy. These results suggest that there is symptom improvement with the co-administration of tamsulosin at a lower dose.

The study will be conducted solely in Asian men from the Asia Pacific region.

# 2. OBJECTIVE(S)

## 2.1. Primary Objective

The primary objective of the study is to assess the efficacy of combination treatment with dutasteride 0.5mg and tamsulosin 0.2mg once daily in providing superior symptomatic improvement in subjects with BPH compared with once daily tamsulosin 0.2mg monotherapy after 2 years of treatment.

The primary efficacy endpoint is presented in Section 7.2.1 of this protocol.

## 2.2. Secondary Objective(s)

### 2.2.1. Efficacy

The secondary efficacy objective is:

To assess efficacy of combination treatment with dutasteride 0.5mg and tamsulosin 0.2mg on the clinical outcomes of AUR or BPH-related prostatic surgery compared with tamsulosin 0.2mg monotherapy after 2 years of treatment.

The secondary efficacy endpoints are presented in Section 7.2.1.1 of this protocol.

### 2.2.2. Safety

The safety objective is to assess the safety and tolerability of co-administered dutasteride 0.5 mg once daily and tamsulosin 0.2 mg once daily compared to tamsulosin monotherapy 0.2 mg once daily.

The safety endpoints are presented in Section 7.3.1 of this protocol.

### 2.2.3. Health Outcomes

The health outcome objective is:

- To assess the effects of combination treatment with dutasteride 0.5mg and tamsulosin 0.2mg and tamsulosin 0.2mg monotherapy on health outcome measures (BII, Q8 of IPSS, PAS-SFI).

The health outcomes endpoints are presented in Section 7.2.1.3 of this protocol.

## 2.3. Exploratory Pharmacogenetics (PGx) Research Objective

The exploratory PGx objectives for this study are to investigate the relationships between genetic variants in DNA from patient blood and any unexplained or unexpected response to treatment (as monitored by safety, tolerability, and efficacy parameters) that may have an underlying genetic mechanism.

## 2.4. Exploratory Population Pharmacokinetics (PPK) Research Objective

To characterize the PPK of dutasteride when given in combination with tamsulosin to Chinese men with BPH.

# 3. STUDY DESIGN

This is a multicentre, randomized, double-blind, parallel group study.The aim of the study is to investigate whether combination therapy with dutasteride and tamsulosin is more effective than tamsulosin monotherapy for improvement of symptoms and health outcomes in a population of men at risk of BPH clinical progression including older men (≥50yrs), with moderate-severe symptoms of BPH, enlarged prostates (≥30cc) and PSA≥1.5ng/mL.

Subjects who provide informed consent will be screened for inclusion into the study and eligible subjects will receive placebo tamsulosin and placebo dutasteride for four weeks. Following the four-week single-blind, placebo run-in period, each subject will be randomized to one of the following two treatment groups, according to a pre-determined randomisation schedule (1:1 ratio) for the double-blind phase of the study:

- Dutasteride 0.5mg once daily + tamsulosin 0.2mg once daily
- Dutasteride placebo once daily + tamsulosin 0.2mg once daily

Subjects will self-administer the study medication once daily for up to 104 weeks (2 years). Subjects will return to the clinic at 13 week intervals post-randomisation during the 2 year treatment period (i.e. at 13, 26, 39, 52, 65, 78, 91, and 104 weeks), for the assessments listed in the Time and Events Schedule, Section 7.

The total study duration for each subject will be up to 110 weeks, involving 11 scheduled visits. Due to the circadian changes in urinary flow measurements in BPH subjects, study visits for an individual subject should be conducted consistently in either the morning or afternoon hours to assess all urinary flow measurements.

Every effort will be made to ensure that all randomized subjects complete study assessments. The investigator and site staff are reminded that the subject should make every effort to adhere to all scheduled protocol visits/procedures and their associated windows. In circumstances where this is not possible, e.g. subject is on holiday and is late/early or even misses a study visit, this should be documented in the subject notes with reasons. The investigator should make every effort to ensure the subject always has sufficient study medication between study visits. If visit windows associated with each visit are utilized, the next visit should be scheduled in line with the randomisation baseline visit (Visit 2).

Every effort will be made to ensure that all randomized subjects complete study assessments refer to Appendix 2.

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

The term ‘study treatment’ is used throughout the protocol to generally describe the combination of products or individual products under evaluation in this protocol. When referring to specific compounds, the compound names will be used.

Supplementary study conduct information not mandated to be present in this protocol is provided in the accompanying Study Procedures Manual (SPM). The SPM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

## 3.1. Discussion of Design

The study design has been well established. The design is based on previous BPH dutasteride monotherapy trials and the co-administration BPH trials. The trial includes a 4 week placebo run-in period to reduce subjective "placebo responses" in subsequent results reported after randomization with active treatment.

There is no placebo control group in this trial, since the clinical benefits from active treatments used in this trial have been previously demonstrated. Dutasteride 0.5mg and tamsulosin 0.2mg are both approved for treatment of BPH treatments either as monotherapies or in mutual co- administration.

The dose of tamsulosin 0.2mg is the approved and widely used dose in the Asia Pacific region. Tamsulosin PK data showed that in Japanese subjects taking tamsulosin 0.4mg, the Cmax was higher compared to Caucasian subjects taking the same dose. The lower dose of tamsulosin is preferred in Asia, considering a key complication associated with the higher dose; postural hypotension.

The pharmacokinetics of dutasteride and tamsulosin in Western subjects is well-understood (CIB). In contrast, pharmacokinetic data for these two drugs in Chinese subjects are limited. Following a request to provide this information from the Regulatory Authority in China, subjects of Chinese origin living in China will participate in a PPK sub-study in this study,which aims to characterize the PK of dutasteride when dosed in combination with tamsulosin to Chinese men with BPH.

The benefits of tamsulosin 0.2mg co-administered with dutasteride 0.5mg has been previously demonstrated in a Japanese phase III study where subjects were allowed to take tamsulosin 0.2mg concomitantly with dutasteride.

# 4. SUBJECT SELECTION AND DISCONTINUATION/ COMPLETION CRITERIA

## 4.1. Subject Selection Criteria

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety or rights. Therefore, adherence to the criteria as specified in the protocol is essential.

### 4.1.1. Number of Subjects

Approximately 586 men with symptomatic BPH will be randomized into the treatment phase. It is expected that approximately 1000 patients will need to be screened to allow

for a screening failure rate of approximately 40%. The overall enrolment target number may be adjusted depending on the actual experience of enrolment and retention of participants, to ensure that the overall evaluable subject number target is met. See Section 9.2.1 for sample size assumptions.

### 4.1.2. Inclusion Criteria

Subjects eligible for enrolment in the study must meet all of the following criteria:

1. males, aged ≥50 years
2. clinical diagnosis of BPH by medical history and physical examination, including a digital rectal examination (DRE)
3. International Prostate Symptom Score (IPSS) ≥12 points at Screening
4. prostate volume ≥30cc (by transrectal ultrasonography; TRUS)
5. total serum Prostate Specific Antigen (PSA) ≥1.5ng/mL and ≤ 10 ng/mL at Screening
6. maximum urinary flow rate (Qmax) >5mL/sec and ≤15mL/sec and minimum voided volume of≥125mL at Screening
7. Asparate aminotransferase (AST) and Alanine aminotransferase (ALT) < 2x upper limit of normal (ULN); alkaline phosphatase and bilirubin ≤ 1.5xULN (isolated bilirubin > 1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
8. Fluent and literate in local language with the ability to comprehend and record information on the IPSS, BHS, BII, and PAS- SFI questionnaires
9. Men with a female partner of childbearing potential must agree to use a condom up to 6 months after the last dose (applies only to countries where the local product monograph for dutasteride mandates condom use for men with a female partner of childbearing potential)

### 4.1.3. Exclusion Criteria

Subjects meeting the following criteria must not be enrolled in the study:

*Medical Condition Exclusions:*

1. History or evidence of prostate cancer (e.g. positive biopsy or ultrasound, suspicious DRE). Patients with suspicious ultrasound or DRE who have had a negative biopsy within the preceding 6 months and stable PSA are eligible for the study.

   Note: If total serum PSA is >4ng/mL and unless PSA value has been stable for at least the past 2 years, the investigator should make every appropriate effort to exclude the possibility of prostate cancer, including consideration of prostate biopsy.

2. Previous prostatic surgery (including TURP, laser, HIFU (transrectal high intensity focused ultrasounds), thermotherapy, TUNA, (transurethral needle ablation), balloon dilatation, and stent replacement) or other invasive procedures to treat BPH.
3. History of flexible/rigid cystoscopy or other instrumentation of the urethra within 7 days prior to the Screening Visit. Catheterisation (<10F) is acceptable with no time restriction.
4. History of AUR within 3 months prior to Screening Visit.
5. Post-void residual volume >250mL (suprapubic ultrasound) at Screening.
6. Any conditions other than BPH, which may in the judgment of the investigator, result in urinary symptoms or changes in flow rate (e.g. neurogenic bladder, bladder neck contracture, urethral stricture, bladder malignancy, acute or chronic prostatitis, or acute or chronic urinary tract infections).
7. Unstable liver disease (chronic stable hepatitis B and C are acceptable if subject meets entry criteria).
8. History of renal insufficiency, or serum creatinine >1.5 times the upper limit of normal at Screening.
9. Any unstable, serious co-existing medical condition(s) including, but not limited to:

a. Myocardial infarction, coronary bypass surgery, unstable angina, cardiac arrhythmias, clinically evident congestive heart failure, or cerebrovascular accident within 6 months prior to Screening visit; uncontrolled diabetes or peptic ulcer disease which is uncontrolled by medical management.

b. Postural hypotension, dizziness, vertigo 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.

c. Any serious and/or unstable pre-existing medical, psychiatric disorder, or other conditions that could interfere with subject's safety*, obtaining informed consent or compliance to study procedures in the opinion of the investigator or GSK medical monitor.

d. History of breast cancer or clinical breast examination finding suggestive of malignancy.

e. History of malignancy within the past five years, except for basal cell carcinoma of the skin. Subjects with a priori malignancy who have had no evidence of disease for at least the past 5 years are eligible.

*Investigator may consult with GSK Medical Monitor if condition could interfere with subject's safety

*10.* Current or Previous Use of the following medications*:*

a. Use of any 5-alpha-reductase inhibitor (e.g. Proscar, Propecia), any drugs with antiandrogenic properties (e.g. spironolactone, flutamide, bicalutamide, cimetidine, ketoconazole, progestational agents), or other drugs noted for gynaecomastia effects, or that could affect prostate volume, within the 6 months preceding the historical TRUS or Screening Visit and throughout the study (other than as study medication). Previous use of AVODART™ should not be within 6 months of the baseline or historical TRUS.

b. Anabolic steroids (subject must discontinue for 6 months prior to study entry to be eligible) and agree not to take them for the duration of the study.

c. Phytotherapy for BPH within 2 weeks of Screening Visit and/or predicted to need phytotherapy during the study.

d. Use of any alpha-adrenoreceptor blockers within 2 weeks of Screening Visit (i.e. indoramin, prazosin, terazosin, tamsulosin, alfuzosin, doxazosin, silodosin) and/or predicted to need any alpha blockers other than the study prescribed tamsulosin.

e. Use of any alpha-adrenoreceptor agonists (e.g. pseudoephedrine, phenylephedrine, ephedrine) or anticholinergics (e.g. oxybutynin,tolterodine, darifenacin, solifenacin,propantheline) or cholinergics (e.g. bethanecol chloride) within 48 hours prior to all uroflowmetry assessments.

f. Use of selective beta 3-adrenoceptor agonist (mirabegron) within 2 weeks prior to all uroflowmetry assessments.

11. Hypersensitivity to any alpha-/beta- adrenoreceptor blocker or 5-alpha-reductase inhibitor, or other chemically-related drugs.
12. Participation in any investigational or marketed drug trial within 30 days (or 5 half-lives of drug, whichever is the longer) preceding the Screening Visit and/or plans to participate in such a trial during the course of this study.

### 4.1.4. Other Eligibility Criteria Considerations

In order to assess any potential impact on subject eligibility with regard to safety, the Investigator must refer to the relevant document(s) for detailed information regarding warnings, precautions, contraindications, adverse events, drug interactions, and other significant data pertaining to the study drug(s) being used in this study. These documents include, but may not be limited to, the following: the dutasteride Clinical Investigator's Brochure (CIB) or equivalent document provided by GlaxoSmithKline (GSK), the dutasteride (AVODART) local product monograph, where available, the approved product label(s) for tamsulosin (Harnal D, Flomax) and dutasteride (AVODART), if applicable. Study Procedures Manuals will outline information contained in the local product monographs that must be relayed to patients (e.g. use of a condom to avoids exposure of his partner when taking the study drugs), as applicable to a specific country.

#### 4.1.4.1. Precautions

Investigator must refer to the relevant document(s) for detailed information regarding precautions as mentioned above. Local product monograph should be checked carefully to adhere to local labelling guidelines.

## 4.2. Permanent Discontinuation from Study Treatment and Subject Completion Criteria

### 4.2.1. Permanent Discontinuation from Study Treatment

Subjects will receive study treatment until completion of 2 years of study. In addition, study treatment may be permanently discontinued for any of the following reasons:

- deviation(s) from the protocol
- adverse event
- request of the subject
- subject who has BPH-related prostatic surgery or any minimally-invasive/non-surgical intervention for treatment of BPH symptoms at any time during the study period
- investigator's discretion
- subject is lost to follow-up
- study is closed or terminated.

A subject, who experiences an AUR, does not need to be withdrawn from the study treatment. Any subject who has BPH-related prostatic surgery or any minimally-invasive/non-surgical intervention for treatment of BPH symptoms at any time during the study period must be withdrawn from the study treatment.

The primary reason for permanent discontinuation of study treatment must be documented in the subject's medical records and eCRF.

Once a subject has permanently discontinued from study treatment, the subject will not be allowed to be retreated or replaced.

All subjects who prematurely discontinue from study treatment may not necessarily be withdrawn from the study as further study procedures or follow-up may be performed (Section 6.3).

Subjects with sexual function related adverse events (contact GSK Medical Monitor if in doubt) leading to study withdrawal, will be followed up for up to 6 months after the last dose of study drug. The sexual function Targeted Follow-Up Questionnaire to be used for these subjects follow-up can be found in the Study Procedures Manual.

### 4.2.2. Subject Completion

A subject will be considered to have completed the study if he completes the 4-week placebo run-in and the 104 week study treatment period.

# 5. STUDY TREATMENTS

The term 'study treatment' is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments.

## 5.1. Investigational Product

Dutasteride 0.5mg capsules along with commercially sourced tamsulosin 0.2mg tablets and placebo will be provided to sites by GSK.

The dutasteride 0.5mg and placebo, manufactured for GSK by Catalent Pharma Solutions in Beinheim, France will be supplied as plain, oblong, opaque, dull yellow soft gelatin capsules.

Commercially available tamsulosin 0.2mg tablets will be supplied by GSK.

An oral disintegrating placebo tamsulosin tablet will be supplied by GSK for the run-in period.

### 5.1.1. Dosage and Administration

Two treatment groups will be studied in parallel.

**Run-in phase (single-blind):**

Each subject qualifying for the study according to the inclusion/exclusion criteria will be entered into a placebo run-in phase and will be dispensed single-blind medication at the second screening visit, Visit 1b (this is to permit return of PSA/ haematology/ biochemistry results before dispensing placebo medication). Subjects will receive a 1-month supply of study medication. All subjects will be instructed to take one soft gelatin placebo capsule (swallowed whole and not chewed) and one oral disintegrating placebo tablet (dissolved on the tongue then swallowed not chewed), following the first meal each day for four weeks. They will then be randomized to a double-blind treatment phase for a further 104 weeks.

**Randomized treatment phase (double-blind):**

Subjects will be randomized in a 1:1 ratio to receive either:

Dutasteride 0.5mg + tamsulosin 0.2mg once daily for 104 weeks, **OR**

Dutasteride placebo +tamsulosin 0.2mg once daily for 104 weeks,X

At randomisation, Visit 2, subjects will receive a 3-month supply of study medication. Study subjects will be instructed to take 1 dutasteride capsule (swallowed whole and not chewed) and one tamsulosin tablet (dissolved on the tongue then swallowed not chewed) following the first meal each day for 104 weeks.

Study medication will be resupplied at 13 week intervals during scheduled clinic visits (Visits 3-9).

The investigator or designee should not make any adjustments to the dosage or frequency of study medication.

Subjects will be reminded to return all medication to the study centre during scheduled clinic visits. Study staff at the centre will conduct counts of all returned study medication to ensure compliance. At the end of the study, all bottles (used and unused) must be returned to the sponsor or destroyed (and destruction documented) according to local site/local operating company procedures.

## 5.2. Packaging and Labeling

Dutasteride study medication for both phases of the study will be provided in high density, polyethylene bottles with plastic child-resistant closures. Dutasteride 0.5mg and its matching placebo will be packaged to be indistinguishable irrespective of treatment.

Commercially available tamsulosin 0.2mg will be provided by GSK.

The tamsulosin tablet placebos will be packaged in blister packs.

## 5.3. Handling and Storage of Study Treatment

Investigational product must be dispensed or administered according to procedures described herein. Only subjects enrolled in the study may receive investigational product, in accordance with all applicable regulatory requirements. Only authorized site staff may supply or administer investigational product. All investigational products must be stored in a secure area with access limited to the investigator and authorized site staff and under physical conditions that are consistent with investigational product-specific requirements.

Dutasteride is absorbed through the skin; therefore, women who are pregnant or may be pregnant should not handle dutasteride because of the possibility of absorption and the potential risk of a male foetal abnormality. If contact is made with leaking capsules, the contact area should be washed immediately with soap and water.

The dutasteride capsules should be stored at temperatures up to 25°C (77°F). The commercial tamsulosin and placebo should be stored as per the instructions on the label. Relevant label details will be provided in the study SPM.

All study drug shipped to the investigator will be accompanied by a packing slip which will detail the contents of the shipment. The investigator or designee must sign and date the form where indicated confirming receipt of the investigational product shipment as listed. The form should be retained for the investigator’s records.

A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from GSK upon request.

Final disposition (e.g. destroyed at the site, returned to GSK or a third party contractor) of unused study medication will be specified in the Study Procedure Manual.

## 5.4. Treatment Assignment

Subjects will be identified by a unique subject number that will remain consistent for the duration of the study.

Upon completion of all the required screening assessments, eligible subjects will be registered into RAMOS (Registration and Medication Ordering System), the GSK interactive voice response system (IVRS), by the investigator or authorized site staff.

Subjects will be randomized by investigative site using a randomization schedule generated by the GSK Biostatistical Department, which will assign subjects in a 1:1 ratio to either dutasteride 0.5mg + tamsulosin 0.2mg or placebo + tamsulosin 0.2mg. Once a randomization number has been assigned it must not be re-assigned even in cases of errors.

## 5.5. Blinding

Once study treatment is initiated, all subjects will receive tamsulosin 0.2mg as open-labeled medication.

The investigator or treating physician may unblind a subject's treatment assignment (dutasteride or placebo) **only in the case of an emergency**, when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject. Whenever possible, the investigator must first discuss options with the GSK Medical Monitor or through the appropriate GSK study personnel **before** unblinding the subject's treatment assignment. If this is impractical, the investigator must notify GSK as soon as possible, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study. The date and reason for the unblinding must be recorded in the eCRF.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to clinical investigators in accordance with local regulations and/or GSK policy.

Unblinding will be conducted through RAMOS. Additional details are provided in the SPM.

## 5.6. Product Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of GSK investigational product dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to GSK, when applicable. Product accountability records must be maintained throughout the course of the study. Refer to the SPM for further detailed instructions on product accountability.

## 5.7. Treatment Compliance

Compliance with study treatment will be assessed through querying the subject during the site visits and documented in the source documents and eCRF.

A record of the number of capsules and tablets dispensed to and taken by each subject must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates will be recorded in the eCRF.

## 5.8. Dose Modifications

Dose modification will not be conducted in this study.

If a subject's treatment has been interrupted for more than 30 days. The Investigator must contact the GSK Medical Monitor to review the subject's condition in order to resume the study treatment.

# 6. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

## 6.1. Permitted Medications and Non-Drug Therapies

All concomitant medications taken during the study will be recorded in the eCRF with indication, dose information, and dates of administration.

Although discouraged, use of dietary supplements (e.g. selenium, Vitamin E) are permitted during the study.

## 6.2. Prohibited Medications and Non-Drug Therapies

Use of the following medications will be prohibited during the study:

a. Not permitted at any time:

- Finasteride (Proscar, Propecia)
- Any other investigational or marketed 5α-reductase inhibitors (other than study medication)
- Any alpha-adrenoreceptor blockers (other than study medication)
- BPH-related phytotherapy

- Concurrent use of anabolic steroids
- Drugs with antiandrogenic properties (e.g. spironolactone, flutamide, bicalutamide, cimetidine, ketoconazole, progestational agents) or other drugs that are noted for gynaecomastia effects or could affect prostate volume.
- Any PDE-5 inhibitor (e.g. sildenafil, vardenafil, tadalafil)
- Ginseng utilised for the treatment of BPH or sexual dysfunction

b. Not permitted within 48 hours prior to each IPSS or peak flow assessment:

- Any alpha-adrenoreceptor agonist (e.g. pseudoephedrine, phenylephedrine, ephedrine)
- Anticholinergics (e.g. oxybutynin, propantheline, danifenacin, solifenacin, tolterodine)
- Cholinergics (e.g. bethanecol chloride)

c. Not permitted within 2 weeks prior to each IPSS or peak flow assessment:

- Selective beta 3-adrenoceptor agonist (mirabegron)

Questions regarding permitted and prohibited concomitant medications and non drug therapies should be directed to the GSK Medical Monitor for clarification.

### 6.2.1. Non-Drug Therapies

Any occurrence of BPH-related prostatic surgical intervention and/or any minimally-invasive/non-surgical procedures for treatment of BPH performed during the conduct of the study will be recorded in the eCRF.

Surgical interventions for BPH include but are not limited to adenomectomy, balloon dilatation, prostatotomy, prostatectomy and transurethral resection of the prostate (TURP) or laser surgery. Non-surgical or minimally-invasive procedures for BPH include but are not limited to transrectal high intensity focused ultrasound (HIFU), transurethral needle ablation (TUNA) and transurethral microwave thermotherapy (TUMT).

## 6.3. Treatment after Discontinuation of Study treatment or Discontinuation of Study

Post study treatment will not be provided as part of the protocol. Upon discontinuation from assigned study treatment, subjects may receive additional (non protocol) therapy at the discretion of the treating physician. The investigator is responsible for ensuring that consideration has been given to the post-study care of the patient's medical condition whether or not GSK is providing specific post-study treatment.

If a subject discontinues study treatment permanently after Visit 2 (post-randomisation) for any reason, other than lost to follow-up, the investigator should make every effort to complete the following activities listed below: (Note: the subject has the right to refuse any further contact for study-related follow-up information).

- End of Study Treatment Assessments as outlined in Section 7.2.2.5.
- Biannual follow-up for clinical events via telephone contact every 6 months relative to baseline visit (Visit 2) until the 2 year anniversary of randomisation. Any occurrence of death, AUR, BPH-related prostatic surgery or minimally-invasive/non-surgical intervention for BPH, prostate cancer /biopsy reported after premature withdrawal of study treatment, and outcomes of sexually related adverse events reported during the treatment period, should be fully documented in the eCRF and source documents. The purpose of the collection of these data is to more fully document study endpoints and related events.

No additional study activities other than those that are stated above are planned after a subject's permanent discontinuation from study treatment

A subject is considered a 'withdrawal' from the study when no study procedure has occurred, no follow-up has been performed and no further information has been collected for this subject from the date of withdrawal/last contact.

The primary reason for permanent discontinuation of study must be documented in the subject's medical records and eCRF.

Subjects who are withdrawn from the study after randomisation will not be replaced.

In the event that a subject is prematurely discontinued from the study treatment or withdraw from the study at any time due to an AE (as defined in Section 7.4.1, "Definition of an AE") or SAE (as defined in Section 7.4.2, "Definition of an SAE"), the procedures described in Section 7.4.7 ("AEs and SAEs") must be followed.

## 6.4. Treatment of Study Medication Overdose

In volunteer studies, single doses of dutasteride up to 40mg/day (80 times the therapeutic dose) for 7 days have been administered without significant safety concerns. In clinical studies doses of 5mg daily have been administered to patients for 6 months with no additional adverse effects to those seen at therapeutic doses of 0.5mg.

There is no specific antidote for 5ARI overdose. In cases of suspected overdose, subjects should be managed with appropriate supportive therapy as determined by the investigator.

In case of acute hypotension occurring after overdose with tamsulosin hydrochloride, cardiovascular support should be given. Restoration of blood pressure and normalization of heart rate may be accomplished by lying the patient down. If this is inadequate, administration of volume expanders and if necessary vasopressors should then be used and renal function should be monitored and supported as needed. Laboratory data

indicate that tamsulosin hydrochloride is 94% to 99% protein bound; therefore, dialysis is unlikely to be of benefit in removing tamsulosin from the body.

# 7. STUDY ASSESSMENTS AND PROCEDURES

A signed, written informed consent form must be obtained from the subject prior to any study-specific procedures or assessments.

Refer to the Time and Events Table for the timing of all assessments (Table 1). Details on efficacy and safety assessments are presented in Section 7.2 and Section 7.3 respectively. Further details of study procedures and assessments can be found in the study procedures manual (SPM).

For health outcome measures refer to Section 7.5, for PGx samples refer to Appendix 1

Unscheduled visits/assessment may be performed by the investigator as medically necessary.

Investigators may be requested to perform additional safety tests during the course of the study based on newly available data to ensure appropriate safety monitoring. Appropriate local regulatory and ethical approvals should be obtained before any additional testing is performed.

## Table 1 Time and Events Table

| **Study Procedures** | **Visit 1a Pre-Screen** | **Visit 1b** Screening** (V1a + 14 days) | **Visit 2 Baseline** (V1b + 28d ± 4 days) | **Visit 3** (Baseline + 13 wks ± 14 days) | **Visit 4** (Baseline + 26 wks ± 14 days) | **Visit 5** (Baseline + 39 wks ± 14 days) | **Visit 6** (Baseline + 52 wks ± 14 days) | **Visits 7 - 9** (Years 2, repeat as for V3-V5 of Year 1) | **Visit 10** (Baseline + 104 wks ± 14 days) |
|---|---|---|---|---|---|---|---|---|---|
| | Pre-Screen Visit | Start of Placebo run-in | Start of Treatment Phase Baseline (Randomisation) | 3 months post Randomisation (Rand) | 6 months post Rand | 9 months post Rand | 12 months post Rand | 15,18 & 21 months post Rand respectively | End of Treatment Phase 24 months post Rand[i] |
| ICF | X | | | | | | | | |
| Incl/Exclusion | X | X | | | | | | | |
| Medical Hx/ Demog/CV Hx/ | X | | | | | | | | |
| ECG (12-lead) | | X | | | | | | | |
| Collection of PGx Sample | | | X | | | | | | |
| **Safety evaluations** | | | | | | | | | |
| Concomitant medication | X | X | X | X | X | X | X | ⇒ | X |
| Physical Examination[a] | | X | | | X | | X | X[h] | X |
| Vital signs[b] | | X | X | X | X | X | X | ⇒ | X |
| Haematology/clinical chemistry | X | | | | | | X | | X |
| HBsAG and Hepatitis C Antibody[g] | | | X | | | | | | |
| Total serum PSA[c] | X | | | | X | | X | | X |
| Post-void residual volume (PVR) | X | X*** | X | | X | | X | X[h] | X |
| AEs[d] | | X | X | X | X | X | X | ⇒ | X |
| Suicidality (C-SSRS) | X | | | | X | | X | | X |
| **Efficacy:** | | | | | | | | | |
| BPH symptoms (IPSS) | X | | X | X | X | X | X | ⇒ | X |
| Prostate Volume (TRUS) | | X | | | | | X | | X |
| Peak Urine Flow (Qmax) | X | X*** | X | | X | | X | X[h] | X |
| AUR or BPH-related Surgery | | | X | X | X | X | ⇒ | X | X |

| **Study Procedures** | **Visit 1a Pre-Screen** | **Visit 1b** Screening** (V1a + 14 days) | **Visit 2 Baseline** (V1b + 28d ± 4 days) | **Visit 3** (Baseline + 13 wks ± 14 days) | **Visit 4** (Baseline + 26 wks ± 14 days) | **Visit 5** (Baseline + 39 wks ± 14 days) | **Visit 6** (Baseline + 52 wks ± 14 days) | **Visits 7 - 9** (Years 2, repeat as for V3-V5 of Year 1) | **Visit 10** (Baseline + 104 wks ± 14 days) |
|---|---|---|---|---|---|---|---|---|---|
| | Pre-Screen Visit | Start of Placebo run-in | Start of Treatment Phase Baseline (Randomisation) | 3 months post Randomisation (Rand) | 6 months post Rand | 9 months post Rand | 12 months post Rand | 15,18 & 21 months post Rand respectively | End of Treatment Phase 24 months post Rand[i] |
| **Pharmacokinetics**[j] | | | | | | | | | |
| Serum PK samples[j] | | | | X | X | X | | | |
| **Health Outcomes:** | | | | | | | | | |
| BPH Health Status Q 8 IPSS (BHS) | X | | X | X | X | X | X | ⇒ | X |
| AUR or BPH-related Surgery Medical Resource Utilisation | | | X | X | X | X | X | ⇒ | X |
| BPH Impact Index (BII) | X | | X | X | X | X | X | ⇒ | X |
| PAS-SFI | | X | X | | | | X | | X |
| **Other Efficacy Measures** | | | | | | | | | |
| UTI /Incontinence / Renal Insufficiency | | | X | X | X | X | X | ⇒ | X |
| **Register in RAMOS** | X | | | | | | | | |
| **Study Medication:** | | | | | | | | | |
| Call RAMOS/DispenseMeds | | X[e] | X[f] | X | X | X | X | ⇒ | |
| Compliance check/Collection | | | X | X | X | X | X | ⇒ | X |

## Table 1 Time and Events Table

** This second screening visit is mandatory before dispensing placebo run-in medication. This additional screen visit is designed to allow time for PSA/haem/biochem results to be returned from the laboratory, and repeat Qmax/PVR (if required) before performing TRUS on patients who may not otherwise be eligible for the study.
***REPEAT ONLY IF QMAX inclusion criteria NOT MET at Visit 1a
⇒ ongoing assessment
a. Including DRE and qualitative breast examination
b. Blood pressure and pulse to be taken after sitting quietly for 5 minutes
c. PSA sample must be taken before TRUS
d. Only Serious AEs (related to study participation) occurring between Screening (Visit 1a) and the start of placebo run-in medication need to be recorded
e. Single-blind medication to be dispensed at Visit 1b only
f. Double-blind medication dispensed from Visit 2 onwards.
g. Hepatitis B surface antigen and hepatitis C antibody (if hepatitis C antibody positive, a hepatitis C RNA test should be reflexively performed to confirm the result)
h. Only performed at Visit 8 (Month 18)
i. Performed for End of Study Treatment Assessments as well when a subject discontinues the study treatment (see Section 6.3 and Section 7.2.2.5)
j. Serum PK samples are only applicable to subjects of Chinese origin living in China (see Appendix 7 for more details)

## 7.1. Critical Baseline Assessments

Demographic characteristics will be collected during screening. Subject's year of birth, race, height (in centimeters), and weight (in kilograms) will be recorded in the eCRF. In addition the following assessments will be completed at screening:

- Cardiovascular medical history/risk factors including history of angina pectoris, myocardial infarction, stroke, diabetes, hypertension, and hyperlipidemia
- Smoking history
- Premature Cardiovascular disease in first degree relatives.
- Medical history, a complete physical examination (including DRE and breast examination)
- A 12-lead ECG, vital signs; clinical laboratory including hematology, clinical chemistry; total PSA; prostate volume*; post void residual volume (PVR); peak urinary flow (Qmax) and health outcomes questionnaires: IPSS, BHS, BII and PAS SFI and C-SSRS questionnaire

*All subjects will undergo a TRUS at Screening (Visit 1b) for determination of prostate volume, unless this has been performed within the previous 6 months. However, if a previous TRUS is to be used, the prostate volume must have been calculated using the formula in Section 7.2.2.2 or the raw data for dimensions must be available to use in the ellipsoidal formula.

## 7.2. Efficacy

### 7.2.1. Primary Endpoint

- The primary efficacy endpoint of this study is change in IPSS from baseline at Year 2 (see Section 7.2.2.1 for details of the IPSS).

#### 7.2.1.1. Secondary Endpoints

The secondary efficacy endpoints of this study are:

- Percent change in prostate volume from baseline
- Proportion of subjects with IPSS improvement of ≥2 points and ≥3 points from baseline and, separately, ≥25% improvement from baseline
- Change in Qmax from baseline
- Proportion of subjects with Qmax improvement of ≥3mL/sec and, separately, ≥30% improvement from baseline
- Time to event/ proportion of subjects with AUR or BPH related prostatic surgery
- Time to event/proportion of subjects with AUR
- Time to event/proportion of subjects undergoing BPH related prostatic surgery

#### 7.2.1.2. Other Efficacy Measures

The following are potential BPH disease related events not captured as primary or secondary endpoints. They will be collected in this study for possible comparison to historical BPH studies and to insure consistency of disease-related adverse event definition (see Section 7.4.2.5).

- Urinary tract infection/urosepsis
- Urinary incontinence (overflow/urge)
- Renal insufficiency

#### 7.2.1.3. Health Outcome Measures Endpoints

Change in BPH-related Health Status (Q8 of IPSS) from Baseline

Change in BPH Impact Index (BII) from Baseline

Change in Problem Assessment Scale of the Sexual Function Inventory (PAS-SFI), from Baseline

Resource Use related to AUR and BPH-related surgical events.

### 7.2.2. Efficacy Assessment

See the Time and Events Table (Section 7) for the schedule of efficacy assessments. Assessments must be performed on a calendar schedule. For post baseline assessments, a window of [±14 days] is permitted to allow for flexible scheduling.

#### 7.2.2.1. International Prostate Symptom Score (IPSS)

The IPSS is a 7 item instrument (essentially the same as the American Urological Association Symptom Index, AUA-SI) designed to quantify urinary symptoms but with an additional, independent eighth question on quality of life (See Appendix 5). The IPSS will be administered at Pre-screening (Visit 1a), at Baseline (Visit 2) and at every 13 week clinic visit thereafter during the study treatment period. At Pre-screening (Visit 1a), subjects with IPSS <12 points (based on the first 7 questions) should be excluded from the study. Also, subjects must be instructed to abstain from using any alpha adrenergic agonist, cholinergic or anticholinergic agents including anti-histamines or decongestants within 48 hours prior to conducting each IPSS. In addition subjects must also abstain from taking selective beta 3-adrenoceptor agonist (mirabegron) for over-active bladder syndrome two weeks prior to each IPSS. If the subject did not adhere to these guidelines, study procedures should not be performed and the visit should be rescheduled.

For details of the IPSS assessment see Section 7.5.1.

#### 7.2.2.2. Prostate Volume

Prostate volume measurements will be conducted at screening Visit 1b and annually post-randomisation at Visits 6, and 10, during the two year treatment period. The

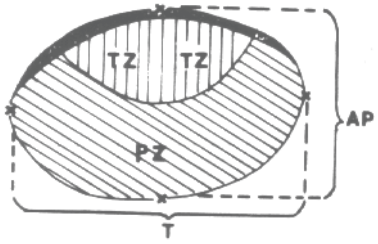
anteroposterior, cephalocaudal, and transverse diameters of the prostate will be obtained by TRUS to calculate the prostate volume using the following formula:

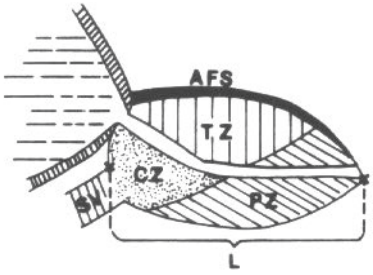
**π/ 6 (anteroposterior width X cephalocaudal width X transverse width).**

Prostate volume calculated by pre-programmed equipment will be accepted if the anteroposterior, cephalocaudal and transverse are also outputted and recorded in the eCRF. If the prostate volume calculated by pre-programmed equipment is utilised for a subject, then the same equipment and hence calculator, must be used for the duration of the subject's participation in the study.

For each individual subject, all TRUS procedures should be performed by the same technique and, if possible, the same individual and, ideally, that individual will not be responsible for soliciting adverse events or assessing relatedness of adverse events to study medication. At Visit 1b, if the prostate volume is <30cc the patient should not be randomized to the double blind phase.

The diagrams below show how the maximum dimension of each section will be determined. The transverse (T) dimension and the anteroposterior (AP) dimension are to be measured in the transverse plane. Scanning in the sagittal (longitudinal) plane would allow for the cephalocaudal (L) measurement of the prostate length from the apex to the bladder neck.




Transverse Scan Sagittal Scan

[TZ=transition zone; PZ=peripheral zone; CZ=central zone; SV=seminal vesicle; AFS=anterior fibromuscular stroma]

### 7.2.2.3. Urinary Flow Measurement

Measurements of urinary flow will be conducted using a Uroflow Meter (details will be provided in the study procedures manual) at Screening Visit 1a/b, Baseline (Visit 2) and every scheduled 26 week clinic visit post-randomisation thereafter during the treatment period.

The following assessments will be collected:

- peak (maximum) flow ($Q_{max}$) at a voided volume ≥125 ml at all visits

- voided volume (ml)

**During screening, the patient should undergo a urine flow assessment at the same visit, i.e. at Pre-screening (Visit 1a), if possible**. If a subject is unable to perform the urine flow at the first screening visit (Visit 1a), then the subject can retry at Visit 1b, prior to starting the placebo run-in period. The subject will only be eligible to be enrolled in the study if Qmax is >5mL/sec and ≤15mL/sec and the voided volume is ≥125mL for one assessment. If the voided volume is less than 125mL at any assessment, the subject should be instructed to drink more water until his bladder is full when the test can be repeated. During the study, if the repeat voided volume is less than 125ml the first voided volume will be recorded in the eCRF.

All uroflow traces should incorporate subject identifiers, date and time of assessment and should be signed and dated by the investigator and retained with the subjects study records. During continuous use, the correct functioning of the uroflow meter will be checked once a week (especially if moved) and appropriate actions taken to ensure good maintenance of the machine.

Due to the circadian changes in urinary flow measurements in BPH subjects, study visits for an individual subject should be conducted consistently in either the morning or afternoon hours to assess all urinary flow measurements. Subjects should be instructed to drink at least 2 glasses of water 2-3 hours prior to their clinic visit and to keep drinking every 15 minutes filling the bladder. Also, subjects must be instructed to abstain from using any alpha adrenergic agonist, cholinergic or anticholinergic agents including anti-histamines or decongestants within 48 hours prior to conducting this test. In addition subjects must also abstain from taking selective beta 3-adrenoceptor agonist (mirabegron) for over-active bladder syndrome for two weeks prior to this test. If the subject did not adhere to these guidelines, study procedures should not be performed and the visits should be rescheduled.

When conducting uroflow measurements, the funnel should be kept at the subject's knee level and the printout away from the subject's view. Subjects should be blinded from all uroflow measurement data throughout the study.

#### 7.2.2.4. Definition of Other Efficacy Measures

Other efficacy measures are noted in Section 7.2.1.2. The following provides clinical definition for these measures.

Renal insufficiency is defined as >=50% sustained rise in baseline serum creatinine and >=1.5mg/dL; BPH-relatedness will be assessed by the investigator.

Urinary tract infection (UTI) is defined as symptomatic infection of $10^5$ cfu/mL during the study; recurrent UTI is defined as two or more UTI episodes during the study. BPH-relatedness will be assessed by the investigator.

Incontinence (overflow or urge) is defined as socially or hygienically unacceptable involuntary leakage of urine). BPH-relatedness will be assessed by the investigator.

#### 7.2.2.5. End of Study Treatment Assessments

During the study period that is between the scheduled visits, if a subject discontinues study treatment permanently after Visit 2 (post-randomisation) for any reason, other than lost to follow-up, the investigator should make every effort to schedule a visit by the subject to the study site and complete the following assessment:

- Concomitant medications
- Adverse events
- Physical exam including vital signs, DRE and qualitative breast examination
- Obtain blood samples for hematology, clinical chemistry and PSA determinations
- Administer health outcome questionnaires (IPSS, BHS,BII and PAS-SFI)
- Administration of C-SSRS questionnaire
- Record any episodes of AUR, and, BPH-related prostatic surgery or minimally-invasive/non-surgical interventions
- Record any episodes of UTI/urosepsis, urinary incontinence (first episode or consistent worsening), and renal insufficiency
- Retrieve any unused double-blind study medication, assess compliance and record date of last dose of study medication
- Discuss the biannual follow-up phone call schedule
- Complete subject eCRF

If the decision for a subject's study treatment discontinuation is made during a regularly scheduled visit, the procedure that are stated above should be completed, in addition to any scheduled procedure that is not listed above.

### 7.2.3. Short Messaging Service Reminder System

To help with the retention of the subjects and planning of their scheduled follow up throughout the study, subjects will be sent text messages via their mobile telephone, or email reminders, regarding their scheduled appointments. Sites will gain consent from the subject in the ICF before enrolling their mobile phone number or e-mail address into the secure short messaging service (SMS) reminder system. The system will then transmit text messages or e-mails to the subject in the local language regarding their next appointment.

- Subject participation in the SMS reminder system is voluntary and refusal to participate will not indicate withdrawal from the clinical study. Refusal to participate will involve no penalty or loss of benefits to which the subject would otherwise be entitled. The SMS reminder system may not be available for all study sites or countries. Even if available, study sites or countries may choose not to participate in the SMS reminder system. All text message/e-mail content will be reviewed and approved by the IRB/IEC prior to use.

## 7.3. Safety

### 7.3.1. Endpoints

- Change in total serum PSA from baseline
- Vital signs
- Post-void residual volume
- Clinical laboratory measurements (including haematology, chemistry)
- Adverse events (including AUR or BPH-related surgery and Prostate Cancer and prostate biopsy)
- Physical examination: digital rectal examination (DRE) and qualitative breast examination
- An assessment of suicidality

See Section 7.4 for a complete description of adverse event assessments.

### 7.3.2. Medical History, Concomitant Medications, ECG, Physical Examination

**A medical history** will be obtained at Pre-screening Visit 1a with particular attention paid to the following:

- Approximate time (date) LUTS first noted by patient; time since diagnosis of BPH; previous usage of alpha-1-adrenoreceptor antagonists and/or phytotherapy.
- A thorough review of body systems, both past or current conditions including conditions of interest, smoking history, alcohol, and an assessment of sexual activity/sexual dysfunction;
- Family history of premature cardiovascular disease
- Pharmacotherapy, chronic use of any medication (prescribed and over the counter, including dietary supplements);
- History of allergies or idiosyncratic reactions to drugs;
- Family history of prostate cancer
- Family history of male/female breast cancer

**Concomitant medications** will be assessed at every clinic visit. Use of dietary supplements (i.e. selenium, Vitamin E) during the study is discouraged but not prohibited. All concomitant medications and use of dietary supplements will be recorded in the eCRF. Additional details related to concomitant medications are addressed in Section 6 of this protocol.

**A good quality 12-lead ECG recording** will be obtained for each subject at Screening Visit 1b. The subject should rest supine for 5 minutes before the 12-lead ECG is recorded. Additionally a rhythm strip will be obtained to assess for presence of

arrhythmias. The ECG must be calibrated, labelled and initialled by the person performing the recording. The ECG tracing must be signed and dated by the examining physician to indicate review and any clinically important abnormalities reported on the appropriate page of the eCRF. A copy of the ECG tracing will remain with the subject's medical notes at the site.

**A complete physical examination** will be conducted at Screening Visit 1b and will include measurements of height, weight, blood pressure, digital rectal exam, and a qualitative breast exam (nipple tenderness and/or palpable breast tissue).

Weight will be measured on a standard calibrated scale. Subjects should be dressed in light indoor clothing without shoes. Weight will be documented in kilograms to the nearest tenth of a kilogram using the following conversion factor:

Pounds x 0.4536 = kg

For height measurements, subjects should be measured without shoes. Height will be documented to the nearest tenth of a centimeter using the following formula:

Inches x 2.54 = centimeters

The physical exam will be performed by a licensed physician. Full details of the physical examination will be recorded in the source documents at the site.

### 7.3.3. Physician's assessments and vital signs

At each clinic visit prior to dispensing study drug, a physician will assess the subject's continued eligibility and safety.

Vital signs (blood pressure followed by pulse) will be assessed at Screening Visit 1b, Baseline Visit 2 and at each scheduled 13 week clinic visit thereafter. The subject must be sitting quietly for at least 5 minutes before measurements are taken. No other procedures will be performed during this 5 minute stabilisation period. Pulse rate will be measured for 30 seconds.

In addition, a physical examination will be conducted at Visit 4 (26 weeks post-randomisation) and at 26 week intervals thereafter during the treatment period, and will include a digital rectal exam and a qualitative breast examination (nipple tenderness and/or palpable breast tissue).

The physical exam will be performed by a licensed physician. Full details of the physical examination will be recorded in the source documents at the site.

### 7.3.4. Clinical Laboratory Assessments

Blood samples for all laboratory assessments throughout the study will be collected prior to undergoing any clinical procedures. In order to determine each subject's eligibility to participate in the study, the results of the screening clinical laboratory tests must be assessed by the principal investigator or designee prior to study drug administration. Any

subject having a laboratory result that falls outside the specifications noted in the inclusion or exclusion criteria will be excluded from the study.

Out-of-threshold range values indicated on the clinical laboratory test reports must be assessed as “not clinically significant” (NCS), “clinically significant” (CS), or “repeat” (to indicate a repeat test will be performed). If any laboratory values are deemed clinically significant, the subject must return to the clinic for re-evaluation. All clinically significant changes from baseline will be followed until resolution or stabilization as determined by the principal investigator or designee. The results of all clinical laboratory tests must be assessed by the investigator in order to determine each subject's eligibility to continue in the study.

Haematology and clinical chemistry assessments will be performed at Pre-screening (Visit 1a) to establish eligibility for enrolment and annually post-randomisation at Visits 6, 10. Additionally, a blood draw for HBsAG, and Hepatitis C Antibody should be performed at Visit 2 (baseline).

| Laboratory Assessment | Visit Frequency |
|---|---|
| Hematology | Visits 1a,6, 10 |
| Clinical Chemistry | Visits 1a, 6, 10 |
| PSA | Visits 1a, 4, 6, 10 |
| HBsAG and Hepatitis C Antibody | Visit 2 |

#### 7.3.4.1. Haematology and Clinical Chemistry

Haematological and biochemical analyses will be conducted by a central laboratory designated by GlaxoSmithKline. The following tests will be performed:

| **Haematology** | **Clinical Chemistry (Serum)** |
|---|---|
| Total WBC Count | Glucose |
| Platelet Count | |
| Haemoglobin | Sodium |
| RBC | Potassium |
| | Total protein |
| **PSA (Serum)** | Total bilirubin |
| Total PSA | BUN or urea |
| | Albumin |
| **HBsAG and Hepatitis C Antibody** | ALT (SGPT) |
| | AST (SGOT) |
| | Alkaline Phosphatase |
| | Creatinine |

All clinical laboratory analyses will be conducted at a Central Laboratory selected by GSK. Laboratory data will be electronically transferred from the contract Central Laboratory to GSK or their designee. A printout of results will be transmitted via facsimile to the investigator or designee and must be retained in each subject's study file. In addition to the facsimile results, the investigator will be notified of alert values (out-of-threshold range values or exclusions) by telephone.

#### 7.3.4.2. Prostate Specific Antigen (PSA)

Total serum PSA concentrations will be assessed at Pre-screening Visit 1a and post-randomisation at Visit 4, (Month 6), and annually at Visits 6 and 10. For total PSA, the actual value will be reported at Pre-screening; an adjusted value will be reported for all assessments after 6 months of treatment – see below.

A number of clinical situations (e.g. prostatitis, biopsy, prostatic abscess) can cause transient rises in PSA. Therefore, blood samples for evaluating PSA levels must be collected within the study-defined time windows and prior to performing any clinical procedures (i.e. TRUS and DRE). If a situation arises requiring interim intervention, PSA determinations must be postponed for a period of 1 month following any procedure performed on the prostate and for 3 months following initiation of treatment for acute bacterial prostatis.

Screening PSA results will be reported immediately to the investigators to determine eligibility of study subjects. All post-baseline PSA levels will subsequently be reported following blinding adjustment of the PSA result (where appropriate) as described below.

In order to maintain investigator blinding to study treatment, an independent reviewer who is unblinded to the PSA results as well as the drug random code, will adjust PSA values for appropriate participants. After a subject completes six month of treatment, PSA results will be reported to the principal investigators using the following methods: (1) for subjects on tamsulosin monotherapy, the actual PSA value will be reported; (2) for subjects receiving combination therapy, the PSA value will be multiplied by two (x 2) to account for the known effect of 5ARI's on reducing PSA (data from Phase IIIa and CombAT studies of dutasteride in BPH patients demonstrated a decrease in serum PSA levels by approximately 50% after 6 months of treatment). In dutasteride-treated subjects receiving combination therapy, the doubled PSA value will be randomly stated as the doubled value or a value 0.1 units higher or lower, so that all doubled values expressed to one decimal place will not automatically be reported as an even number.

**Note**: Dutasteride reduces total serum PSA concentration by approximately 40% following 3 months of treatment and by approximately 50% following 6, 12, and 24 months of treatment. PSA measurements should not be performed prior to 6 months of treatment because of the variable effect of dutasteride on serum PSA during this time. Although discouraged, if an additional PSA measurement outside the scheduled assessments is necessary, it should be assayed through the study central laboratory.

Central laboratory, study sites, and monitors will remain blinded to treatment assignments throughout the duration of the study.

### 7.3.5. Post Void Residual Volume

Post void residual volume will be measured suprapubically by ultrasound (immediately following the urinary flow measurement) at Pre-screening Visit 1a/1b (if Qmax inclusion criteria not met at Visit 1A), at Baseline (Visit 2) and at 26 week clinic visits thereafter during the treatment period. Subjects with post void residual volumes >250mL as

measured at Screening (Visit 1a/1b) should be excluded from participating in the study. The time of bladder scan and the time of the preceding void will also be recorded.

### 7.3.6. Acute Urinary Retention

A subject is considered to have acute urinary retention (AUR) when he is unable to urinate and requires bladder catheterisation.

At Visit 2 (Baseline) and each scheduled 13 week clinic visit post-randomisation, the investigator will record in the designated section of the eCRF any incidence of AUR the subject experiences during his participation in the study.

Any occurrence of AUR should not be captured as an adverse event unless considered by the investigator to be more severe than expected for the subject's condition or unrelated to BPH. See Section 7.4.1 and Section 7.4.7 . If in the investigator's opinion, the event meets the definition of serious as outlined in Section 7.4.2 then the event must be reported as an SAE (see also Section 7.4.7.).

### 7.3.7. Surgical and Minimally-Invasive/Non-surgical Interventions for BPH

At Visit 2 (Baseline) and each scheduled 13 week clinic visit post-randomization, the investigator will record in the designated section of the eCRF any BPH-related prostatic surgery and/or any minimally-invasive/non-surgical procedures undergone by the subject during his participation in the study (see Appendix 4 for a glossary of prostatic surgical and minimally-invasive/non-surgical interventions.).

Any resected tissue from patients undergoing prostatic surgery during the study should be sent to the local pathology laboratory for routine histopathology analysis. Information including the date of surgery, reason for surgery and histology results (including high grade prostatic intraepithelial neoplasia (HGPIN) diagnosis and Gleason score, if prostate cancer diagnosis) will be collected and recorded in the eCRF, as applicable.

### 7.3.8. For-Cause Biopsy for Diagnosis of Prostate Cancer

TRUS-guided for-cause biopsies may be conducted at any time during a subject's participation in the study if, in the judgement of the investigator, there is a clinically significant medical trigger, such as:

- Adverse change in digital rectal exam
- Clinically significant increase in serum PSA
- Nodular areas suspicious detected on TRUS

Tissue from all for-cause biopsy cores will be sent to the local pathology laboratory for histopathology analysis.

For all subjects undergoing for-cause biopsy during the study, information including the date of biopsy, reason for biopsy, biopsy results, number of cores obtained, high grade prostatic intraepithelial neoplasia (HGPIN) diagnosis, and surgery outcome will be

collected and recorded in the eCRF, as applicable. In addition, for those subjects with a positive biopsy, information about prostate cancer, including date of diagnosis, Gleason score (classic scoring or modified scoring system) at biopsy and/or surgery, percentage of core involved (semi-quantification of volume of prostate cancer), cancer positive cores (reported as number of positive cores over total number of cores) will be collected and recorded in the eCRF.

### 7.3.9. Suicidality

Dutasteride is considered to be an active compound in human central nervous system (CNS) that may affect mood or behavior via effects on the CNS (directly or indirectly). A GSK review of published literature and clinical trial data for dutasteride has shown that dutasteride is not associated with an increased risk of suicidal thinking or behavior when given to this patient population.

There has been some concern that some CNS-active drugs may be associated with an increased risk of suicidal thinking or behavior when given to some subjects with certain conditions. Although these drugs and other similar drugs of the same class have not been associated with an increased risk of suicidal thinking or behavior when given to this patient population, GSK considers it important to monitor for such events before or during clinical studies with compounds such as this.

Subjects in Study ARI114265 will be assessed for suicidality and unusual changes in behavior using the Columbia Suicide Severity Rating Scale (C-SSRS). To protect subjects in the study, scores from C-SSRS tests will be reviewed in real time by the investigator and appropriate advice given to participants. Consideration should be given to discontinuing study treatments in subjects who experience signs of suicidal ideation or behavior. Refer to Section 7.4.6 for more information.

### 7.3.10. Collection of Other Efficacy Measures

At Visit 2 (Baseline) each scheduled 13 week clinic visit, the investigator will record in the designated section of the eCRF defined incidences of urinary tract infection/urosepsis, urinary incontinence, and renal insufficiency the subject experiences during his participation in the study.

## 7.4. Adverse Events

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE as outlined in Section 7.4.1 and Section 7.4.2.

### 7.4.1. Definition of an AE

Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits, abuse, or misuse. Examples of events meeting the definition of an AE include:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or grade of the condition
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE) unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae)

"Lack of efficacy" or "failure of expected pharmacological action" *per se* is not to be reported as an AE or SAE. However, any signs and symptoms and/or clinical sequelae resulting from "lack of efficacy" will be reported as an AE or SAE, if they fulfill the definition of an AE or SAE.

Events that **do not** meet the definition of an AE include:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

### 7.4.2. Definition of a SAE

A serious adverse event is any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires hospitalization or prolongation of existing hospitalization

NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-subject setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in disability/incapacity, or

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect.

f. Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

g. All events of possible drug-induced liver injury with hyperbilirubinaemia, defined as ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct) (or ALT ≥ 3xULN and INR>1.5, if INR measured) termed 'Hy's Law' events (INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants.)

NOTE: bilirubin fractionation is performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick indicating direct bilirubin elevations and suggesting liver injury. If testing is unavailable and a subject meets the criterion of total bilirubin ≥ 2xULN, then the event is still reported as an SAE. If INR is obtained, include values on the SAE form. INR elevations >1.5 suggest severe liver injury.

Other events that must be reported as Serious AEs in this study, regardless of satisfying criteria a-g, are:

h. Male Breast Cancer

i. Spontaneous Abortion in female partner of male subject (see Partner Pregnancy, Section 7.4.5)

#### 7.4.2.1. Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (hematology, or clinical chemistry) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator are to be recorded as AEs or SAEs.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are **not** to be reported as AEs or SAEs

#### 7.4.2.2. Cardiovascular Events

Investigators will be required to fill out event specific data collection tools for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularisation

This information should be recorded in the specific cardiovascular eCRF within one week of when the AE/SAE(s) are first reported.

#### 7.4.2.3. Death Events

In addition, all deaths will require a specific death data collection tool to be completed. The death data collection tool includes questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

This information should be recorded in the specific death eCRF within one week of when the death is first reported.

#### 7.4.2.4. Sentinel Events

A Sentinel Event is a GSK-defined SAE that is not necessarily drug-related but has been associated historically with adverse reactions for other drugs and is therefore worthy of heightened pharmacovigilance. Medical monitor review of all SAEs for possible Sentinel Events is mandated at GSK. The GSK medical monitor may request additional clinical information on an urgent basis if a possible Sentinel Event is identified on SAE review. The current GSK-defined Sentinel Events are listed below:

- Acquired Long QT Syndrome
- Agranulocytosis/Severe Neutropenia
- Anaphylaxis & Anaphylactoid Reactions
- Hepatotoxicity
- Acute Renal Failure
- Seizure
- Stevens Johnson syndrome/Toxic epidermal necrosis

#### 7.4.2.5. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

A disease-related event is an event generally associated with the disease under study and is not typically associated with the use of the investigational product. In this study, disease-related events will be captured as part of efficacy assessments and hence will be reported as AEs or SAEs only under the following circumstances:

- If a disease-related event is considered by the investigator to be more severe than expected for the subject's condition, but does not meet the definition of serious as outlined in Section 7.4.2, the event should be reported as an AE.
- If a disease-related event is considered by the investigator to be more severe than expected for the subject's condition and meets the definition of serious as outlined in Section 7.4.2, the event must be reported as an SAE.
- If a disease-related event is life-threatening or fatal, regardless of the investigator's assessment of severity expected for the subject's condition, the event must be reported as an SAE.

Disease-related events for this study are listed below.

- BPH symptoms (incomplete emptying, frequency, intermittency, urgency, weak stream, straining, nocturia)
- Changes in Qmax
- Changes in subject's response to questions asked in the IPSS and humanistic assessments.

- Acute urinary retention
- Urinary tract infection/urosepsis
- Urinary incontinence (overflow/urge)
- BPH-related Renal insufficiency

### 7.4.3. QTc Events

If QTc events occur the investigator should promptly contact the medical monitor to receive advice on measures to be taken.

### 7.4.4. Liver Events

If serious liver events occur the investigator should follow the standard serious event reporting process described in the protocol. For non-serious liver events that are clinically significant, the investigator will contact the medical monitor to receive advice on measures to be taken.

### 7.4.5. Partner Pregnancy

As with other 5-alpha reductase inhibitors, dutasteride inhibits the conversion of testosterone to dihydrotestosterone and may, if administered to a woman carrying a male fetus, inhibit the development of the external genitalia of the fetus (see CIB). Small amounts of dutasteride have been recovered from the semen in subjects receiving dutasteride 0.5 mg per day. Based on studies in animals, it is unlikely that a male fetus will be adversely affected if his mother is exposed to the semen of a patient being treated with dutasteride (the risk of which is greatest during the first 16 weeks of pregnancy). Even though it is unlikely that a male fetus will be adversely affected if his mother is exposed to the semen of a partner being treated with dutasteride, some countries recommend the use of condoms in the local dutasteride labels. For these countries it is recommended that the patient avoids exposure of his partner to semen by use of a condom for 6 months after drug discontinuation.

#### 7.4.5.1. Time period for collecting partner pregnancy information

Pregnancy information should be collected on any female partner of a male study subject who is pregnant or becomes pregnant while the subject is participating in the study. All pregnancies in female partners of male subjects will be collected after the start of dosing until 6 months after the subject’s last dose of study drug.

#### 7.4.5.2. Action to be taken if partner pregnancy occurs

The investigator or designee should make every effort to collect pregnancy information on any female partner who is pregnant or becomes pregnant by a male subject during his participation in this study. The investigator, or his/her designee, should record pregnancy information on the appropriate form and submit this to GSK within 2 weeks of learning that a study subject's partner is pregnant, having first obtained the necessary written informed consent from the female partner directly. The subject's female partner should be followed to determine the outcome of the pregnancy. Information on the status of the

mother and child will be forwarded to GSK. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or a SAE. A spontaneous abortion will always be reported as a SAE.

Any SAE occurring as a result of a post-study pregnancy (6-months after last dose) **and** considered reasonably related to the investigational product by the investigator will be reported to GSK. While the investigator is not obligated to actively seek this information in former study participants, he/she may learn of an SAE through spontaneous reporting.

See the Clinical Investigator Brochure and AVODART approved product label (if applicable) for additional details about dutasteride's potential effects on the male fetus.

### 7.4.6. Suicidality Monitoring

Assessment of suicidality will be performed using the C-SSRS which will be administered at baseline, during the course of study, and at the end of the study. Training to investigators and sites on suicidality assessment will be integral to the study implementation. Any AEs which, in the investigator's opinion, are possibly suicidality-related, will be recorded in the Possible Suicidality Related Adverse Event form (PSRAE); a supplemental CRF form designed to collect detailed information on the circumstances of reported AEs related to suicidality.

The ‘baseline/screening’ version of C-SSRS will be used at the pre-screening visit (V1a). The ‘since last visit’ version of C-SSRS will be used at Visits 4, 6 and 10 (6, 12 and 24 months post randomization respectively).

A trained rater will administer the C-SSRS questionnaires according to the schedule detailed in Table 1. The C-SSRS questionnaire will be completed during the clinical visit separately from the medical history and the standard adverse event questions.

### 7.4.7. Time Period and Frequency of Detecting AEs and SAEs

The investigator or site staff is responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

AEs will be collected from the start of the placebo run-in phase until the end of the two year study period.

SAEs will be collected over the same time period as stated above for AEs. However, any SAEs assessed **as related** to study participation (e.g., investigational product, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication, will be recorded from the time a subject consents to participate in the study up to the end of the two year study period. All SAEs will be reported to GSK within 24 hours, as indicated in Section 7.4.8.

After discontinuation of study treatment, the investigator will monitor all AEs/SAEs that are ongoing until resolution or stabilization of the event or until the subject is lost to follow-up. Investigators are not required to actively seek information on adverse events occurring after the follow-up contact, but may report any adverse event that they believe may be related to investigational product regardless of when the event occurs.

### 7.4.8. Prompt Reporting of Serious Adverse Events and Other Events to GSK

SAEs, partner pregnancies, and liver function abnormalities and any other events meeting pre-defined criteria will be reported promptly by the investigator to GSK as described in the following table once the investigator determines the event meets the protocol definition for that event.

| | Initial Reports | | Follow-up Information on a Previous Report | |
|---|---|---|---|---|
| **Type of Event** | **Time Frame** | **Documents** | **Time Frame** | **Documents** |
| All SAEs | 24 hours | SAE data collection tool | 24 hours | Updated SAE data collection tool |
| Partner Pregnancy | 2 Weeks | Pregnancy Notification Form | 2 Weeks | Pregnancy Follow up Form |
| ALT≥3xULN and bilirubin ≥2xULN (>35% direct) (or ALT≥3xULN and INR>1.5, if INR measured) [2] | 24 hours[1] | SAE data collection tool. | 24 hours | Updated SAE data collection tool. |

1. GSK to be notified at onset of liver chemistry elevations to discuss subject safety.
2. INR measurement is not required; if measured, the threshold value stated will not apply to subjects receiving anticoagulants.

The method of detecting, recording, evaluating and follow-up of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in the SPM. Procedures for post-study AEs/SAEs are provided in the SPM.

### 7.4.9. Regulatory reporting requirements for SAEs

Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

## 7.5. Health Outcomes

### 7.5.1. BPH-related Quality of Life

The effect of study treatment on BPH-related quality of life will be assessed using three self-administered questionnaires: the BPH-related health status (question 8 of IPSS); the BPH Impact Index (BII) and Problem Assessment Scale of the Sexual Function Index (PAS SFI). Each questionnaire is briefly described below and will measure impact of BPH symptoms, health-related quality of life and sexual function.

**a. International Prostate Symptom Score (IPSS) [Badia, 1997; Barry, 1992]**

The IPSS is a 7 item instrument (essentially the same as the American Urological Association Symptom Index, AUA-SI) designed to quantify urinary symptoms but with an additional, independent eighth question BPH on quality of life (see Appendix 5). The IPSS will be administered at Pre-screening (Visit 1a), at Baseline (Visit 2) after completion of the placebo run-in period and at every 13 week clinic visit thereafter during the study treatment period. At Pre-screening (Visit 1a), subjects with IPSS <12 points (based on the first 7 questions) should be excluded from the study

**b. BPH Impact Index (BII) [Barry, 1995]**

The BII is a 4 item instrument which assesses the overall impact of BPH on a patient's general sense of well being and measures aspects of physical discomfort, worry and bother, all of which can be affected by BPH and its symptoms (See Appendix 6).

The BII will be administered at Pre-screening (Visit 1a), at Baseline (Visit 2) after completion of the placebo run-in period and at every 13 week clinic visit thereafter during the study treatment period.

**c. Problem Assessment Scale of the Sexual Function Inventory (PAS-SFI) [O'Leary, 1995]**

Because BPH and subsequent medical treatments may potentially affect sexual functioning, a brief Sexual Function Index will be included in this trial to capture information about various aspects of patients' sexual functioning [O'Leary, 1995] (See Appendix 6). The PAS-SFI will be administered at screening (visit 1b, during (Baseline) Visit 2 after completion of the placebo run-in, then annually thereafter following randomization.

### 7.5.2. Questionnaire administration

The subject will complete self-administered questionnaires according to the schedule detailed on the Time and Events Table.

The investigator will ask the study subject to complete a questionnaire during the clinical visit separately from the medical history and the standard adverse event questions.

Questionnaires should be completed in a quiet place (preferably the same place each time, if possible), and at as consistent a time during the study visit as possible. To avoid biasing responses, subjects should not be told the results of diagnostic tests prior to completing the questionnaire. Regardless of when the questionnaire is completed, the subject should be given adequate time to complete all items. No stated or implied time limit for completing the questionnaire items will be given.

The subject should be asked to complete the questionnaires as completely and as accurately as possible. If the subject requests help or clarification of any question, he should be asked to read the instructions again and to give the best answer possible to each question. Subjects should be encouraged to report their own experiences and opinions. The investigator will not provide the subject with an answer to any question nor interpret any portion of the question.

### 7.5.3. Recording of data

The use of black ink is required for subject completed questionnaires. If any changes are necessary, subjects must be instructed to make any changes by drawing a line through the undesired response, initialling the change, and then recording the desired response. Once a subject returns the questionnaire, no change will be allowed.

#### 7.5.3.1. Collection and storage of subject questionnaires

Upon completion of the questionnaires, the investigator will retrieve the questionnaires from the subject, and check that the header section (Subject Number, Visit Date, etc) is completed. The investigator (or qualified designated member of their staff) will use the subject completed questionnaires to enter the recorded data into the appropriate section of the eCRF. The original version of the completed questionnaires will stay with the subject's source documents. A completed questionnaire should not be given back to the subject once it has been returned to the source documents

### 7.5.4. Medical resource utilisation

At Visit 2 (Baseline) and each scheduled 13 week clinic visit post-randomisation, the investigator will record details of any health care utilisation associated with an episode of acute urinary retention, BPH-related prostatic surgery and/or other minimally-invasive prostatic procedures for treatment of BPH. The following information will be collected in the eCRF as follows:

- Incidence of hospital admissions for AUR and/or surgical interventions; number and type of procedures carried out

- Length of hospital stay (in days, hours) associated with incidence of AUR and/or surgical interventions, and associated ward type

## 7.6. Pharmacogenetics

An important objective of the clinical study is PGx research. Participation in PGx is optional but all subjects who are eligible for the clinical study will be given the opportunity to participate. Subjects may decline participation without effect on their medical care or care during the clinical study. A separate consent signature is required for PGx research.

Patients who provide consent will have a blood sample taken for analysis at Visit 2. The presence/absence of genetic variations in patient genes in DNA from blood will be analysed to determine their relationship with response (safety, tolerability, and efficacy) to treatment with either the combination of dutasteride and tamsulosin or tamsulosin alone.

Information regarding pharmacogenetic research is included in Appendix 1. The IEC/IRB and, where required, the applicable regulatory agency must approve the PGx assessments before these can be conducted at the site. The approval(s) must be in writing and will clearly specify approval of the PGx assessments (i.e., approval of Appendix 1). In some cases, approval of the PGx assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the PGx assessments is being deferred and the study, except for PGx assessments, can be initiated. When PGx assessments will not be approved, then the approval for the rest of the study will clearly indicate this and therefore, PGx assessments will not be conducted.

## 7.7. Population Pharmacokinetics (Chinese Subjects Only)

A population pharmacokinetics (PPK) substudy will be performed only in subjects of Chinese origin, living in China, and participation in this substudy will be mandatory for these subjects. This substudy will estimate the PK parameters of dutasteride when dosed orally in combination (dutasteride 0.5 mg once daily and tamsulosin 0.2 mg once daily) in Chinese men with BPH. See Appendix 7 for more details on the PPK substudy.

Serum PK samples will be collected as indicated in Table 1. The actual date and time of each blood sample collection will be recorded, as well as the timing of the last dose of combination taken before the PK sample. Details of blood sample collection (including volume to be collected), processing, storage, and shipping procedures are provided in the SPM.

# 8. DATA MANAGEMENT

For this study, data will be collected using defined electronic case report forms (eCRFs), transmitted electronically to GSK and combined with data provided from other sources in a validated data system.

Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing

errors and inconsistencies in the data. Adverse events and concomitant medications terms will be coded using MedDRA and an internal validated medication dictionary, GSK Drug. Laboratory data (i.e., hematology and clinical chemistry) will be stored in a database maintained by the central laboratory and transferred to GSK at agreed times.

An appropriate medical dictionary that covers all approved drugs in the region must be referenced.

eCRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy.

In all cases, subject initials will not be collected or transmitted to GSK according to GSK policy.

# 9. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

## 9.1. Hypotheses

The primary endpoint is change from baseline IPSS. Let the following represent the mean change from baseline IPSS for each treatment group:

$H_{dut+tam}$: combination (0.5mg dutasteride and 0.2mg tamsulosin) treatment group

$H_{tam}$: 0.2mg tamsulosin treatment group

Then the primary null and alternative hypotheses to be tested at Year 2 are as follows:

| Description | Null Hypothesis | Alternative Hypothesis |
|---|---|---|
| Combination versus 0.2mg tamsulosin | $H_{dut+tam} = H_{tam}$ | $H_{dut+tam} \neq H_{tam}$ |

Two-sided tests of the null hypothesis will be conducted at the 0.05 level of significance to show superiority of the combination treatment group compared to 0.2mg tamsulosin at 2 years of treatment.

## 9.2. Study Design Considerations

### 9.2.1. Sample Size Assumptions

The sample size was calculated based on estimates of IPSS change from baseline using information obtained from the CombAT study. Sample size estimates were computed in terms of a continuous response variable assuming a normal distribution, IPSS change from baseline mean difference between treatment groups of 1.8, a standard deviation of 6, and considering 90% power. With these assumptions, the required minimum sample size is 234 subjects per arm. Therefore, since a 20% treatment phase discontinuation rate is assumed, then randomization of 293 subjects per treatment arm (586 total) is required for 90% power.

### 9.2.2. Sample Size Sensitivity

Following is a chart showing scenarios of treatment differences of IPSS change from baseline after 2 years using assumptions above and the corresponding power estimates.

| Scenario | IPSS change from baseline: difference in Combination and 0.2mg Tamsulosin | Power |
|---|---|---|
| Alternative #1 | 1.6 | 82% |
| Planned | 1.8 | 90% |
| Alternative #2 | 2.0 | 95% |

### 9.2.3. Sample Size Re-estimation

Sample size-re-estimation is not planned.

## 9.3. Data Analysis Considerations

### 9.3.1. Analysis Populations

The Intent-to-Treat (ITT) population will comprise all randomized subjects regardless of whether or not treatment was administered. This population will be based on the treatment to which the subject was randomized and will be the primary population for the analysis of efficacy and safety data. Any subject who receives a treatment randomisation number will be considered to have been randomized.

### 9.3.2. Per Protocol Populations

The Per Protocol (PP) population will comprise all ITT subjects and who comply closely with the protocol. Major protocol deviations that would exclude subjects from the PP population will be defined and documented in the Reporting and Analysis Plan (RAP) prior to unblinding. The PP population will not be analysed if this population comprises more than 80% of the ITT population.

### 9.3.3. PPK Population

The PPK population wil comprise all ITT subjects of Chinese origin, recuited in China, randomized to receive the combination (0.5mg dutasteride and 0.2mg tamsulosin) who have available PPK samples.

### 9.3.4. Analysis Data Sets

Endpoints measured at specific visits and analysed in terms of visit numbers include: IPSS, Qmax, prostate volume, PSA, post void residual volume, suicidality and health outcomes. Analysis of the data collected in terms of visit numbers will be performed using two different approaches to account for missing data.

1. LOCF (Last Observation Carried Forward) analysis: This involves bringing (carrying) forward the last non-missing post-baseline assessment for subjects with missing visit data and/or for subjects who discontinued from the study.
2. At Visit analysis: Missing values at post-baseline assessments are not replaced and are regarded as missing.

The LOCF approach will be considered primary. If the LOCF and At Visit results are not consistent with regard to the statistical analyses and conclusions, then further data analyses will be undertaken.

Endpoints measured in terms of event calendar days and analyzed in terms of survival methodology include AUR and BPH-related surgical intervention. These analyses will use the observed-cases approach in which actual date of event is used; missing values post-baseline are not replaced and are regarded as missing.

Analysis datasets will be created with a structure to reflect the above noted approaches for each endpoint.

### 9.3.5. Treatment Comparisons

#### 9.3.5.1. Primary Comparison of Interest

The primary comparison of interest at year 2 (Month 24 visit) is the combination therapy versus 0.2mg tamsulosin in terms of change from baseline IPSS. The primary population of interest will be the ITT population and the primary comparison will be made using LOCF data.

If the Month 24 IPSS change from baseline two-sided p-value is ≤0.05 and the treatment difference supports combination superiority, then conclude that combination is superior to 0.2mg tamsulosin.

If the IPSS primary efficacy endpoint is statistically significant and treatment difference supports combination superiority at Month 24, as defined above, then statistical testing and interpretation of earlier visit timepoints (Month 21, Month 18, Month 15, Month 12, Month 9, Month 6, Month 3 – in this order) will occur in a step-down manner [producing a closed test procedure] at the 0.05 level of significance. Multiplicity control for secondary endpoints will be defined in the RAP.

#### 9.3.5.2. Other Comparisons of Interest

Secondary endpoint treatment comparisons of interest are included in this section

Secondary Efficacy Endpoints:

- Prostate volume % change from baseline
- IPSS improvement of ≥2 points and ≥3 points and, separately, ≥25% improvement from baseline
- Qmax change from baseline
- Proportion of subjects with Qmax improvement of ≥3ml/sec and, separately, ≥30% improvement from baseline
- Time to event/ proportion of subjects with AUR or BPH related prostatic surgery
- Time to event/proportion of subjects with AUR
- Time to event/proportion of subjects undergoing BPH related prostatic surgery

Health Outcomes Endpoints:

- BPH Impact Index (BII) change from baseline
- BPH-related Health Status (Q8 of IPSS) change from baseline
- Problem Assessment Scale of the Sexual Function Inventory (PAS- SFI) change from baseline

### 9.3.6. Interim Analysis

No interim efficacy analyses are planned for this study.

### 9.3.7. Key Elements of Analysis Plan

Data will be listed and summarized according to the GSK reporting standards, where applicable. Complete details will be documented in the RAP. Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the RAP and final study report.

As it is anticipated that accrual will be spread thinly across centers and summaries of data by center would be unlikely to be informative, data from all participating centers will be pooled prior to analysis. Investigative centers will be pooled a priori into clusters based on geographic location; these clusters may be used in analyses to adjust for site effects. Clusters will be defined once all investigative sites have been identified and randomisation has been completed.

All data up to the time of study completion/withdrawal from study will be included in the analysis, regardless of duration of treatment.

Analyses will be performed as appropriate using the LOCF along with the At Visit approach or the observed-cases approach and which will be assigned in subsequent sections. Missing individual responses for the IPSS questionnaire will be imputed when at least four of the seven questions are answered (non-missing). Missing individual responses for the BII questionnaire will be imputed when at least two of the four questions are answered (non-missing). For the imputation, the average of the non-missing responses will be calculated and rounded to the nearest integer. This average score will be imputed for the original missing response(s). If at least 20% of the subjects have at least one imputed score for either IPSS or BII then that questionnaire's statistical analyses will be repeated based on non-imputed scores.

For purposes of data analyses, the baseline value of a particular type of assessment for a given subject will be defined as the last assessment prior to the start of randomized treatment. Change from baseline for each subject will be computed as post-baseline value minus baseline value. Endpoints will be log-transformed where this will improve the assumptions underlying the analyses. Endpoints with log-transformations performed within the analysis model include prostate volume.

Demographic and baseline characteristics will be summarized.

#### 9.3.7.1. Efficacy Analyses

**Primary Analysis**

The primary efficacy parameter after two years of study treatment is change from baseline IPSS. Symptom improvement is measured using the IPSS and evaluated using change from baseline.

Total IPSS, change from baseline IPSS, and percentage change from baseline IPSS will be summarized by treatment group using both the LOCF and At Visit approaches at each scheduled post-baseline assessment. Change in baseline IPSS will be compared at each scheduled post-baseline assessment for combination therapy versus 0.2mg tamsulosin using a general linear model with effects for treatment, cluster, and baseline IPSS at alpha=0.05.

Missing individual responses for the IPSS questionnaire will be imputed as defined in Section 9.3.7.

**Secondary Analyses**

The year 2 secondary efficacy endpoints include: Qmax; prostate volume; IPSS improvement of ≥2 points, ≥3 points and, separately, ≥25% improvement from baseline; and Qmax improvement of ≥3ml/sec and, separately, ≥30% improvement from baseline. Time to AUR or BPH-related surgical intervention is also a secondary efficacy endpoint.

The following describes the year 2 secondary efficacy endpoints and associated analyses. All treatment comparisons referenced are in terms of the combination therapy versus 0.2 mg tamsulosin.

- Prostate volume, change from baseline prostate volume, and percentage change from baseline prostate volume will be summarized by treatment group using both the LOCF and At Visit approaches at each scheduled post-baseline assessment. Percentage change from baseline prostate volume will be compared at each scheduled post-baseline assessment using the following general linear model:

  log(post-baseline prostate volume/baseline prostate volume) =

  log(baseline prostate volume) + treatment + cluster

- Symptom improvement is measured using the IPSS and also evaluated using a categorical change from baseline improvement of ≥2 points and ≥3 points and, separately, ≥25% improvement from baseline. Treatment comparisons will utilise a Mantel-Haenszel test controlling for cluster at alpha=0.05.
- Maximum urinary flow (Qmax), change from baseline Qmax, and percentage change from baseline Qmax will be summarized by treatment group using both the LOCF and At Visit approaches at each scheduled post-baseline assessment. Change from baseline Qmax will be compared at each scheduled post-baseline assessment using a general linear model with effects for treatment, cluster, and baseline Qmax.
- Qmax improvement of ≥3mL/sec and, separately, ≥30% improvement from baseline will be computed by treatment group. Treatment comparisons will utilise a Mantel-Haenszel test controlling for cluster at alpha=0.05.
- Time to first AUR or BPH-related surgical intervention will be defined as the number of days from date of first dose of randomized study drug to date of the first event (earliest occurring of either AUR or BPH-related surgery) for each subject. Censoring will occur at the earliest of the following dates as applicable: the date of prostatectomy, the date of last contact for AUR and surgical intervention assessment,

and the date of death. As an additional summary the number of subjects having the first AUR or BPH-related surgery event on or after first dose of study drug will be tabulated by treatment and by annual time period along with the number of subjects at risk during each of these time periods. Treatments will be compared in terms of time to first AUR or BPH-related surgery for the ITT population using a log rank test at the 0.05 level of significance.

**Summary of Other Efficacy Measures**

Urinary tract infection/urosepsis, urinary incontinence, and renal insufficiency are captured as potential BPH disease related events; reference Section 7.2.1.2. Frequencies of each event will be presented by treatment group; no formal treatment comparisons are planned.

### 9.3.7.2. Safety Analyses

The Intent-to-Treat population will be used for the analysis of safety data. Complete details of the safety analyses will be provided in the RAP.

**Extent of Exposure**

Study drug exposure in days will be calculated for each subject as treatment stop date minus treatment start date plus one and will be summarized by treatment group. Study drug compliance between visits and cumulative study drug compliance will be calculated by dividing the number of study drug capsules used by the total number of study drug capsules prescribed and multiplying the result by 100. Study drug compliance between visits and cumulative study drug compliance will be summarized by treatment group.

**Adverse Events**

Adverse events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA). The frequency of events, the frequency of subjects and the percentage of subjects reporting each adverse event will be summarized by treatment group for all AEs and separately for drug-related AEs. The proportion of subjects reporting at least one AE, at least one drug-related AE, at least one serious AE, and at least one AE leading to withdrawal will be computed for each treatment group. Comparisons of treatment groups for each of these sets of AEs will be performed using Fisher's exact test.

Special interest adverse events will be defined in the RAP.

The incidence of deaths and the primary cause of death will be summarized.

**Clinical Laboratory Evaluations**

For purposes of statistical analyses, the final value of the laboratory test prior to the start of the randomized treatment will be used as the baseline value. Only those laboratory tests with a numeric normal range and at least one post baseline value will be analysed statistically.

A laboratory value that is on or within the normal range is considered normal. A laboratory value that is outside the testing laboratory's normal range is considered an abnormal laboratory value. A laboratory value that is above the upper limit of the normal range is considered high abnormal. A laboratory value that is below the lower limit of the normal range is considered low abnormal.

To describe the laboratory values at baseline, the frequency of subjects with an abnormal laboratory value at baseline among subjects with a baseline laboratory value and a post baseline laboratory value will be computed by treatment group. Among subjects with a normal value at baseline, the frequency of abnormal values, high abnormal values, and low abnormal values at any post baseline laboratory will be computed by treatment group. Among subjects with a normal or low abnormal value at baseline, the frequency of high abnormal values at any post baseline will be computed by treatment group. Among subjects with a normal or high abnormal value at baseline, the frequency of low abnormal values at any post baseline laboratory will be computed by treatment group.

The threshold laboratory values are defined in terms of a multiplicative factor of the testing laboratory's normal range. A laboratory value that is above the upper limit factor multiplied by the upper limit of the normal range is considered a high threshold value. A laboratory value that is below the lower limit factor multiplied by the lower limit of the normal range is considered a low threshold value.

To describe the laboratory values at baseline, the frequency of subjects with a threshold laboratory value at baseline among subjects with a baseline laboratory value and a post baseline laboratory value will be computed by treatment group. Among subjects whose baseline value was not classified as threshold, the frequency of subjects with threshold values at any post baseline laboratory will be computed by treatment group. Among subjects whose baseline value was not high threshold, the frequency of subjects with high threshold values at any post baseline laboratory will be computed by treatment group. Among subjects whose baseline value was not low threshold, the frequency of subjects with low threshold values at any post baseline laboratory will be computed by treatment group.

Differences in laboratory values between baseline and the final scheduled laboratory assessment will be calculated for each laboratory test and summarized by treatment group.

#### *9.3.7.2.1. Other Safety Measures*

**Serum PSA**

Total PSA, change from baseline total PSA, and percentage change from baseline total PSA will be summarized by treatment group using both the LOCF and At Visit approaches at each scheduled post-baseline assessment.

Change from baseline total PSA will be compared at each scheduled post-baseline assessment using a general linear model with effects for treatment and baseline total PSA. Statistical analysis of the change from baseline total PSA comparing the treatment groups will begin using data from the final scheduled assessment. Abnormalities at any assessment will be listed by treatment and subject.

**Post Void Residual Volume**

Post void residual volume, change from baseline post void residual volume, and percentage change from baseline post void residual volume will be summarized using both LOCF and At Visit approaches at each scheduled post-baseline assessment. Treatment groups will be compared in terms of the change from baseline distribution at each post baseline visit using a nonparametric van Elteren test controlling for cluster.

**Qualitative Breast Examination**

The percentage of subjects with any abnormal change in the qualitative breast examination will be summarized. The incidence of abnormal changes in these evaluations will be compared between treatment using Fisher's exact test.

**Blood Pressure, Pulse and DRE**

The percentage of subjects exceeding the threshold criteria for blood pressure and pulse at any post-baseline assessment will be summarized by treatment group. The percentage of subjects with any abnormal change in the DRE evaluations will be summarized. The incidence of abnormal changes in these evaluations will be compared across treatment groups using Fisher's exact test.

**Suicidality**

To protect subjects in the study, scores from C-SSRS tests will be reviewed in real time by the investigator and appropriate advice given to participants.

The C-SSRS scale has 10 outcomes, with binary (yes/no) responses. At the end of study, results will be assessed as follows:

- Suicidal ideation will be defined as a positive response at any time during treatment to any one of the five suicidal ideation questions (Categories 1-5) on the C-SSRS.
- Suicidal behavior will be defined as a positive response at any time during treatment to any one of the five suicidal behaviour questions (Categories 6-10) on the C-SSRS.
- Suicidal ideation or behavior will be defined as a positive response at any time during treatment to any one of the ten suicidal ideation and behaviour questions (Categories 1-10) on the C-SSRS.

The numbers of subjects with a positive response for suicidal ideation or suicidal behaviour will be reported at baseline and during study treatment at Visits 4, 6 and 10 (6, 12 and 24 months post randomization respectively). Scores on treatment will be compared with baseline scores and, for Visits 6 and 10, with scores at last visit to determine the incidence of treatment-emergent suicidality. An increase in C-SSRS total score to 4 or 5 will be considered as serious treatment-emergent suicidality. Due to the low numbers of subjects expected to exhibit suicidal behaviours, formal statistical testing will not be performed.

#### 9.3.7.3. Health Outcomes Analyses

BPH-related quality of life (QOL) will be assessed using BPH-related Health Status, question 8 of IPSS (BHS), BPH Impact Index (BII) and sexual function with the Problem Assessment Scale of the Sexual Function Inventory (PAS SFI).

**BPH-related Health Status**

The BPH-related Health Status (BHS) score is collected on the IPSS questionnaire (Q8 of IPSS) and ranges from 0 to 6. Total BHS, change from baseline BHS, and percentage change from baseline BHS will be summarized by treatment group using both the LOCF and At Visit approaches at each scheduled post-baseline assessment. Change in baseline BHS will be compared at each scheduled post-baseline assessment using a general linear model with effects for treatment, cluster, and baseline BHS.

**BPH Impact Index**

The BPH Impact Index (BII) is the sum of four questions with a total score range of 0 to 13. Individual questionnaire missing responses will be imputed, if applicable, as defined in Section 9.3.7. Total BII, change from baseline BII, and percentage change from baseline BII will be summarized by treatment group using both the LOCF and At Visit approaches at each scheduled post-baseline assessment. Change in baseline BII will be compared at each scheduled post-baseline assessment using a general linear model with effects for treatment, cluster, and baseline BII.

**Problem Assessment Scale of the Sexual Function Inventory**

The Problem Assessment Scale of the Sexual Function Inventory (PAS SFI) is the sum of three questions each ranging from 0 to 4. Total score, change from baseline score, and percentage change from baseline will be summarized by treatment group using both the LOCF and At Visit approaches. Change in baseline score will be compared at each scheduled post-baseline assessment using a general linear model with effects for treatment, cluster, and baseline score.

### 9.3.8. Medical Resource Utilisation

Summary statistics will be tabulated for the following:

- Incidence of hospital admissions for AUR and/or BPH-related surgical interventions; number and type of procedures carried out
- Length of hospital stay (in days, hours) associated with incidence of AUR and/or BPH-related surgical interventions and associated ward type

### 9.3.9. Pharmacogenetic Analyses

Further details on PGx analyses will be addressed in Appendix 1 and the RAP.

### 9.3.10. Population Pharmacokinetic Analyses

Details on PPK analyses will be addressed in Appendix 7 and the RAP.

# 10. STUDY CONDUCT CONSIDERATIONS

## 10.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of subjects begins.

## 10.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, GSK will obtain approval from the appropriate regulatory agency to conduct the study in accordance with applicable country-specific regulatory requirements.

The study will be conducted in accordance with Good Clinical Practice (GCP), all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008, including, but not limited to:

- Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review and approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements.

GSK will provide full details of the above procedures, either verbally, in writing, or both.

Written informed consent must be obtained from each subject prior to participation in the study. The contents and process of obtaining consent will be in accordance with all applicable regulatory requirements.

## 10.3. Quality Control (Study Monitoring)

In accordance with applicable regulations, GCP, and GSK procedures, the site will be contacted prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the eCRF will serve as the source document.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents and to allocate their time and the time to their staff to monitor to discuss findings and any issues.

Monitoring visits will be conducted in a manner to ensure that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

## 10.4. Quality Assurance

To ensure compliance with ICH GCP and all applicable regulatory requirements, GSK may conduct quality assurance audits of the site. Regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an audit or inspection, the investigator (and institution) must agree to grant the auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss any findings/relevant issues.

## 10.5. Study and Site Closure

The end of study is defined as last subject, last visit.

Upon completion or termination of the study, the monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, ICH GCP, and GSK Standard Operating Procedures.

GSK reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe noncompliance. If GSK determines that such action is required, GSK will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, GSK will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for **safety reasons**, GSK will promptly inform all investigators, heads of the medical institutions (where applicable),and/or institutions conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

## 10.6. Records Retention

Following closure of the study, the investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The

investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

GSK will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK standard operating procedures, and/or institutional requirements.

The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

## 10.7. Provision of Study Results to Investigators, Posting to the Clinical Trials Register and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

The results summary will be posted to the Clinical Study Register no later than 12 months after the last subject's last visit (LSLV) or sooner if required by legal agreement, local law or regulation. In addition, a manuscript will be submitted to a peer-reviewed journal for publication within 18 months of LSLV. When manuscript publication in a peer-reviewed journal is not feasible, further study information will be posted to the GSK Clinical Study Register to supplement the results summary.

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# 12. APPENDICES

## 12.1. Appendix 1: PGx

### Pharmacogenetic Research

#### Pharmacogenetics – Background

Pharmacogenetics (PGx) is the study of variability in drug response due to hereditary factors in different populations. There is increasing evidence that an individual's genetic composition (i.e., genotype) may impact the pharmacokinetics (absorption, distribution, metabolism, elimination), pharmacodynamics (relationship between concentrations and pharmacologic effects or the time course of pharmacologic effects) and/or clinical outcome (in terms of efficacy and/or safety and tolerability). Some reported examples of PGx analysis include:

| Drug | Disease | Gene | Outcome |
|---|---|---|---|
| Abacavir | HIV [Hetherington, 2002; Mallal, 2002] | HLA-B*5701 | Individuals with HLA-B*5701 variant may be at increased risk for experiencing hypersensitivity to abacavir. Clinical assays are available for HLA-B*5701 but none has been validated. HLA-B*5701 screening would supplement but never replace abacavir clinical risk management strategies aimed at minimising rare but serious outcomes associated with abacavir hypersensitivity. |
| Warfarin | Cardiovascular [Neergard, 2006; Wilke, 2005] | CYP2C9 | Serious Adverse Events (SAEs) experienced by some patients on warfarin may be explained by variations in the CYP2C9 gene that influences the degree of anticoagulation achieved. |
| Irinotecan | Cancer [FDA News Release, 2005] | UGT1A1 | Variations in the UGT1A1 gene can influence a patient's ability to break down irinotecan, which can lead to increased blood levels of the drug and a higher risk of side effects. A dose of irinotecan that is safe for one patient with a particular UGT1A1 gene variation, might be too high for another patient without this variation, raising the risk of certain side-effects. A genetic blood test (Invader UGT1A1 molecular assay) is available that can detect variations in the gene. |

A key component to successful PGx research is the collection of samples during the conduct of clinical studies.

"Collection of whole blood samples, even when no *a priori* hypothesis has been identified, may enable PGx analysis to be conducted if at any time it appears that there is a potential unexpected or unexplained variation in handling or response to the combination treatment of dutasteride and tamsulosin or tamsulosin monotherapy.

## Pharmacogenetic Research Objectives

The objective of the PGx research (if there is a potential unexpected or unexplained variation) is to investigate a possible genetic relationship to handling or response to the combination treatment of dutasteride and tamsulosin or tamsulosin monotherapy. If at any time it appears there is potential variability in response in this clinical study or in a series of clinical studies with the combination treatment of dutasteride and tamsulosin or tamsulosin monotherapy that may be attributable to genetic variations of subjects, the following objectives may be investigated:

- Relationship between genetic variants and safety and/or tolerability of study treatment
- Relationship between genetic variants and efficacy of study treatment]

## Study Population

Any subject who has given informed consent to participate in the clinical study, has met all the entry criteria for the clinical study, and receives study treatment may take part in the PGx research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the PGx research.

Subject participation in the PGx research is voluntary and refusal to participate will not indicate withdrawal from the clinical study. Refusal to participate will involve no penalty or loss of benefits to which the subject would otherwise be entitled.

## Study Assessments and Procedures

A whole blood sample (~6mL) will be collected for the PGx research using a tube containing EDTA. It is recommended that the blood sample be taken at Baseline (the first opportunity after a subject has been randomized and provided informed consent for PGx research), but may be taken at any time while the subject is participating in the clinical study. For the purposes of this trial, the PGx sample will be collected at Visit 2 (Baseline). However if the investigators deems it appropriate, the PGx sample may be taken at a later visit.

The PGx sample is labelled (or “coded”) with a study specific number that can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number). The blood sample is taken on a single occasion unless a duplicate sample is required due to inability to utilize the original sample.

The DNA extracted from the blood sample may be subjected to sample quality control analysis. This analysis will involve the genotyping of several genetic markers to confirm

the integrity of individual samples. If inconsistencies are noted in the analysis, then those samples may be destroyed.

The need to conduct PGx analysis may be identified after a study (or set of studies) of dutasteride or tamsulosin treatment or studies on prostate-related disease has been completed and the study data reviewed. In some cases, the samples may not be studied. e.g., no questions are raised about how people respond to dutasteride or tamsulosin.

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will use samples collected from the study for the purpose stated in this protocol and in the informed consent form.

Subjects can request their sample to be destroyed at any time.

### Subject Withdrawal from Study

If a subject who has consented to participate in PGx research and has a sample taken for PGx research withdraws from the clinical study for any reason other than lost to follow-up, the subject will be given the following options:

- The sample is retained for PGx research.
- Any PGx sample is destroyed.

If a subject withdraws consent from the PGx research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records. In either case, GSK will only keep study information collected/generated up to that point.

### Screen and Baseline Failures

If a blood sample for PGx research has been collected and it is determined that the subject does not meet the entry criteria for participation in the clinical study, then the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

### Pharmacogenetics Analyses

1. Specific sections of DNA may be selected from areas of the genome (e.g., candidate genes) known to encode the drug target, drug metabolizing enzymes, areas associated with mechanisms underlying response or adverse events, and those linked to study disease and, thus, linked to drug response. In addition, continuing research may identify other enzymes, transporters, proteins or receptors that may be involved in response to dutasteride and tamsulosin or tamsulosin monotherapy. The genes that may code for these proteins may also be studied..

2. DNA Sequence analysis may be performed to determine genetic associations and interactions with treatment response

The results of PGx investigations will be reported either as part of the main clinical study report or as a separate report. All endpoints of interest from all comparisons will be descriptively and/or graphically summarized as appropriate to the data. In all cases, appropriate statistical methods will be used to analyze the genetic markers in the context of other clinical data. Statistical methods may include, but are not limited to Hardy-Weinberg Equilibrium testing, Comparison of Demographic and Baseline Characteristics by Genotype, Evaluation of Genotypic Effects, Evaluation of Treatment by Genotype and Gene-Gene Interaction, Linkage Disequilibrium, Multiple Comparison and Multiplicity and/or Power and Sample Size Considerations. Detailed description of the analyses to be conducted will be documented in the Pharmacogenetics Reporting and Analysis Plan.

## Informed Consent

Subjects who do not wish to participate in the PGx research may still participate in the clinical study. PGx informed consent must be obtained prior to any blood being taken for PGx research.

## Provision of Study Results and Confidentiality of Subject's PGx Data

GSK may summarize the cumulative PGx research results in the clinical study report.

In general, GSK does not inform the investigator, subject or anyone else (e.g., family members, study investigators, primary care physicians, insurers, or employers) of the PGx research results unless required by law. The information generated from PGx research is preliminary in nature, and the significance and scientific validity of the results are undetermined at such an early stage of research.

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## 12.2. Appendix 2: Study Assessment Schedule In Order of Performance

***ALL SUBJECTS MUST SIGN AN INFORMED CONSENT PRIOR TO ANY STUDY MEASUREMENTS/PROCEDURES.***

**Visit 1 (Pre-Screening Visit 1a and Screening Visit 1b)**

During Screening (Visits 1a and 1b) the procedures listed below will be completed **in the following sequential order when possible.** It is important that the IPSS questionnaire be administered first.

**Visit 1a (Pre-screening)**

1. Obtain informed consent from subject
2. Administer patient self-assessment questionnaires: International Prostate Symptom Score [IPSS], BHS Q8 BPH Impact Index [BII]
3. Administer suicidality questionnaire [C-SSRS]
4. Complete medical history, Cardiovascular history and demographics
5. Review concomitant medications
6. Measure peak urinary flow
7. Measure post void residual volume
8. Review inclusion/exclusion criteria for patient eligibility
9. Call RAMOS to register subject and obtain unique registration number
10. Collect blood samples for clinical laboratory tests including PSA
11. Schedule next clinic visit to complete screening procedures

**Visit 1b (Placebo run-in)**

Visit 1b should be conducted a maximum of 14 days after V1a (allowing sufficient time for lab results from V1a to be returned to site).

1. Review pre-screening PSA/laboratory results
2. Administer Problem Assessment Scale of the Sexual Function Index (PAS-SFI)
3. Perform physical examination, including digital rectal exam, qualitative breast examination, height, weight, and vital signs blood pressure and pulse after 5 mins sitting
4. Obtain a 12-lead electrocardiogram (after 5 mins supine)
5. Assess SAEs
6. Measure peak urinary flow (if required)
7. Measure post void residual volume (if required)

8. Measure prostate volume by transrectal ultrasound (TRUS) if suitable TRUS not available
9. Review inclusion/exclusion criteria, including concomitant medications, and confirm patient eligibility
10. Call RAMOS
11. Dispense placebo run-in medication and provide dosing instructions
12. Schedule next clinic visit

**Visit 2 (Baseline/Randomisation)**

Visit 2 should be conducted 28 days (± 4 days) after Visit 1b. For each subject, all visits should be scheduled at a similar time of day: morning or afternoon. During Visit 2 the procedures listed below will be completed **in the following sequential order:**

1. Administer patient self-assessment questionnaires: International Prostate Symptom Score [IPSS], BHS Q8,BPH Impact Index [BII], Problem Assessment Scale of the Sexual Function Index (PAS-SFI)
2. Review concomitant medication and assess continuing eligibility
3. Record any episodes of AUR or prostatic surgical and minimally-invasive/non-surgical interventions along with associated resource utilization.
4. Record any episodes of UTI/urosepsis, urinary incontinence (first episode or consistent worsening), and renal insufficiency
5. Collect blood samples for PGx and HBsAG and Hepatitis C Antibody
6. Measure vital signs: blood pressure and pulse after 5 mins sitting
7. Assess AEs
8. Measure peak urinary flow
9. Measure post void residual volume
10. Call RAMOS to randomize subject
11. Collect unused placebo run-in medication and assess compliance
12. Dispense a 3-month supply (of blinded study medication and provide dosing instructions
13. Schedule next clinic visit

**Visit 3 (3 months post-randomisation)**

Visit 3 will be conducted 13 weeks (± 14 days) after Visit 2. For each subject, all visits should be scheduled at a similar time of day: morning or afternoon. The following study procedures will be conducted:

1. Administer patient self-assessment questionnaires: International Prostate Symptom Score [IPSS], BHS Q8, BPH Impact Index [BII],

2. Review concomitant medication and assess continuing eligibility
3. Measure vital signs after 5 mins sitting
4. Chinese origin subjects, recuited in China only: Blood sample for PPK
5. Assess AEs
6. Record any episodes of AUR or prostatic surgical and minimally-invasive/non-surgical interventions along with associated resource utilization.
7. Record any episodes of UTI/urosepsis, urinary incontinence (first episode or consistent worsening), and renal insufficiency
8. Collect unused study medication and assess compliance
9. Call RAMOS and Dispense a 3-month supply of study medication
10. Schedule next clinic visit

**Visit 4 (6 months post-randomisation)**

Visit 4 will be conducted 26 weeks (± 14 days) after Visit 2. For each subject, all visits should be scheduled at a similar time of day: morning or afternoon. The following study procedures will be conducted:

1. Administer patient self-assessment questionnaires: International Prostate Symptom Score [IPSS], BHS Q8, BPH Impact Index [BII]
2. Administer suicidality questionnaire [C-SSRS]
3. Review concomitant medication and assess continuing eligibility
4. Perform physical examination, including digital rectal exam, qualitative breast examination and vital signs blood pressure and pulse after 5 mins sitting
5. Collect blood sample for PSA
6. Chinese origin subjects, recuited in China only: Blood sample for PPK
7. Assess AEs
8. Record any episodes of AUR or prostatic surgical and minimally-invasive/non-surgical interventions along with associated resource utilization.
9. Record any episodes of UTI/urosepsis, urinary incontinence (first episode or consistent worsening), and renal insufficiency
10. Measure peak urinary flow
11. Measure post void residual volume
12. Collect unused study medication and assess compliance
13. Call RAMOS and Dispense a 3-month supply of blinded study medication
14. Schedule next clinic visit

**Visit 5 (9 months post-randomisation)**

Visit 5 will be conducted 39 weeks (± 14 days) after Visit 2. For each subject, all visits should be scheduled at a similar time of day: morning or afternoon. The following study procedures will be conducted:

1. Administer patient self-assessment questionnaires: International Prostate Symptom Score [IPSS], BHS,Q8, BPH Impact Index [BII],
2. Review concomitant medication and assess continuing eligibility
3. Measure vital signs after 5 mins sitting
4. Chinese origin subjects, recuited in China only: Blood sample for PPK
5. Assess AEs
6. Record any episodes of AUR or prostatic surgical and minimally-invasive/non-surgical interventions along with associated resource utilization
7. Record any episodes of UTI/urosepsis, urinary incontinence (first episode or consistent worsening), and renal insufficiency
8. Collect unused study medication and assess compliance
9. Call RAMOS and Dispense a 3-month supply of study medication.
10. Schedule next clinic visit

**Visit 6 (12 months post-randomisation)**

Visit 6 will be conducted 52 weeks (± 14 days) after Visit 2. For each subject, all visits should be scheduled at a similar time of day: morning or afternoon. The following study procedures will be conducted:

1. Administer patient self-assessment questionnaires: International Prostate Symptom Score [IPSS], BHS Q8, BPH Impact Index [BII], Problem Assessment Scale of the Sexual Function Index [PAS-SFI]
2. Administer suicidality questionnaire [C-SSRS]
3. Collect blood samples for clinical laboratory tests including PSA
4. Review concomitant medication and assess continuing eligibility
5. Perform physical examination, including digital rectal exam, qualitative breast examination and vital signs blood pressures and pulse after 5 mins sitting
6. Assess AEs
7. Record any episodes of AUR or prostatic surgical and minimally-invasive/non-surgical interventions along with associated resource utilization
8. Record any episodes of UTI/urosepsis, urinary incontinence (first episode or consistent worsening), and renal insufficiency.
9. Measure peak urinary flow

10. Measure post void residual volume
11. Measure prostate volume by transrectal ultrasound (TRUS)
12. Collect unused study medication and assess compliance
13. Call RAMOS and Dispense a 3-month supply of blinded study medication
14. Schedule next clinic visit

**Visits 7, 8, 9, (15, 18, and 21 months post-randomisation)**

Visits 7 to 9 in Year 2 will be conducted at successive 13 week intervals (± 14 days) thereafter. For each subject, all visits should be scheduled at a similar time of day: morning or afternoon. The study procedures at Visits 7, 8, and 9 will be the same as those performed at Visit 5 except the following:

- Physical Examination is scheduled to be performed at Month 18 (Visit 8).
- Post-void residual volume (PVR) and Peak Urine Flow (Qmax) are scheduled to be performed at Month 18 (Visit 8)

**Visit 10 (24 months post-randomisation)**

Visit 10 will be conducted 104 weeks (± 14 days) after Visit 2. For each subject, all visits should be scheduled at a similar time of day: morning or afternoon. The following study procedures will be conducted:

1. Administer patient self-assessment questionnaires (International Prostate Symptom Score [IPSS], BHS Q8, BPH Impact Index [BII], Problem Assessment Scale of the Sexual Function Index (PAS-SFI)
2. Adminster suicidality questionnaire [C-SSRS]
3. Collect blood samples for clinical laboratory tests including PSA
4. Review concomitant medication and assess continuing eligibility
5. Perform physical examination, including digital rectal exam, qualitative breast examination and vital signs (after 5 mins sitting)
6. Assess AEs
7. Record any episodes of AUR or prostatic surgical and minimally-invasive/non-surgical interventions along with associated resource utilization
8. Record any episodes of UTI/urosepsis, urinary incontinence (first episode or consistent worsening), and renal insufficiency.
9. Measure peak urinary flow
10. Measure post void residual volume
11. Measure prostate volume by transrectal ultrasound (TRUS)
12. Collect unused study medication and assess compliance
13. Call RAMOS to register the subject's end of treatment visit

**End of Study Treatment Assessment Visit**

If a subject discontinues study treatment permanently after Visit 2 (post-randomisation) and between the scheduled visits, the investigator should make every effort to schedule a visit by the subject to the study site and complete the following assessments if possible:

- Concomitant medications
- Adverse events
- Physical exam including vital signs, DRE and qualitative breast examination
- Obtain blood samples for hematology, clinical chemistry and PSA determinations
- Administer health outcome questionnaires (IPSS, BHS,BII and PAS-SFI)
- Administer suicidality questionnaires [C-SSRS]
- Record any episodes of AUR, and, BPH-related prostatic surgery or minimally-invasive/non-surgical interventions
- Record any episodes of UTI/urosepsis, urinary incontinence (first episode or consistent worsening), and renal insufficiency
- Retrieve any unused double-blind study medication, assess compliance and record date of last dose of study medication
- Discuss the biannual follow-up phone call schedule
- Complete subject eCRF

If the decision for a subject's study treatment discontinuation is made dung a regularly scheduled visit, the procedures that are stated above should be completed, in addition to any scheduled procedure (e.g. Prostate Volume, Qmax) that is not listed above.

## 12.3. Appendix 3: Country Specific Requirements

There are no country specific requirements.

## 12.4. Appendix 4: Prostatic Surgical and Minimally-invasive/Non surgical Interventions for BPH

The following is a glossary of prostatic surgical and minimally-invasive/non-surgical interventions, including but not limited to:

Adenomectomy

Ballon dilatation

Electroresection

Thermotherapy (microwave or radiofrequency)

Laser resection

Prostatectomy (open, partial, retropubic with or without nerve sparing, suprapubic, transvesical, perineal, salvage, laparoscopic, laparoscopic assisted)

Prostatotomy

Transurethral resection of the prostate (TURP)

Transurethral drainage of prostatic abscess

Drainage of prostatic cysts

Radioactive seeding of the prostate (brachytherapy)

Prostatic urethral stenting

Incision of periuretheral stricture

Ethanol injections into the prostate

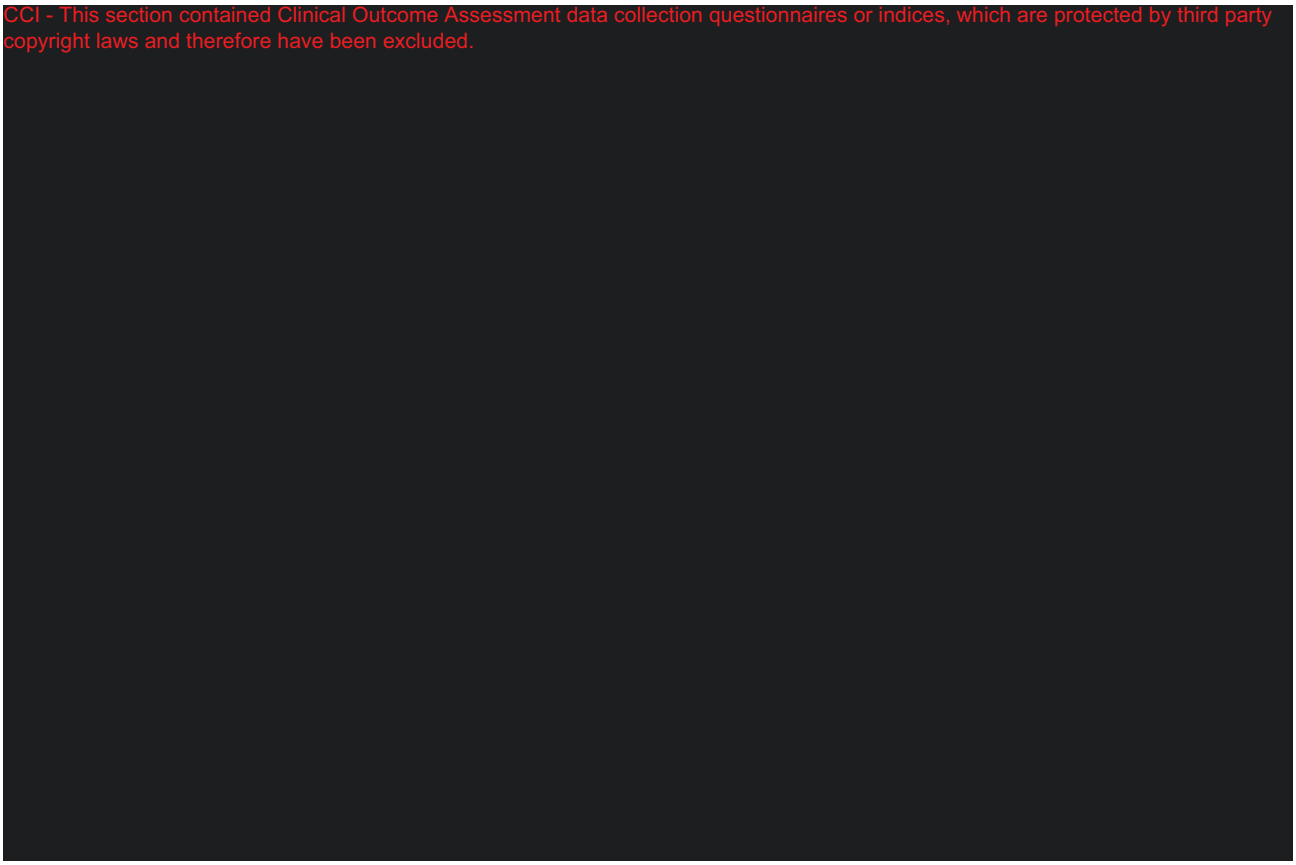
Transrectal high intensity focussed ultrasound (HIFU)

Transurethral needle ablation (TUNA)

Transurethral microwave thermotherapy (TUMT)

## 12.5. Appendix 5: IPSS Questionnaire

### International Prostate Symptom Score (IPSS)



## 12.6. Appendix 6: Health Outcomes / QoL Questionnaires

BPH-Related Health Status, IPSS Q 8

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

**BPH IMPACT INDEX (BII)**

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

A BRIEF SEXUAL FUNCTION INVENTORY

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

## 12.7. Appendix 7: Population Pharmacokinetic Substudy (Chinese Subjects Only)

Population PK (PPK) is the study of the sources and correlates of variability in drug concentrations among individuals who are the target patient population receiving clinically relevant doses of a drug of interest [Aarons, 1991]. Certain patient demographical, physiological, and therapeutic features, such as body weight, excretory and metabolic functions, and the presence of other therapies, may alter dose concentration relationships. PPK studies seek to identify the measurable physiologic factors that cause changes in the dose-concentration relationship and the extent of these changes so that, if such changes are associated with clinically significant shifts in the therapeutic index, dose can be appropriately modified.

The pharmacokinetics of dutasteride and tamsulosin in Western subjects is well-understood (CIB). In contrast, pharmacokinetic data of these two drugs in Chinese subjects are limited. Following a request to provide this information from the Regulatory Authority in China, subjects of Chinese origin living in China will participate in a PPK sub-study in this study,which aims to characterize the PK of dutasteride when dosed in combination with tamsulosin to Chinese men with BPHSerum PK sampling

Serum PK samples will be obtained on Visits 3, 4, and 5 (Table 1). Subjects must contribute to PK sampling to be considered evaluable. It is planned to use these data to develop population PK models in the target patient population and account for both inter-individual and inter-occasion variability in dutasteride PK. These data will also be used to assess the influence of covariates (e.g., age, gender, weight) on the population PK parameters of dutasteride and their associated variability.

### Processing, storage and shipping procedures are provided in the SPM

#### Sample Analysis

Only samples from those subjects who received the combination (dutasteride 0.5 mg once daily and tamsulosin 0.2 mg once daily) will be analysed. Serum analysis will be performed under the control of PTS-DMPK/Scinovo, GlaxoSmithKline, the details of which will be included in the SPM. Concentrations of GI198745 (dutasteride) will be determined in serum samples using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SPM).

#### Population Pharmacokinetic Analyses

Population pharmacokinetic models will be developed with the use of the nonlinear mixed effects modeling program (NONMEM) to characterize the pharmacokinetics of dutasteride following daily dosing in combination (dutasteride 0.5 mg once daily and tamsulosin 0.2 mg once daily).

Due to the sparseness of the PK samples, a Bayesian approach may be used. Namely, the two-compartment model with first-order absorption and parallel linear and non-linear elimination pathway published by [Gisleskog, 1999] may be used *a priori*. Data from the study will be used for generating a posterior model. The influence of covariates (e.g., age, gender, weight) on the population PK parameters of dutasteride and their associated variability may be evaluated.

Analysis of the pharmacokinetics data is the responsibility of Clinical Pharmacology Modeling and Simulation (CPMS), GSK. Further details of pharmacokinetic analyses will be described in RAP; results of the analyses may be included in a report separate from the clinical study report.

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Gisleskog PO, Hermann D, Hammarlund-Udenaes M, Karlsson MO. The pharmacokinetic modelling of GI198745 (dutasteride), a compound with parallel linear and nonlinear elimination. *Br J Clin Pharmacol.* 1999 Jan;47(1):53-8.

## 12.8. Appendix 8: Protocol Amendment Changes

### Protocol Amendment 1 main changes are listed below:

- Change in the storage conditions for the study drug
- Clarification on the collection of partner pregnancy information,
- Correction to the treatment assignment language
- Clarification on the collection of the questionnaires and their sequence
- Deleted references to Pharmacokinetics
- Updates and clarifications to the PGx language
- Updates and clarifications to AE and SAE definition
- Clarification on study treatment discontinuation and study discontinuation
- Clarification of the language on protocol waivers
- Clarification on the wording regarding the number of subjects for enrolment
- Removal of detailed information on the investigation product bottle fill counts and details on packaging and labeling as updated details will be in the Study Procedures Manual.
- Correction to T & E table, spelling errors and re-wording to provide clarification
- Addition of total serum PSA at visit 4 (6 months) as per the updated global data sheet
- Addition of three supplementary efficacy measures,
- Addition of vital sign measures at Visit 3 and Visit 5
- The addition of the follow-up of sexually related AEs when a subject discontinues study treatment.
- Addition of a SMS text messaging system to aid retention and follow-up
- Addition of text to allow unscheduled visits when medically necessary

This amendment includes re-wording and clarifications as listed:

**Section:** Title Page

**Action:** List of Authors updated

**Rationale:** New team members added/replaced

**Original Text:** Author(s): PPD

**Updated Text: Author:** PPD

**Section:** Sponsor information

**Action:** Sponsor medical monitor contact name and details updated

**Rationale:** An additional medical monitor has been assigned to the study and contact details added

**Original Text:** Sponsor Medical Monitor Contact Information: PPD M.D.

**Updated Text:**

Primary:

PPD MD

2301 Renaissance Blvd,

RN0410 King of Prussia,

Pennsylvania PA 19406 . US

Office: PPD ; Cell: PPD

Secondary:

PPD M.D.

2301 Renaissance Blvd,

RN0410 King of Prussia,

Pennsylvania PA 19406 . US

Office: PPD ; Cell: PPD

**Section:** Protocol Summary

**Action:** Clarification changes listed are from baseline

**Rationale:** Clarification that the health outcome measure will be the change from baseline in the BPH impact Index and Problem Assessment Scale of the Sexual Function Inventory

**Original Text:**

- Health Outcome Measures:
  - change from baseline in BPH-related Health Status (Q8 of IPSS),

- change in BPH Impact Index (BII), and
- change in Problem Assessment Scale of the Sexual Function Inventory (PAS-SFI).

**Updated Text:**

- Health Outcome Measures:
  - Change from baseline in BPH-related Health Status (Q8 of IPSS),
  - Change from baseline in BPH Impact Index (BII), and
  - Change from baseline in Problem Assessment Scale of the Sexual Function Inventory (PAS-SFI).

**Section:** Protocol Summary

**Action:** Include PSA at Visit 4 (6 months)

**Rationale:** As per the updated Global Data Sheet

**Original Text:** Peak urinary flow (Qmax), and post void residual volume (PVR) will be measured at baseline and every 26 weeks thereafter, a physical examination with a qualitative breast examination at baseline and every 26 weeks thereafter, measures of the total PSA at baseline and every 52 weeks thereafter.

**Updated Text:** Peak urinary flow (Qmax), and post void residual volume (PVR) will be measured at baseline and every 26 weeks thereafter, a physical examination with a qualitative breast examination at baseline and every 26 weeks thereafter, measures of the total PSA at baseline, 6 months and every 52 weeks thereafter.

**Section 1.1**: Background

**Action:** References updated

**Rationale:** References have been updated to reflect the most up to date reference/guidance.

**Original Text:** The potentially progressive nature of the disease has been associated with an increased risk of acute urinary retention (AUR) and the need for surgery [McConnell, 1998]

The aim of BPH therapy is to improve symptoms and quality of life of patients, and to prevent or reduce the risk of BPH-related complications such as urinary retention or upper urinary tract dilatation [AUA Practice Guidelines Committee, 2003; Madersbacher, 2004].

**Updated Text:** The potentially progressive nature of the disease has been associated with an increased risk of acute urinary retention (AUR) and the need for surgery [Oelke, 2011].

The aim of BPH therapy is to improve symptoms and quality of life of patients, and to prevent or reduce the risk of BPH-related complications such as urinary retention or upper urinary tract dilatation [AUA, 2010 Practice Guidelines Committee; Oelke, 2011].

**Section1.1:** Background

**Action:** Additional Text added

**Rationale:** To provide additional relevant information

**Added Text:** In addition, at 4 years, dutasteride and tamsulosin in combination significantly reduced the risk of AUR and BPH related surgery compared to tamsulosin monotherapy.

**Section 1.1:** Background

**Action:** Additional Text added

**Rationale:** To provide clarity regarding the FDC approval

**Original Text:**In another study (ARI109882), bioequivalence between a newly developed fixed-dose combination (dutasteride 0.5mg / tamsulosin hydrochloride 0.4mg) and the co-administration therapy was demonstrated, and approved in Europe in March 2010 and in the US June 2010.

**Added Text:** In another study (ARI109882), bioequivalence between a newly developed fixed-dose combination (dutasteride 0.5mg / tamsulosin hydrochloride 0.4mg) and the co-administration therapy was demonstrated, and the fixed dose combination product was approved in Europe in March 2010 and in the US June 2010.

**Section 1.1:** Background

**Action**: Additional text added

**Rationale**: To reference to the CIB/approved product label to provide risk:benefit information on investigational product.

**Added Text**: Specific information regarding warnings, precautions, contraindications, AEs, and other pertinent information on the study treatments is provided in the approved label and in the clinical investigator brochure (CIB).

**Section 2.3**: Exploratary Pharmacogenetics (PGx) Research Objective

**Action:** Text added

**Rationale:** As per new GSK template wording and deleted the reference to pharmacokinetics.

**Original Text**: The PGx objectives for this study are to investigate the relationships between genetic variants in DNA from patient blood and response to treatment (as monitored by safety, tolerability, pharmacokinetics, and efficacy parameters).

**Updated Text:** The exploratory PGx objectives for this study are to investigate the relationships between genetic variants in DNA from patient blood and any unexplained or unexpected response to treatment (as monitored by safety, tolerability, and efficacy parameters) that may have an underlying genetic mechanism.

**Section 3**: Study Design

**Action:** Text modified

**Rationale:** As per new GSK template wording

**Original Text**: Protocol waivers or exemptions are not allowed. Therefore adherence to the study design requirements, including those specified in the Time and Events Table are essential

**Amended Text**: Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

**Section 4.1.1:** Number of Subjects

**Action:** Text corrected and updated

**Rationale:** To correct the approximate number of subjects screened and clarify and correct previous wording. To include a statement re: adjustment of enrolment target if needed to ensure overall number of evaluable subjects.

**Original Text**: Approximately 586 men with symptomatic BPH will be randomized into a single blind placebo run-in phase followed by a 2-arm double-blind treatment phase. It is expected that approximately 1050 patients will need to be screened to allow for up to 40% screening failures and drop-outs during the placebo run in period.

**Updated Text:** Approximately 586 men with symptomatic BPH will be randomized into the treatment phase. It is expected that approximately 1000 patients will need to be screened to allow for a screening failure rate of approximately 40%. The overall enrolment target number may be adjusted depending on the actual experience of enrolment and retention of participants, to ensure that the overall evaluable subject number target is met.

**Section 4.1.4**: Other Eligibility Criteria Considerations

**Action:** Text added

**Rationale:** Information in local product monographs may impact consideration of a subject's eligibility differently. Additional wording added to guide investigators to locate relevant information readily and to ensure better compliance.

**Original Text:** These documents include, but may not be limited to, the following: the dutasteride Clinical Investigator's Brochure (CIB) or equivalent document provided by GlaxoSmithKline (GSK), the dutasteride (AVODART) local product monograph, where available, the approved product label(s) for tamsulosin (Harnal D, Flomax) and dutasteride (AVODART), if applicable.

**Added Text:** These documents include, but may not be limited to, the following: the dutasteride Clinical Investigator's Brochure (CIB) or equivalent document provided by GlaxoSmithKline (GSK), the dutasteride (AVODART) local product monograph, where available, the approved product label(s) for tamsulosin (Harnal D, Flomax) and dutasteride (AVODART), if applicable. Study Procedures Manuals will outline information contained in the local product monographs that must be relayed to patients (e.g. use of a condom to avoids exposure of his partner when taking the study drugs), as applicable to a specific country.

**Section 4.1**.:Precautions

**Action:** Paragraphs removed

**Rationale:** Study sites should exam all precautions that are stated in the product labels. Local countries to adhere to local labelling guidelines. Precautions in the ICF will be in accordance with local labelling.

**Original Text:** Women of childbearing potential, pregnant women, and lactating women should avoid exposure to study medication. Inhibitors of 5α-reductase block the conversion of testosterone to dihydrotestosterone; the latter plays an important role in the development of external genitalia in the male fetus. Consequently, male offspring of women exposed to therapeutic concentrations of a 5α-reductase inhibitor may be born with abnormal male genitalia.

The dose of dutasteride in a unit of blood donated by a dutasteride-treated subject receiving 0.5 mg daily has been calculated to be below the no effect dose for DHT suppression in humans and as a single dose is well below the exposure in a study in rhesus monkeys that produced no effect on male fetal masculinization (see CIB). However, to allow an extra margin of safety, men being treated with dutasteride should not donate blood while taking study medication and until at least 6 months following administration of the last dose. The purpose of this deferred period is to prevent administration of dutasteride to a pregnant female transfusion recipient.

Dutasteride has been reported to decrease sperm count and motility, and reduce semen volume in healthy volunteers (see CIB). The clinical significance of dutasteride's effect on sperm and semen characteristics for an individual man's fertility is not known.

**Updated Text**: Investigator must refer to the relevant document(s) for detailed information regarding precautions as mentioned above. Local product monograph should be checked carefully to adhere to local labelling guidelines.

**Section 4.2.1**: Permanent Discontinuation from study Treatment

**Action:** Text modified

**Rationale**: To provide clarification on discontinuation of study treatment vs discontinuation of study

**Added Text**: adverse event

**Added Text** (moved from Section 6.3): A subject, who experiences an AUR, does not need to be withdrawn from the study treatment. Any subject who has BPH-related prostatic surgery or any minimally-invasive/non-surgical intervention for treatment of BPH symptoms at any time during the study period must be withdrawn from the study treatment.

**Added Text:** All subjects who prematurely discontinue from study treatment may not necessarily be withdrawn from the study as further study procedures or follow-up may be performed (Section 6.3).

**Deleted Text** : Subjects who prematurely discontinue study treatment will be followed via telephone contact for clinical outcomes including AUR or BPH related prostatic surgery, through the remainder of the 2 year treatment period(see Section 6.3)

**Section 4.2.2:**Subject Completion

**Action:** Deletion of repetitive text

**Rationale:** Deletion of repetitive text for clarification as the additional information is stated elsewhere in the protocol

**Original Text**: A subject will be considered to have completed the study if he completes the 4-weekplacebo run-in and the 104 week study treatment period. A subject will be considered tohave prematurely discontinued the study if the subject died, is lost to follow-up,withdraws consent, or if the study is closed/terminated.

**Updated Text:** A subject will be considered to have completed the study if he completes the 4-week placebo run-in and the 104 week study treatment period.

**Section 5.1:** Investigational Product

**Action:** Clarification

**Rationale:** Clarify that the oral disintegrating placebo is for the tamsulosin placebo

**Original Text:** Oral disintegrating placebos will be supplied by GSK.

**Amended Text:** An oral disintegrating placebo tamsulosin tablet will be supplied by GSK for the run-in period.

**Section 5.1.1:** Dosage and Administration

**Action:** Removal of bottle fill counts and detailed subject dosing instructions

**Rationale:** Updated details on the study drug will be in the Study Procedures Manual.

**Original Text (Run-in phase (single-blind)):** Subjects will receive a 1-month supply of study medication (one bottle containing 35 capsules and one blister card containing 36 tablets). All subjects will be instructed to take one soft gelatin placebo capsule (swallowed whole and not chewed) and one oral disintegrating placebo tablet(dissolved on the tongue then swallowed not chewed) , approximately one-half hour following the first meal each day for four weeks. They will then be randomized to adouble-blind treatment phase for a further 104 weeks.

**Amended Text (Run-in phase (single-blind)):** Subjects will receive a 1-month supply of study medication. All subjects will be instructed to take one soft gelatin placebo capsule (swallowed whole and not chewed) and one oral disintegrating placebo tablet (dissolved on the tongue then swallowed not chewed), following the first meal each day for four weeks. They will then be randomized to a double-blind treatment phase for a further 104 weeks.

**Original Text (Randomized treatment phase (double-blind)):** one tamsulosin tablet (dissolved on the tongue then swallowed not chewed) approximately one-half hour following the first meal each day for 104 weeks

**Amended Text (Randomized treatment phase (double-blind)):** one tamsulosin tablet (dissolved on the tongue then swallowed not chewed) following the first meal each day for 104 weeks.

**Section 5.2:** Packaging and Labeling

**Action:** Remove detailed text on packaging, fill counts and labelling

**Rationale:** Updated details on the study drug and the fill counts will be in the Study Procedures Manual

**Original Text:** Dutasteride study medication for both phases of the study will be provided in high density, polyethylene bottles with plastic child-resistant closures. For the Run-In Phase, dutasteride placebo will be packaged as 35 capsules per bottle. For the Treatment Phase, dutasteride 0.5mg and its matching placebo will be packaged to be indistinguishable irrespective of treatment with 100 capsules per bottle, sufficient for 3 months treatment . Each bottle will be labelled with a multi-language booklet label.

Commercially available tamsulosin 0.2mg will be provided by GSK. Each pack will be labelled with a multi-language booklet label.

Placebo ODT will be packaged in blister cards with 36 tablets per card. Each blister card will be labelled with a multi-language booklet label

**Updated Text:** Dutasteride study medication for both phases of the study will be provided in high density, polyethylene bottles with plastic child-resistant closures. Dutasteride 0.5mg and its matching placebo will be packaged to be indistinguishable irrespective of treatment.

Commercially available tamsulosin 0.2mg will be provided by GSK.

The tamsulosin tablet placebos will be packaged in blister packs.

**Section 5.3:** Handling and Storage of Study Treatment

**Action:** Text updated

**Rationale:** Change in the storage conditions for study drug. Gelatin cross linking is temperature dependent. Reducing the storage temperature conditions will mitigate risk of shelf life failure. All new supplies will be labeled with the new storage conditions, "Store up to 25°C".

**Original Text:** Prior to dispensing, all study medication will be kept safely locked and stored protectedfrom light and moisture. The dutasteride capsules should be stored at or below 30°C. The commercial tamsulosin can be stored at room temperature and the placebo ODT at room temperature (15-30°C).

**Updated Text:** The dutasteride capsules should be stored at temperatures up to 25°C (77°F).The commercial tamsulosin and placebo should be stored as per the instructions on the label. Relevant label details will be provided in the study SPM.

**Section 5.4:** Treatment Assignment

**Action:** Treatment assignment clarified

**Rationale:** The subjects will be randomized by investigative sites, reference to central randomization removed,

**Original Text:** Subjects will be centrally randomized using a randomization schedule generated by the GSK Biostatistical Department

**Updated Text:** Subjects will be randomized by investigative site using a randomization schedule generated by the GSK Biostatistical Department

**Section 6.2:** Prohibited Medications and Non-Drug Therapies

**Action:** Text added

**Rationale:** Addition of the text on concomitant medications and non-drug therapies allow more consistent interpretation throughout the study sites.

**Added Text:** Questions regarding permitted and prohibited concomitant medications and non drug therapies should be directed to the GSK Medical Monitor for clarification.

**Section 6.3**: Treatment after Discontinuation of Study treatment or Discontinuation of Study

**Action:** Text modified

**Rationale:** To provide clarification on discontinuation of study treatment vs discontinuation of study

**Original Text**: If a subject discontinues study participation after Visit 2

**Amended Text**: If a subject discontinues study treatment permanently after Visit 2.

**Original Text**: End of Study Assessments as outlined in Section 7.2.2.5

**Amended Text:** End of Study Treatment Assessments as outlined in Section 7.2.2.5

**Added Text**: No additional study activities other than those that are stated above are planned after a subject's permanent discontinuation from study treatment.

A subject is considered a 'withdrawal' from the study when no study procedure has occurred, no follow-up has been performed and no further information has been collected for this subject from the date of withdrawal/last contact.

The primary reason for permanent discontinuation of study must be documented in the subject's medical records and eCRF.

**Original Text:** In the event that a subject is prematurely discontinued from the study at any time due to an AE

**Amended Text:** In the event that a subject is prematurely discontinued from the study treatment or withdraw from the study at any time due to an AE

**Deleted Text (moved to Section 4.2):** A subject, who experiences an AUR, does not need to be withdrawn from the study. Any subject who has BPH-related prostatic surgery or any minimally-invasive/non-surgical intervention for treatment of BPH symptoms at any time during the study period must be withdrawn from the study

**Action:** Text added

**Rationale:** The addition of text on the follow-up of sexually related AEs when a subject discontinues study treatment allow more fully document study related events.

**Original Text:** after premature withdrawal of study treatment, should be fully documented in the eCRF and source documents.

**Updated Text:** after premature withdrawal of study treatment, and outcomes of sexually related adverse events reported during the treatment period, should be fully documented in the eCRF and source documents.

**Section 7:** Study Assessements and Procedures

**Action**: Text Aded

**Rationale:** The added text allows necessary visit/assessment to be performed when necessary.

**Added Text:** Unscheduled visits/assessment may be performed by the investigator as medically necessary

**Action:** Corrections to the Time and Events table

**Rationale:**. Additions and revisions to the T & E table to ensure consistency with protocol text [addition of PSA serum collection at visit 4, addition of vital signs at visits 3 & 5, addition of AUR or BPH-related surgery at visits 2-10, addition of other efficacy measures (UTI/Incontinence/Renal Insufficiency at visits 2-10)].

## Original Text:

| **Study Procedures** | **Visit 1a Pre-Screen** | **Visit 1b** Screening** (V1a + 14 days) | **Visit 2 Baseline** (V1b + 28d ± 4 days) | **Visit 3** (Baseline + 13 wks ± 14 days) | **Visit 4** (Baseline + 26 wks ± 14 days) | **Visit 5** (Baseline + 39 wks ± 14 days) | **Visit 6** (Baseline + 52 wks ± 14 days) | **Visits 7 - 9** (Years 2, repeat as for V3-V5 of Year 1) | **Visit 10** (Baseline + 104 wks ± 14 days) |
|---|---|---|---|---|---|---|---|---|---|
| | Pre-Screen Visit | Start of Placebo run-in | Start of Treatment Phase Baseline | | | | | | End of Treatment Phase |
| ICF | X | | | | | | | | |
| Incl/Exclusion | X | X | | | | | | | |
| Medical Hx/ Demog/CV Hx/ | X | | | | | | | | |
| ECG (12-lead) | | X | | | | | | | |
| Collection of PGx Sample | | | X | | | | | | |
| **Safety evaluations** | | | | | | | | | |
| Concomitant medication | X | X | X | X | X | X | X | ⇒ | X |
| Physical [a] Examination [a] | | X | | | X | | X | ⇒ | X |
| Vital signs [b] | | X | X | | X | | X | ⇒ | X |
| Haematology/clinical chemistry HBsAG and Hepatitis C Antibody [g] | X | | X | | | | X | ⇒ | X |
| Total serum PSA[c] | X | | | | | | X | ⇒ | X |
| Post-void residual volume (PVR) | X | X*** | X | | X | | X | ⇒ | X |
| AEs [d] | | X | X | X | X | X | X | ⇒ | X |
| **Efficacy:** | | | | | | | | | |
| BPH symptoms (IPSS) | X | | X | X | X | X | X | ⇒ | X |
| Prostate Volume (TRUS) | | X | | | | | X | ⇒ | X |
| Peak Urine Flow (Qmax) | X | X*** | X | | X | | X | | X |

| **Study Procedures** | **Visit 1a Pre-Screen** | **Visit 1b** Screening** (V1a + 14 days) | **Visit 2 Baseline** (V1b + 28d ± 4 days) | **Visit 3** (Baseline + 13 wks ± 14 days) | **Visit 4** (Baseline + 26 wks ± 14 days) | **Visit 5** (Baseline + 39 wks ± 14 days) | **Visit 6** (Baseline + 52 wks ± 14 days) | **Visits 7 - 9** (Years 2, repeat as for V3-V5 of Year 1) | **Visit 10** (Baseline + 104 wks ± 14 days) |
|---|---|---|---|---|---|---|---|---|---|
| | Pre-Screen Visit | Start of Placebo run-in | Start of Treatment Phase Baseline | | | | | | End of Treatment Phase |
| **Health Outcome:** BPH Health Status Q 8 IPSS (BHS) | X | | X | X | X | X | X | | X |
| AUR or BPH related Surgery Medical Resource Utilisation | | X | X | X | X | X | X | X | X |
| BPH Impact Index (BII) | X | | X | X | X | X | X | ⇒ | X |
| PAS-SFI | | X | X | | | | X | ⇒ | X |
| **Register in RAMOS** | X | | | | | | | | |
| **Study Medication:** | | | | | | | | | |
| Call RAMOS/Dispense Meds/ | | X [e] | X [f] | X | X | X | X | ⇒ | |
| Compliance check / Collection | | | X | X | X | X | X | ⇒ | X |

****** This second screening visit is mandatory before dispensing placebo run-in medication. This additional screen visit is designed to allow time for PSA/haem/biochem results to be returned from the laboratory, and repeat Qmax/PVR **(if required) before performing TRUS on patients who may not otherwise be eligible for the study.**

*****REPEAT ONLY IF QMAX inclusion criteria NOT MET at Visit 1a**

a. Including DRE and qualitative breast examination
b. Blood pressure and pulse to be taken after sitting quietly for 5 minutes
c. PSA sample must be taken before TRUS
d. Only Serious AEs (related to study participation) occurring between Screening (Visit 1a) and the start of placebo run-in medication need to be recorded
e. Single-blind medication to be dispensed at Visit 1b only
f. Double-blind medication dispensed from Visit 2 onwards.
g. Hepatitis B surface antigen and hepatitis C antibody (if hepatitis C antibody positive, a hepatitis C RIBA immunoblot assay should be reflexively performed on the same sample to confirm the result

## Updated Text:

| **Study Procedures** | **Visit 1a Pre-Screen** | **Visit 1b** Screening** (V1a + 14 days) | **Visit 2 Baseline** (V1b + 28d ± 4 days) | **Visit 3** (Baseline + 13 wks ± 14 days) | **Visit 4** (Baseline + 26 wks ± 14 days) | **Visit 5** (Baseline + 39 wks ± 14 days) | **Visit 6** (Baseline + 52 wks ± 14 days) | **Visits 7 - 9** (Years 2, repeat as for V3-V5 of Year 1) | **Visit 10** (Baseline + 104 wks ± 14 days) |
|---|---|---|---|---|---|---|---|---|---|
| | Pre-Screen Visit | Start of Placebo run-in | Start of Treatment Phase Baseline (Randomisation) | 3 months post Randomisation (Rand) | 6 months post Rand | 9 months post Rand | 12 months post Rand | 15,18 & 21 months post Rand respectively | End of Treatment Phase 24 months post Rand [i] |
| ICF | X | | | | | | | | |
| Incl/Exclusion | X | X | | | | | | | |
| Medical Hx/ Demog/CV Hx/ | X | | | | | | | | |
| ECG (12-lead) | | X | | | | | | | |
| Collection of PGx Sample | | | X | | | | | | |
| **Safety evaluations** | | | | | | | | | |
| Concomitant medication | X | X | X | X | X | X | X | ⇒ | X |
| Physical [a] Examination [a] | | X | | | X | | X | X [h] | X |
| Vital signs [b] | | X | X | X | X | X | X | ⇒ | X |
| Haematology/clinical chemistry | X | | | | | | X | | X |
| HBsAG and Hepatitis C Antibody [g] | | | X | | | | | | |
| Total serum PSA[c] | X | | | | X | | X | | X |
| Post-void residual volume (PVR) | X | X*** | X | | X | | X | X [h] | X |
| AEs [d] | | X | X | X | X | X | X | ⇒ | X |
| **Efficacy:** | | | | | | | | | |
| BPH symptoms (IPSS) | X | | X | X | X | X | X | ⇒ | X |
| Prostate Volume (TRUS) | | X | | | | | X | | X |
| Peak Urine Flow (Qmax) | X | X *** | X | | X | | X | X [h] | X |
| AUR or BPH-related Surgery | | | X | X | X | X | ⇒ | X | X |
| **Health Outcomes:** | | | | | | | | | |
| BPH Health Status Q 8 IPSS | X | | X | X | X | X | X | ⇒ | X |

| **Study Procedures** | **Visit 1a Pre-Screen** | **Visit 1b** Screening** (V1a + 14 days) | **Visit 2 Baseline** (V1b + 28d ± 4 days) | **Visit 3** (Baseline + 13 wks ± 14 days) | **Visit 4** (Baseline + 26 wks ± 14 days) | **Visit 5** (Baseline + 39 wks ± 14 days) | **Visit 6** (Baseline + 52 wks ± 14 days) | **Visits 7 - 9** (Years 2, repeat as for V3-V5 of Year 1) | **Visit 10** (Baseline + 104 wks ± 14 days) |
|---|---|---|---|---|---|---|---|---|---|
| | Pre-Screen Visit | Start of Placebo run-in | Start of Treatment Phase Baseline (Randomisation) | 3 months post Randomisation (Rand) | 6 months post Rand | 9 months post Rand | 12 months post Rand | 15,18 & 21 months post Rand respectively | End of Treatment Phase 24 months post Rand [i] |
| (BHS) | | | | | | | | | |
| AUR or BPH-related Surgery Medical Resource Utilisation | | | X | X | X | X | X | ⇒ | X |
| BPH Impact Index (BII) | X | | X | X | X | X | X | ⇒ | X |
| PAS-SFI | | X | X | | | | X | | X |
| **Other Efficacy Measures** | | | | | | | | | |
| UTI /Incontinence / Renal Insufficiency | | | X | X | X | X | X | ⇒ | X |
| **Register in RAMOS** | X | | | | | | | | |
| **Study Medication:** | | | | | | | | | |
| Call RAMOS/DispenseMeds | | X [e] | X [f] | X | X | X | X | ⇒ | |
| Compliance check/Collection | | | X | X | X | X | X | ⇒ | X |

****** This second screening visit is mandatory before dispensing placebo run-in medication. This additional screen visit is designed to allow time for PSA/haem/biochem results to be returned from the laboratory, and repeat Qmax/PVR (if required) before performing TRUS on patients who may not otherwise be eligible for the study.

***REPEAT ONLY IF QMAX inclusion criteria NOT MET at Visit 1a

a. Including DRE and qualitative breast examination
b. Blood pressure and pulse to be taken after sitting quietly for 5 minutes
c. PSA sample must be taken before TRUS
d. Only Serious AEs (related to study participation) occurring between Screening (Visit 1a) and the start of placebo run-in medication need to be recorded
e. Single-blind medication to be dispensed at Visit 1b only
f. Double-blind medication dispensed from Visit 2 onwards.
g. Hepatitis B surface antigen and hepatitis C antibody (if hepatitis C antibody positive, a hepatitis C RIBA immunoblot assay should be reflexively performed on the same sample to confirm the result
h. Only performed at Visit 8 (Month 18)
i. Performed for assessment of Subject Completion as well when a subject discontinues the study (see Section 6.3 and Section 7.2.2.5)

**Section: 7.2.1.2** Other Efficacy Measures

**Action:** Addition of new section

**Rationale:** Additions to the list of potential disease related events to allow possible comparison to historical BPH studies and to insure consistency of disease-related adverse event definition .

**Updated Text:**. The following are potential BPH disease related events not captured as primary or secondary endpoints. They will be collected in this study for possible comparison to historical BPH studies and to insure consistency of disease-related adverse event definition (see Section 7.4.2.2).

- Urinary tract infection/urosepsis
- Urinary incontinence (overflow/urge)
- Renal insufficiency

**Section 7.2.1.3:** Health Outcome Measures Endpoints (previously Section 7.2.1.2)

**Action:** Clarification

**Rationale:** Clarification and correction of previous wording

**Original Text:** Change in Resources Use related to changes in safety events

**Updated Text:** Resource Use related to AUR and BPH-related surgical events.

**Section 7.2.2.4:** Definition of Other Efficacy Measures

**Action:** Added the section to define other efficacy measures.

**Rationale:** To provide clinical definitions for the measures as stated in Section 7.2.1.2.

**Updated Text:** Other efficacy measures are noted in Section 7.2.1.2. The following provides clinical definition for these measures.

Renal insufficiency is defined as >=50% sustained rise in baseline serum creatinine and >=1.5mg/dL; BPH-relatedness will be assessed by the investigator.

Urinary tract infection (UTI) is defined as symptomatic infection of $10^5$ cfu/mL during the study; recurrent UTI is defined as two or more UTI episodes during the study. BPH-relatedness will be assessed by the investigator.

Incontinence (overflow or urge) is defined as socially or hygienically unacceptable involuntary leakage of urine). BPH-relatedness will be assessed by the investigator.

**Section 7.2.2.5:** End of study treatment Assessment

**Action:** Text modified

**Rationale:** To be consistent with the added text on other efficacy measures defined in Section 7.2.1.2 and with the clarification made concerning discontinuation of study treatment vs study

**Updated Text**: Record any episodes of UTI/urosepsis, urinary incontinence (first episode or consistent worsening), and renal insufficiency.

**Original Text**: Assessment of Subject Completion

**Amended Text**: End of Study Treatment Assessment

**Added Text**: During the study period that is between the scheduled visits, if a subject discontinues study treatment permanently after Visit 2 (post-randomisation) for any reason, other than lost to follow-up, the investigator should make every effort to schedule a visit by the subject to the study site and complete the following assessment:

**Deleted Text**: The End of Study Assessments comprise an essential safety evaluation that should be completed prior to discharging any subject from the study

**Added Text**: Discuss the biannual follow-up phone call schedule

**Added Text**: If the decision for a subject's study treatment discontinuation is made during a regularly scheduled visit, the procedure that are stated above should be completed, in addition to any scheduled procedure that is not listed above.

**Section 7.2.3**: Short Messaging Service Reminder System

**Action:** Additional Paragraph added

**Rationale:** An SMS messaging reminder system will be used to help with subject retention and follow-up

**Updated Text:Short Messaging Service Reminder System**

To help with the retention of the subjects and planning of their scheduled follow up throughout the study, subjects will be sent text messages via their mobile telephone, or email reminders, regarding their scheduled appointments. Sites will gain consent from the subject in the ICF before enrolling their mobile phone number or e-mail address into the secure short messaging service (SMS) reminder system. The system will then transmit text messages or e-mails to the subject in the local language regarding their next appointment.

Subject participation in the SMS reminder system is voluntary and refusal to participate will not indicate withdrawal from the clinical study. Refusal to participate will involve no penalty or loss of benefits to which the subject would otherwise be entitled. The SMS reminder system may not be available for all study sites or countries. Even if available, study sites or countries may choose not to participate in the SMS reminder system. All text message/e-mail content will be reviewed and approved by the IRB/IEC prior to use.

**Section 7.3.1:** Endpoints

**Action**: Text added

**Rationale**: Clarification that the change in PSA will be from baseline

**Original Text:** Change in total serum PSA

**Updated Text**: Change in total serum PSA from baseline

**Section 7.3.3**: Physician's Assessments and vital signs

**Action:** Correction of the text on vital sign to include Visit 3 and Visit 5 assessments

**Rationale:** To better evaluate subjects' health status at Visit 3 and Visit 5 and to allow possible comparison to the data of historical BPH studies.

**Original Text**: Vital signs (blood pressure followed by pulse) will be assessed at Pre-Screening Visit 1, Baseline Visit 2 and every 6 months thereafter.

**Amended Text**: Vital signs (blood pressure followed by pulse) will be assessed at Pre-Screening Visit 1, Baseline Visit 2 and at each scheduled 13 week clinic visit thereafter.

**Section 7.3.4**: Clinical Laboratory Assessments

**Action:** PSA test added at Visit 4

**Rationale:** As per the change in the Global Data Sheet

**Original Text:**

| Laboratory Assessment | Visit Frequency |
|---|---|
| Hematology | Visits 1a, 6, 10 |
| Clinical Chemistry | Visits 1a, 6, 10 |
| PSA | Visits 1a, 6, 10 |
| HBsAG and Hepatitis C Antibody | Visit 2 |
| PGx | Visit 2 |

**Updated Text:**

| Laboratory Assessment | Visit Frequency |
|---|---|
| Hematology | Visits 1a,6, 10 |
| Clinical Chemistry | Visits 1a, 6, 10 |
| PSA | Visits 1a, 4, 6, 10 |
| HBsAG and Hepatitis C Antibody | Visit 2 |
| PGx | Visit 2 |

**Section: 7.3.4.2** Prostate Specific Antigen (PSA)

**Action:** PSA added at visit 4 and text amended

**Rationale:** As per the change in the Global Data Sheet and amended allow the implementation of the added measure in a consistent way.

**Original Text**: Total serum PSA concentrations will be assessed at Pre-screening Visit 1a and annually post-randomisation at Visits 6 and 10.

**Updated Text:** Total serum PSA concentrations will be assessed at Pre-screening Visit 1a and post-randomisation at Visit 4, (Month 6), and annually at Visits 6 and 10.Total.

**Original Text**: All post-baseline PSA levels will subsequently be reported within 1 weeks of blood draw following blinding adjustment of the PSA result (where appropriate) as described below.

In order to maintain investigator blinding to study treatment, an independent reviewer who is unblinded to the PSA results as well as the drug random code, will adjust PSA values for appropriate participants. After a subject completes one year of treatment, PSA results will be reported to the principal investigators using the following methods:

**Updated Text:** All post-baseline PSA levels will subsequently be reported following blinding adjustment of the PSA result (where appropriate) as described below.

In order to maintain investigator blinding to study treatment, an independent reviewer who is unblinded to the PSA results as well as the drug random code, will adjust PSA values for appropriate participants. After a subject completes six month of treatment, PSA results will be reported to the principal investigators using the following methods:

**Section 7.3.9:** Collection of Other Efficacy Measures

**Action:** Text added

**Rationale:** To provide details on collection of other efficacy measures added in Section 7.2.1.2.

**Updated Text:** At Visit 2 (Baseline) each scheduled 13 week clinic visit, the investigator will record in the designated section of the eCRF defined incidences of urinary tract infection/urosepsis, urinary incontinence, and renal insufficiency the subject experiences during his participation in the study.

**Section 7.4.1:** Definition of an AE

**Action:** Additional text added

**Rationale:** Updated as per GSK updated template

**Updated Text**: Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator.

Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE) unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae)

Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.

**Section 7.4.2:** Definition of an SAE

**Action:** Clarification"

**Rationale:** To clarify that spontaneous abortion is referred to the female partner of a male subject

**Original Text:** Spontaneous Abortion (see Partner Pregnancy, Section 7.4.3)

**Amended Text:** Spontaneous Abortion in female partner of male subject (see Partner Pregnancy, Section 7.4.3)

**Section 7.4.2.2**: Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

**Action:** Additional Disease related event added

**Rationale:** Additions to the list of potential disease related events to allow possible comparison to historical BPH studies and to insure consistency of disease-related adverse event definition

**Added Text:**

- Urinary tract infection/urosepsis
- Urinary incontinence (overflow/urge)
- Renal insufficiency

**Section: 7.4.3.1.** Time period for collecting partner pregnancy information

**Action:** Clarification of wording

**Rationale:** The timing of the collection of pregnancy information was clarified and updated to collect pregnancy information if the subject's partner is pregnant or becomes pregnant according to GSK standard.

**Original Text:** Pregnancy information should be collected on any female partner who becomes pregnant by a male subject participating in the study, providing the pregnancy occurred between the time of the subject's randomisation to the end of the two year treatment period.

**Updated Text:** Pregnancy information should be collected on any female partner of a male study subject who is pregnant or becomes pregnant while the subject is participating in the study. All pregnancies in female partners of male subjects will be collected after the start of dosing until 37 weeks after the subject's last dose of study drug.

**Section 7.4.2.5**: Action to be taken if partner pregnancy occurs

**Action:** Clarification

**Rationale:** The action to be taken if partner pregnancy occurs was clarified to include subject's partner that are pregnant or may become pregnant

**Original text**: The investigator, or his/her designee, should make every effort to collect pregnancy information on any female partner who becomes pregnant by a male subject during his participation in this study

**Update text:** The investigator or designee should make every effort to collect pregnancy information on any female partner who is pregnant or becomes pregnant by a male subject during his participation in this study

**Section 7.4.2.6**: Time Period and Frequency of Detecting AEs and SAEs

**Action**: Text modified

**Rationale**: To provide clarification on discontinuation of study treatment vs discontinuation of study

**Original Text:** AEs will be collected from the start of the placebo run-in phase until the end of the two year treatment period

**Amended Text**: AEs will be collected from the start of the placebo run-in phase until the end of the two year study period.

**Original Text:** will be recorded from the time a subject consents to participate in the study up to the end of the two year treatment period.

**Amended Text**: will be recorded from the time a subject consents to participate in the study up to the end of the two year study period.

**Section 7.5.3.1**

**Action:** Clarification

**Rationale:** Clarify that the questionnaire data will be entered by the site into the eCRF

**Original Text**: Upon completion of the questionnaires, the investigator will retrieve the questionnaires from the subject, and check that the header section (Subject Number, Visit Date, etc) is completed. A copy of the completed questionnaires will stay with the subject's source documents. A completed questionnaire should not be given back to the subject once it has been returned to the source documents

**Updated Text:**Upon completion of the questionnaires, the investigator will retrieve the questionnaires from the subject, and check that the header section (Subject Number, Visit Date, etc) is completed. The investigator (or qualified designated member of their staff) will use the subject completed questionnaires to enter the recorded data into the appropriate section of the eCRF. A copy of the completed questionnaires will stay with the subject's source documents. A completed questionnaire should not be given back to the subject once it has been returned to the source documents

**Section 7.6:** Pharmacogenetics

**Action:** Removal of text

**Rationale:** There are no PK samples being collected in this study, therefore text referencing PK samples was removed.

**Original Text:** The presence/absence of genetic variations in patient genes in DNA from blood will be analyzed to determine their relationship with response (safety, tolerability, pharmacokinetics, and efficacy) to treatment with either the combination of dutasteride and tamsulosin or tamsulosin alone.

**Updated Text:** . The presence/absence of genetic variations in patient genes in DNA from blood will be analyzed to determine their relationship with response (safety, tolerability, and efficacy) to treatment with either the combination of dutasteride and tamsulosin or tamsulosin alone.

**Section 9.3.6.1:** Efficacy Analysis

**Action:** Text added

**Rationale:** Description of summary of other efficacy measures in alignment with the text added in Section 7.2.1.2.

**Updated Text: Summary of Other Efficacy Measures**

Urinary tract infection/urosepsis, urinary incontinence, and renal insufficiency are captured as potential BPH disease related events; reference Section 7.2.1.2. Frequencies of each event will be presented by treatment group; no formal treatment comparisons are planned.

**Section 12.1:** Appendix 1 Pharmacogenetics

**Action:** Text updated

**Rationale:** PGx language updated to reflect current GSK template.

**Original Text (Pharmacogenetics – Background):** Collection of whole blood samples, even when no *a priori* hypothesis has been identified, may enable PGx analysis to be conducted if at any time it appears that there is a potential unexpected or unexplained variation in handling or response to

**Amended Text (Pharmacogenetics – Background):** Collection of whole blood samples, even when no *a priori* hypothesis has been identified, may enable PGx analysis to be conducted if at any time it appears that there is a potential unexpected or unexplained variation in handling or response to the combination treatment of dutasteride and tamsulosin or tamsulosin monotherapy.

**Added Text** (**Pharmacogenetics – Study Assessments and Procedures)**: However if the investigators deems it appropriate, the PGX sample may be taken at a later visit.

**Original Text (Pharmacogenetic Research Objectives):**If at any time it appears there is potential variability in response in this clinical study or in a series of clinical studies with If at any time it appears there is potential variability in response in this clinical study or in a series of clinical studies with the combination treatment of dutasteride and tamsulosin or tamsulosin monotherapy that may be attributable to genetic variations of subjects, the following objectives may be investigated.

**Amended Text (Pharmacogenetic Research Objectives):** If at any time it appears there is potential variability in response in this clinical study or in a series of clinical studies with the combination treatment of dutasteride and tamsulosin or tamsulosin monotherapy that may be attributable to genetic variations of subjects, the following objectives may be investigated.

**Original Text (Pharmacogenetics Analyses):**. Genome-wide scans involving a large number of polymorphic markers (e.g., single nucleotide polymorphisms) located throughout the genome. This approach is often employed when potential genetic effects are not well understood.

**Replaced with the Text (Pharmacogenetics Analyses):**. In addition, continuing research may identify other enzymes, transporters, proteins or receptors that may be involved in response to dutasteride and tamsulosin or tamsulosin monotherapy. The genes that may code for these proteins may also be studied.

**Section 12.2:** Appendix 2 Study Assessment Schedule in Order of Performance

**Action:** Text added or removed

**Rationale:** Clarification on the collection of the questionnaires and their sequence, removal of reference to number of bottles dispensed as this is to be updated and confirmed in the study procedure manual,addtion of the PSA test at Visit 4, text addition and removal to ensure consistency with the text of the main body of the protocol & the T& E table

**Original Text (Visit 2 and Visit 6)**: Administer patient self-assessment questionnaires: International Prostate Symptom Score [IPSS], BHS Q8,BPH Impact Index [BII], Patient's Perception of Study Medication [PPSM] Questionnaire (Satisfaction)

**Amended Text (Visit 2 and Visit 6)**:: Administer patient self-assessment questionnaires: International Prostate Symptom Score [IPSS], BHS Q8,BPH Impact Index [BII], Problem Assessment Scale of the Sexual Function Index (PAS-SFI)

**Original Text (Visit 3- 5)** :Administer patient self-assessment questionnaires: International Prostate Symptom Score [IPSS], BHS Q8, BPH Impact Index [BII], Problem Assessment Scale of the Sexual Function Index (PAS-SFI).

**Amended Text (Visit 3- 5)**: Administer patient self-assessment questionnaires: International Prostate Symptom Score [IPSS], BHS Q8, BPH Impact Index [BII],

**Original Text (Visit 2-9)**:: Dispense a 3-month supply (2 bottles) of blinded study medication and provide dosing instructions

**Amended Text (Visit 2-9)**:: Dispense a 3-month supply of blinded study medication and provide dosing instructions.

**Added Text (Visit 4):** Collect blood sample for PSA

**Deleted Text (Visit 1b):** Assess resource utilisation for any AUR episode or BPH-related surgery

**Original Text (Visit 2):** Assess resource utilisation associated with any AUR episode or BPH-related surgery

**Amended Text (Visit 2-10):** Record any episodes of AUR or prostatic surgical and minimally-invasive/non-surgical interventions along with associated resource utilizationRecord any episodes of UTI/urosepsis, urinary incontinence (first episode or consistent worsening), and renal insufficiency

**Original Text (Visit 7-9):** Visits 7 to 9 in Year 2 will be conducted at successive 13 week intervals (± 14 days) thereafter. For each subject, all visits should be scheduled at a similar time of day: morning or afternoon. The study procedures at Visits 7, 8, and 9 will be the same as those performed at Visits 3, 4, and 5, respectively

**Amended Text (Visit 7-9):** Visits 7 to 9 in Year 2 will be conducted at successive 13 week intervals (± 14 days) thereafter. For each subject, all visits should be scheduled at a similar time of day: morning or afternoon. The study procedures at Visits 7, 8, and 9 will be the same as those performed at Visits 5 except the following:

- Physical Examination is scheduled to be performed at Month 18 (Visit 8).
- Post-void residual volume (PVR) and Peak Urine Flow (Qmax) are scheduled to be performed at Month 18 (Visit 8)

**Added Text:**

**End of Study Treatment Assessment Visit**

If a subject discontinues study treatment permanently after Visit 2 (post-randomisation) and between the scheduled visits, the investigator should make every effort to schedule a visit by the subject to the study site and complete the following assessments if possible:

- Concomitant medications
- Adverse events
- Physical exam including vital signs, DRE and qualitative breast examination
- Obtain blood samples for hematology, clinical chemistry and PSA determinations
- Administer health outcome questionnaires (IPSS, BHS,BII and PAS-SFI)Record any episodes of AUR, and, BPH-related prostatic surgery or minimally-invasive/non-surgical interventions
- Record any episodes of UTI/urosepsis, urinary incontinence (first episode or consistent worsening), and renal insufficiency
- Retrieve any unused double-blind study medication, assess compliance and record date of last dose of study medication
- Discuss the biannual follow-up phone call schedule
- Complete subject eCRF

If the decision for a subject's study treatment discontinuation is made dung a regularly scheduled visit, the procedures that are stated above should be completed, in addition to any scheduled procedure (e.g. Prostate Volume, Qmax) that is not listed above.

**Protocol Amendment 2 main changes are listed below:**

- Addition of a PPK substudy for subjects of Chinese origin, living in China (only) Section 2.4, Section 7.7, Section 9.3.9 and Appendix 7.
- Addition of suicidality assessments, at pre-screening (V1a), and at 6, 12 and 24 months on treatment. Section 7.3.1, Section 7.3.9, Section 7.4.6, and Section 9.3.6.2.1.
- Addition of information on QTc events, liver events and partner pregnancy. Section 7.4.3, Section 7.4.4 and Section 7.4.5.
- Clarification on the information collected at baseline and at the pre-screening (V1a) and screening (V1b) visits. Protocol Summary.
- Update to Sponsor Signatory, Medical Monitoring Contact Information and List of Authors. Sponsor Information Page.
- Clarification that the study will be posted to clinical trial registries Section 10.1.
- Clarification of condom use for study subjects with female partners of childbearing potential. Section 4.1.2 and Section 7.4.5.
- Clarification on the use of PDE-5 inhibitors. Section 4.1.3 and Section 6.2.
- Update to T & E table to show new assessments for suicidality (all subjects) and PPK (Chinese subjects only). Section 7
- Additional information on definition of SAEs for cardiovascular events and death. Section 7.4.2
- Clarification on the wording for BPH related quality of life
- Administrative changes to correct spelling errors and re-wording to provide clarification and consistency

This amendment includes re-wording and clarifications as listed:

**Section:** Title Page

**Action:** List of Authors updated

**Rationale:** New team members added/replaced

**Original Text:** Author(s): PPD

**Updated Text**: Author(s): PPD

**Section:** Sponsor signatory information

**Action:** Sponsor signatory information updated

**Rationale:** Reflects change in responsibilities for the study

**Original Text:** PPD BSc, MBChB, MRCP, PhD, SVP, Emerging Markets R & D

**Updated Text:** PPD MD, Director Clinical Development, Emerging Markets R&D

**Section:** Sponsor Information Page.

**Action:** Sponsor medical monitor contact name and details updated. There is now only 1 primary contact for medical monitoring.

**Rationale:** Medical monitor contact details have changed.

**Original Text:** Sponsor Medical Monitor Contact Information:

Primary: PPD MD, 2301 Renaissance Blvd, RN0410 King of Prussia, Pennsylvania PA 19406. US Office: PPD ; Cell: PPD

Secondary: PPD M.D., 2301 Renaissance Blvd, RN0410 King of Prussia, Pennsylvania PA 19406 . US. Office: PPD ; Cell: PPD

**Updated Text:**

Primary: PPD MD, Alexander Drive, Research Triangle Park, North Carolina, United States. Cell: PPD

**Section:** Protocol Summary (Study Assessments).

**Action:** Clarification of the assessments performed at pre-screening, screening and baseline.

**Rationale:** Clarification of the text in the Protocol Summary to ensure consistency with the T & E table.

**Original Text:** The planned assessments for all study participants include prostate volume by TRUS at baseline and annually thereafter for up to 2 years. Additionally, IPSS, BPH-related health status Q8 of IPSS, BPH Impact Index (BII) will be administered at baseline and every 13 weeks thereafter. The PAS-SFI will be administered at screening (V1b), baseline and annually thereafter. Peak urinary flow (Qmax), and post void residual volume (PVR) will be measured at baseline and every 26 weeks thereafter, a physical examination with a qualitative breast examination at baseline and every 26 weeks thereafter, measures of the total PSA at baseline, 6 months and every 52 weeks thereafter.

**Updated Text:** The planned assessments for all study participants include prostate volume by TRUS at screening (V1b) and annually thereafter for up to 2 years.

Additionally, IPSS, BPH-related health status Q8 of IPSS, BPH Impact Index (BII) will be administered at pre-screening (V1a), baseline and every 13 weeks thereafter. The PAS-SFI will be administered at screening (V1b), baseline and annually thereafter. Peak urinary flow (Qmax), and post void residual volume (PVR) will be measured at pre-screening (V1a), screening (V1b, if necessary), baseline and every 26 weeks thereafter. A physical examination with a qualitative breast examination, will be conducted at screening (V1b) and every 26 weeks thereafter. Measures of the total PSA will be conducted at pre-screening (V1a), 6 months 52 weeks and every 52 weeks thereafter.

**Section:** 2.2.3 Health Outcomes.

**Action:** Update link to section detailing the health outcomes endpoints.

**Rationale:** Updated, as previous link was to another section.

**Original Text:** The health outcomes endpoints are presented in Section 7.2.1.2 of this protocol.

**Updated Text**: The health outcomes endpoints are presented in Section 7.2.1.3 of this protocol.

**Section:** New Section 2.4 Exploratory Population Pharmacokinetics (PPK) Research Objective.

**Action:** New section added.

**Rationale:** To show PPK substudy as an exploratory objective.

**Original Text:** Not applicable.

**Updated Text:** Exploratory Population Pharmacokinetics (PPK) Research Objective.

To characterize the PPK of dutasteride when given in combination with tamsulosin to Chinese men with BPH.

**Section:** Section 3.1 Discussion of Design.

**Action:** New paragraph added.

**Rationale:** To explain the rationale for the PPK substudy in the study design.

**Original Text:** Not applicable.

**Updated Text: (additional text).**

The pharmacokinetics of dutasteride and tamsulosin in Western subjects is well understood (CIB). In contrast, pharmacokinetic data for these two drugs in Chinese subjects are limited. Following a request to provide this information from the Regulatory Authority in China, subjects of Chinese origin living in China will participate in a PPK sub-study in this study,which aims to characterize the PK of dutasteride when dosed in combination with tamsulosin to Chinese men with BPH.

**Section:** 4.1.2 Inclusion Criteria.

**Action:** Additional inclusion criteria, applicable only to countries where the local product monograph for dutasteride mandates condom use for men with a female partner of childbearing potential to clarify the need for condom useage in men with female partners of childbearing potential.

**Rationale:** Some countries recommend the use of condoms in local dutasteride labels. The addition of this inclusion criteria makes study selection criteria consistent with these local labels.

**Original Text:** Not applicable.

**Updated Text**: Added: 9. Men with a female partner of childbearing potential must agree to use a condom up to 6 months after the last dose (applies only to countries where the local product monograph for dutasteride mandates condom use for men with a female partner of childbearing potential).

**Section:** 4.1.3 Exclusion Criteria.

**Action:** Additional exclusion criteria, to clarify that use of PDE-5 inhibitors are prohibited in the study.

**Rationale:** PDE-5 inhibitors are prohibited in the study.

**Original Text:** Not applicable.

**Updated Text**: Added: 10 f. Phosphodiesterase-5 (PDE-5) inhibitors for Erectile Dysfunction.

**Section:** 4.2.1 Permanent Discontinuation from Study Treatment.

**Action:** Additional text on actions to be taken for follow up of subjects discontinuing treatment because of a sexual function related AEs.

**Rationale:** sexual function related AEs are of particular interest in the indiction of BPH and the protocol amendment aims to clarify that subjects discontinuing treatment because of a sexual function related AEs must be followed up.

**Original Text:** Not applicable.

**Updated Text**: Subjects with sexual function related adverse events (contact GSK Medical Monitor if in doubt) leading to study withdrawal will be followed up for up to 6 months after the last dose of study drug. The sexual function Targeted Follow-Up Questionnaire to be used for these subjects follow-up can be found in the Study Procedures Manual.

**Section:** 6.2 Prohibited Medications and Non-Drug Therapies.

**Action:** Deletion of PDE-5 inhibitors from the list of medications not permitted within 6 hours of taking study medication and addition of PDE-5 inhibitors from the list of medications not permitted at any time.

**Rationale:** PDE-5 inhibitors are now a study exclusion critera.

**Original Text:**

Use of the following medications will be prohibited during the study:

d. Not permitted at any time:

- Finasteride (Proscar, Propecia)
- Any other investigational or marketed 5α-reductase inhibitors (other than study medication)
- Any alpha-adrenoreceptor blockers (other than study medication)
- BPH-related phytotherapy
- Concurrent use of anabolic steroids
- Drugs with antiandrogenic properties (e.g. spironolactone, flutamide, bicalutamide) or other drugs that are noted for gynaecomastia effects or could affect prostate volume.

e. Not permitted within 6 hours of taking study medication:

- Any PDE-5 inhibitor (e.g. sildenafil, vardenafil, tadalafil)

**Updated Text:**

Use of the following medications will be prohibited during the study:

a. Not permitted at any time:

- Finasteride (Proscar, Propecia)
- Any other investigational or marketed 5α-reductase inhibitors (other than study medication)
- Any alpha-adrenoreceptor blockers (other than study medication)
- BPH-related phytotherapy
- Concurrent use of anabolic steroids
- Drugs with antiandrogenic properties (e.g. spironolactone, flutamide, bicalutamide) or other drugs that are noted for gynaecomastia effects or could affect prostate volume
- Any PDE-5 inhibitor (e.g. sildenafil, vardenafil, tadalafil).

**Section:** 7 Table 1: Time and Events Table.

**Action**: Addition of assessments to reflect other amendments to the protocol.

**Rationale:** To make the Time and Events Table consistent with the protocol.

## Original Text: Table 1 Time and Events Table

| **Study Procedures** | **Visit 1a Pre-Screen** | **Visit 1b** Screening** (V1a + 14 days) | **Visit 2 Baseline** (V1b + 28d ± 4 days) | **Visit 3** (Baseline + 13 wks ± 14 days) | **Visit 4** (Baseline + 26 wks ± 14 days) | **Visit 5** (Baseline + 39 wks ± 14 days) | **Visit 6** (Baseline + 52 wks ± 14 days) | **Visits 7 - 9** (Years 2, repeat as for V3-V5 of Year 1) | **Visit 10** (Baseline + 104 wks ± 14 days) |
|---|---|---|---|---|---|---|---|---|---|
| | Pre-Screen Visit | Start of Placebo run-in | Start of Treatment Phase Baseline (Randomisation) | 3 months post Randomisation (Rand) | 6 months post Rand | 9 months post Rand | 12 months post Rand | 15,18 & 21 months post Rand respectively | End of Treatment Phase 24 months post Rand[i] |
| ICF | X | | | | | | | | |
| Incl/Exclusion | X | X | | | | | | | |
| Medical Hx/ Demog/CV Hx/ | X | | | | | | | | |
| ECG (12-lead) | | X | | | | | | | |
| Collection of PGx Sample | | | X | | | | | | |
| **Safety evaluations** | | | | | | | | | |
| Concomitant medication | X | X | X | X | X | X | X | ⇒ | X |
| Physical [a] Examination [a] | | X | | | X | | X | X[h] | X |
| Vital signs [b] | | X | X | X | X | X | X | ⇒ | X |
| Haematology/clinical chemistry | X | | | | | | X | | X |
| HBsAG and Hepatitis C Antibody [g] | | | X | | | | | | |
| Total serum PSA[c] | X | | | | X | | X | | X |
| Post-void residual volume (PVR) | X | X*** | X | | X | | X | X[h] | X |
| AEs [d] | | X | X | X | X | X | X | ⇒ | X |
| **Efficacy:** | | | | | | | | | |
| BPH symptoms (IPSS) | X | | X | X | X | X | X | ⇒ | X |
| Prostate Volume (TRUS) | | X | | | | | X | | X |
| Peak Urine Flow (Qmax) | X | X*** | X | | X | | X | X[h] | X |
| AUR or BPH-related Surgery | | | X | X | X | X | ⇒ | X | X |
| **Health Outcomes:** | | | | | | | | | |
| BPH Health Status Q 8 IPSS | X | | X | X | X | X | X | ⇒ | X |

| **Study Procedures** | **Visit 1a Pre-Screen** | **Visit 1b** Screening** (V1a + 14 days) | **Visit 2 Baseline** (V1b + 28d ± 4 days) | **Visit 3** (Baseline + 13 wks ± 14 days) | **Visit 4** (Baseline + 26 wks ± 14 days) | **Visit 5** (Baseline + 39 wks ± 14 days) | **Visit 6** (Baseline + 52 wks ± 14 days) | **Visits 7 - 9** (Years 2, repeat as for V3-V5 of Year 1) | **Visit 10** (Baseline + 104 wks ± 14 days) |
|---|---|---|---|---|---|---|---|---|---|
| | Pre-Screen Visit | Start of Placebo run-in | Start of Treatment Phase Baseline (Randomisation) | 3 months post Randomisation (Rand) | 6 months post Rand | 9 months post Rand | 12 months post Rand | 15,18 & 21 months post Rand respectively | End of Treatment Phase 24 months post Rand[i] |
| (BHS) | | | | | | | | | |
| AUR or BPH-related Surgery Medical Resource Utilisation | | | X | X | X | X | X | ⇒ | X |
| BPH Impact Index (BII) | X | | X | X | X | X | X | ⇒ | X |
| PAS-SFI | | X | X | | | | X | | X |
| **Other Efficacy Measures** | | | | | | | | | |
| UTI /Incontinence / Renal Insufficiency | | | X | X | X | X | X | ⇒ | X |
| **Register in RAMOS** | X | | | | | | | | |
| **Study Medication:** | | | | | | | | | |
| Call RAMOS/DispenseMeds | | X [e] | X [f] | X | X | X | X | ⇒ | |
| Compliance check/Collection | | | X | X | X | X | X | ⇒ | X |

****** This second screening visit is mandatory before dispensing placebo run-in medication. This additional screen visit is designed to allow time for PSA/haem/biochem results to be returned from the laboratory, and repeat Qmax/PVR (if required) before performing TRUS on patients who may not otherwise be eligible for the study.

***REPEAT ONLY IF QMAX inclusion criteria NOT MET at Visit 1a

a. Including DRE and qualitative breast examination
b. Blood pressure and pulse to be taken after sitting quietly for 5 minutes
c. PSA sample must be taken before TRUS
d. Only Serious AEs (related to study participation) occurring between Screening (Visit 1a) and the start of placebo run-in medication need to be recorded
e. Single-blind medication to be dispensed at Visit 1b only
f. Double-blind medication dispensed from Visit 2 onwards.
g. Hepatitis B surface antigen and hepatitis C antibody (if hepatitis C antibody positive, a hepatitis C RIBA immunoblot assay should be reflexively performed on the same sample to confirm the result
h. Only performed at Visit 8 (Month 18)
i. Performed for End of Study Treament Assessments as well when a subject discontinues the study treatment (see Section 6.3 and Section 7.2.2.5)

## Updated Text: Table 1 Time and Events Table

| **Study Procedures** | **Visit 1a Pre-Screen** | **Visit 1b** Screening** (V1a + 14 days) | **Visit 2 Baseline** (V1b + 28d ± 4 days) | **Visit 3** (Baseline + 13 wks ± 14 days) | **Visit 4** (Baseline + 26 wks ± 14 days) | **Visit 5** (Baseline + 39 wks ± 14 days) | **Visit 6** (Baseline + 52 wks ± 14 days) | **Visits 7 - 9** (Years 2, repeat as for V3-V5 of Year 1) | **Visit 10** (Baseline + 104 wks ± 14 days) |
|---|---|---|---|---|---|---|---|---|---|
| | Pre-Screen Visit | Start of Placebo run-in | Start of Treatment Phase Baseline (Randomisation) | 3 months post Randomisation (Rand) | 6 months post Rand | 9 months post Rand | 12 months post Rand | 15,18 & 21 months post Rand respectively | End of Treatment Phase 24 months post Rand[i] |
| ICF | X | | | | | | | | |
| Incl/Exclusion | X | X | | | | | | | |
| Medical Hx/ Demog/CV Hx/ | X | | | | | | | | |
| ECG (12-lead) | | X | | | | | | | |
| Collection of PGx Sample | | | X | | | | | | |
| **Safety evaluations** | | | | | | | | | |
| Concomitant medication | X | X | X | X | X | X | X | ⇒ | X |
| Physical Examination[a] | | X | | | X | | X | X[h] | X |
| Vital signs[b] | | X | X | X | X | X | X | ⇒ | X |
| Haematology/clinical chemistry | X | | | | | | X | | X |
| HBsAG and Hepatitis C Antibody[g] | | | X | | | | | | |
| Total serum PSA[c] | X | | | | X | | X | | X |
| Post-void residual volume (PVR) | X | X*** | X | | X | | X | X[h] | X |
| AEs[d] | | X | X | X | X | X | X | ⇒ | X |
| Suicidality (C-SSRS) | X | | | | X | | X | | X |
| **Efficacy:** | | | | | | | | | |
| BPH symptoms (IPSS) | X | | X | X | X | X | X | ⇒ | X |
| Prostate Volume (TRUS) | | X | | | | | X | | X |
| Peak Urine Flow (Qmax) | X | X*** | X | | X | | X | X[h] | X |
| AUR or BPH-related Surgery | | | X | X | X | X | ⇒ | X | X |
| **Pharmacokinetics**[j] | | | | | | | | | |

| **Study Procedures** | **Visit 1a Pre-Screen** | **Visit 1b** Screening** (V1a + 14 days) | **Visit 2 Baseline** (V1b + 28d ± 4 days) | **Visit 3** (Baseline + 13 wks ± 14 days) | **Visit 4** (Baseline + 26 wks ± 14 days) | **Visit 5** (Baseline + 39 wks ± 14 days) | **Visit 6** (Baseline + 52 wks ± 14 days) | **Visits 7 - 9** (Years 2, repeat as for V3-V5 of Year 1) | **Visit 10** (Baseline + 104 wks ± 14 days) |
|---|---|---|---|---|---|---|---|---|---|
| | Pre-Screen Visit | Start of Placebo run-in | Start of Treatment Phase Baseline (Randomisation) | 3 months post Randomisation (Rand) | 6 months post Rand | 9 months post Rand | 12 months post Rand | 15,18 & 21 months post Rand respectively | End of Treatment Phase 24 months post Rand[i] |
| Serum PK samples[j] | | | | X | X | X[k] | | | |
| **Health Outcomes:** | | | | | | | | | |
| BPH Health Status Q 8 IPSS (BHS) | X | | X | X | X | X | X | ⇒ | X |
| AUR or BPH-related Surgery Medical Resource Utilisation | | | X | X | X | X | X | ⇒ | X |
| BPH Impact Index (BII) | X | | X | X | X | X | X | ⇒ | X |
| PAS-SFI | | X | X | | | | X | | X |
| **Other Efficacy Measures** | | | | | | | | | |
| UTI /Incontinence / Renal Insufficiency | | | X | X | X | X | X | ⇒ | X |
| **Register in RAMOS** | X | | | | | | | | |
| **Study Medication:** | | | | | | | | | |
| Call RAMOS/DispenseMeds | | X[e] | X[f] | X | X | X | X | ⇒ | |
| Compliance check/Collection | | | X | X | X | X | X | ⇒ | X |

## Updated Text: Table 1 Time and Events Table

** This second screening visit is mandatory before dispensing placebo run-in medication. This additional screen visit is designed to allow time for PSA/haem/biochem results to be returned from the laboratory, and repeat Qmax/PVR (if required) before performing TRUS on patients who may not otherwise be eligible for the study.
***REPEAT ONLY IF QMAX inclusion criteria NOT MET at Visit 1a
⇒ ongoing assessment
a. Including DRE and qualitative breast examination
b. Blood pressure and pulse to be taken after sitting quietly for 5 minutes
c. PSA sample must be taken before TRUS
d. Only Serious AEs (related to study participation) occurring between Screening (Visit 1a) and the start of placebo run-in medication need to be recorded
e. Single-blind medication to be dispensed at Visit 1b only
f. Double-blind medication dispensed from Visit 2 onwards.
g. Hepatitis B surface antigen and hepatitis C antibody (if hepatitis C antibody positive, a hepatitis C RIBA immunoblot assay should be reflexively performed on the same sample to confirm the result
h. Only performed at Visit 8 (Month 18)
i. Performed for End of Study Treament Assessments as well when a subject discontinues the study treatment (see Section 6.3 and Section 7.2.2.5)
j. Serum PK samples are only applicable to subjects of Chinese origin living in China (see Appendix 7 for more details)

**Section:** 7.1 Critical Baseline Assessments Table 1: Time and Events Table.

**Action**: Clarification of demographic information collected.

**Rationale:** Only the subject's year of birth are collected.

**Original Text:** Demographic characteristics will be collected during screening. Subject's date of birth, race, height (in centimeters), and weight (in kilograms) will be recorded in the eCRF. In addition the following assessments will be completed at screening:

**Updated Text:** Demographic characteristics will be collected during screening. Subject's year of birth, race, height (in centimeters), and weight (in kilograms) will be recorded in the eCRF. In addition the following assessments will be completed at screening:

**Section:** 7.2.2.3 Urinary Flow Measurement

Action: The specific make and model of the Uroflow Meter have been removed and will be included in the study procedures manual.

Rationale: The exact make and model of the Uroflow meter may change during the course of the study, and will therefore be specified in the study procedures manual to avoid protocol deviations or protocol amendments.

Original Text:

Measurements of urinary flow will be conducted using a Medtronic (formerly Dantec) Uroflow Meter (Urodyn 1000™ or Duet™) with a Thompson filter at Screening Visit 1a/b, Baseline (Visit 2) and every scheduled 26 week clinic visit post-randomisation thereafter during the treatment period.

Updated Text:

Measurements of urinary flow will be conducted using a Uroflow Meter (details will be provided in the study procedures manual) at Screening Visit 1a/b, Baseline (Visit 2) and every scheduled 26 week clinic visit post-randomisation thereafter during the treatment period.

**Section:** 7.3.1 Safety Endpoints.

**Action**: Addition of suicidality.

**Rationale:** Assessment of suicidality included to comply with GSK internal guidance on suicidality assessment.

**Original Text:**

- Change in total serum PSA from baseline
- Vital signs
- Post-void residual volume
- Clinical laboratory measurements (including haematology, chemistry)
- Adverse events (including AUR or BPH-related surgery and Prostate Cancer and prostate biopsy)
- Physical examination: digital rectal examination (DRE) and qualitative breast examination

See Section 7.4 for a complete description of adverse event assessments.

**Updated Text:** Demographic

- Change in total serum PSA from baseline
- Vital signs
- Post-void residual volume
- Clinical laboratory measurements (including haematology, chemistry)
- Adverse events (including AUR or BPH-related surgery and Prostate Cancer and prostate biopsy)
- Physical examination: digital rectal examination (DRE) and qualitative breast examination
- An assessment of suicidality

See Section 7.4 for a complete description of adverse event assessments.

**Section:** 7.3.3 Physician's assessments and vital signs.

**Action**: Clarification of timepoints for collection of vital signs information.

**Rationale:** The text has been made consistent with the Time and Events Table.

**Original Text:** Vital signs (blood pressure followed by pulse) will be assessed at Pre-Screening Visit 1b, Baseline Visit 2 and at each scheduled 13 week clinic visit thereafter.

**Updated Text:** Vital signs (blood pressure followed by pulse) will be assessed at Screening Visit 1b, Baseline Visit 2 and at each scheduled 13 week clinic visit thereafter.

**Section:** 7.3.4 Clinical Laboratory Assessments.

**Action**: The last row of the table in this section (PGx assessments) has been deleted.

**Rationale:** PGx assessments are described in Section 7.6.

**Original Text:**

| Laboratory Assessment | Visit Frequency |
|---|---|
| Hematology | Visits 1a,6, 10 |
| Clinical Chemistry | Visits 1a, 6, 10 |
| PSA | Visits 1a, 4, 6, 10 |
| HBsAG and Hepatitis C Antibody | Visit 2 |
| PGx | Visit 2 |

**Updated Text:**

| Laboratory Assessment | Visit Frequency |
|---|---|
| Hematology | Visits 1a,6, 10 |
| Clinical Chemistry | Visits 1a, 6, 10 |
| PSA | Visits 1a, 4, 6, 10 |
| HBsAG and Hepatitis C Antibody | Visit 2 |

**Section: 7**.3.9 Suicidality.

**Action:** Addition of new section relating to suicidality.

**Rationale:** Assessment of suicidality included to comply with GSK internal guidance on suicidality assessment.

**Original Text:** Not applicable.

**Updated Text:**

Dutasteride is considered to be an active compound in human central nervous system (CNS) that may affect mood or behavior via effects on the CNS (directly or indirectly). A GSK review of published literature and clinical trial data for dutasteride has shown that dutasteride is not associated with an increased risk of suicidal thinking or behavior when given to this patient population.

There has been some concern that some CNS-active drugs may be associated with an increased risk of suicidal thinking or behavior when given to some subjects with certain conditions. Although these drugs and other similar drugs of the same class have not been associated with an increased risk of suicidal thinking or behavior when given to this patient population, GSK considers it important to monitor for such events before or during clinical studies with compounds such as this.

Subjects in Study ARI114265 will be assessed for suicidality and unusual changes in behavior using the Columbia Suicide Severity Rating Scale (C-SSRS). To protect subjects in the study, scores from C-SSRS tests will be reviewed in real time by the investigator and appropriate advice given to participants. Consideration should be given to discontinuing study treatments in subjects who experience signs of suicidal ideation or behavior. Refer to Section 7.4.6 for more information.

**Section:** 7.4.2 1 Definition of a SAE.

**Action**: Additional subsections created for cardiovascular events and death events.

**Rationale:** To provide additional information on how SAEs are defined.

**Original Text:** Not applicable.

**Updated Text:**

7.4.2.2 Cardiovascular Events

Investigators will be required to fill out event specific data collection tools for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularisation

This information should be recorded in the specific cardiovascular eCRF within one week of when the AE/SAE(s) are first reported.

7.4.2.3 Death Events

In addition, all deaths will require a specific death data collection tool to be completed. The death data collection tool includes questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

This information should be recorded in the specific death eCRF within one week of when the death is first reported.

**Section:** 7.4.3 QTc Events.

**Action:** Addition of new section relating to QTc events.

**Rationale:** To comply with GSK internal guidance.

**Original Text:** Not applicable.

**Updated Text:** If QTc events occur the investigator should promptly contact the medical monitor to receive advice on measures to be taken.

**Section:** 7.4.4 Liver Events.

**Action:** Addition of new section relating to liver events.

**Rationale:** To comply with GSK internal guidance.

**Original Text:** Not applicable.

**Updated Text:** If serious liver events occur the investigator should follow the standard serious event reporting process described in the protocol. For non-serious liver events that are clinically significant, the investigator will contact the medical monitor to receive advice on measures to be taken.

**Section:** 7.4.5 Partner Pregnancy (previously Section 7.4.3).

**Action:** Additional information at the start of the section, to clarify the need for condom useage in men with female partners of childbearing potential.

**Rationale:** Some countries recommend the use of condoms in local dutasteride labels. Addition of this text makes Section 7.4.4 consistent with these local labels.

**Original Text:** Not applicable.

**Updated Text:** As with other 5-alpha reductase inhibitors, dutasteride inhibits the conversion of testosterone to dihydrotestosterone and may, if administered to a woman carrying a male fetus, inhibit the development of the external genitalia of the fetus (see CIB). Small amounts of dutasteride have been recovered from the semen in subjects receiving dutasteride 0.5 mg per day. Based on studies in animals, it is unlikely that a male fetus will be adversely affected if his mother is exposed to the semen of a patient being treated with dutasteride (the risk of which is greatest during the first 16 weeks of pregnancy). Even though it is unlikely that a male fetus will be adversely affected if his mother is exposed to the semen of a partner being treated with dutasteride, some countries recommend the use of condoms in the local dutasteride labels. For these countries it is recommended that the patient avoids exposure of his partner to semen by use of a condom for 6 months after drug discontinuation.

**Section:** **7**.4.5.1. Time period for collecting partner pregnancy information (previously Section 7.4.3.1).

**Action:** Information on the time period for collecting partner pregnancy information changed from 37 weeks to 6 months.

**Rationale:** To be consistent with other sections of the protocol.

**Original Text:** Pregnancy information should be collected on any female partner of a male study subject who is pregnant or becomes pregnant while the subject is participating in the study. All pregnancies in female partners of male subjects will be collected after the start of dosing until 37 weeks after the subject's last dose of study drug.

**Updated Text:** Pregnancy information should be collected on any female partner of a male study subject who is pregnant or becomes pregnant while the subject is participating in the study. All pregnancies in female partners of male subjects will be collected after the start of dosing until 6 months after the subject's last dose of study drug.

**Section:** 7.4.5.2 Action to be taken if partner pregnancy occurs (previously Section 7.4.3.2).

**Action:** Additional clarification of the time period for collecting partner pregnancy information.

**Rationale:** Clarification of timescales for reporting pregnancy-related SAEs.

**Original Text:** Any SAE occurring as a result of a post-study pregnancy and considered reasonably related to the investigational product by the investigator will be reported to GSK. While the investigator is not obligated to actively seek this information in former study participants, he/she may learn of an SAE through spontaneous reporting.

**Updated Text:** Any SAE occurring as a result of a post-study pregnancy (6-months after last dose) and considered reasonably related to the investigational product by the investigator will be reported to GSK. While the investigator is not obligated to actively seek this information in former study participants, he/she may learn of an SAE through spontaneous reporting.

**Section:** 7.4.6 New Section: Suicidality Monitoring.

**Action:** Clarification of the assessment methods for suicidality monitoring.

**Rationale:** To comply with GSK internal guidance on suicidality assessment.

**Original Text:** Not applicable.

**Updated Text:** Assessment of suicidality will be performed using the C-SSRS which will be administered at baseline, during the course of study, and at the end of the study. Training to investigators and sites on suicidality assessment will be integral to the study implementation. Any AEs which, in the investigator's opinion, are possibly suicidality related, will be recorded in the Possible Suicidality Related Adverse Event form (PSRAE); a supplemental CRF form designed to collect detailed information on the circumstances of reported AEs related to suicidality.

The 'baseline/screening' version of C-SSRS will be used at the pre-screening visit (V1a). The 'since last visit' version of C-SSRS will be used at Visits 4, 6 and 10 (6, 12 and 24 months post randomization respectively).

The subject will complete the self-administered C-SSRS questionnaires according to the schedule detailed in Table 1. The investigator will ask the study subject to complete the C-SSRS questionnaire during the clinical visit separately from the medical history and the standard adverse event questions.

**Section:** 7.5.1 BPH-related Health Status assessments/Quality of Life.

**Action:** Clarification of the assessment methods for BPH-related quality of life.

**Rationale:** To provide further clarifications on the assessment tools used.

**Original text:** 7.5.1 BPH-related Health Status assessments Quality of Life.

The effect of study treatment on BPH-related health status will be assessed using three self-administered questionnaires. The International Prostate Symptom Score (IPSS) is a pivotal component of the primary endpoint and the BPH Impact Index (BII) and Problem Assessment Scale of the Sexual Function Index (PAS SFI) are secondary humanistic endpoints. Each questionnaire is briefly described below and will measure impact of BPH symptoms, health-related quality of life and sexual function.

a. International Prostate Symptom Score (IPSS) [Badia, 1997; Barry, 1992]

The IPSS is a 7 item instrument (essentially the same as the American Urological Association Symptom Index, AUA-SI) designed to quantify urinary symptoms but with an additional, independent eighth question BPH Health Status, (BHS) on quality of life (See Appendix 3). The IPSS will be administered at Pre-screening (Visit 1a), at Baseline (Visit 2) after completion of the placebo run-in period and at every 13 week clinic visit thereafter during the study treatment period. At Pre-screening (Visit 1a), subjects with IPSS <12 points (based on the first 7 questions) should be excluded from the study.

**Updated text:** 7.5.1 BPH-related Health Status assessments Quality of Life

The effect of study treatment on BPH-related quality of life will be assessed using three self-administered questionnaires: the BPH-related health status (question 8 of IPSS); the BPH Impact Index (BII) and the Problem Assessment Scale of the Sexual Function Index (PAS SFI). Each questionnaire is briefly described below and will measure impact of BPH symptoms, health-related quality of life and sexual function.

a. International Prostate Symptom Score (IPSS) [Badia, 1997; Barry, 1992]

The IPSS is a 7 item instrument (essentially the same as the American Urological Association Symptom Index, AUA-SI) designed to quantify urinary symptoms but with an additional, independent eighth question on quality of life (See Appendix 5). The IPSS will be administered at Pre-screening (Visit 1a), at Baseline (Visit 2) after completion of the placebo run-in period and at every 13 week clinic visit thereafter during the study treatment period. At Pre-screening (Visit 1a), subjects with IPSS <12 points (based on the first 7 questions) should be excluded from the study.

**Section:** 7.6 Pharmacogenetics.

**Action:** Addition information on date for pharmacogenetics sample.

**Rationale:** Additional clarification of Visit at which sample for pharmacogenetics is taken.

**Original Text:** Patients who provide consent will have a blood sample taken for analysis. The presence/absence of genetic variations in patient genes in DNA from blood will be analysed to determine their relationship with response (safety, tolerability, and efficacy) to treatment with either the combination of dutasteride and tamsulosin or tamsulosin alone.

**Updated Text:** Patients who provide consent will have a blood sample taken for analysis at Visit 2. The presence/absence of genetic variations in patient genes in DNA from blood will be analysed to determine their relationship with response (safety, tolerability, and efficacy) to treatment with either the combination of dutasteride and tamsulosin or tamsulosin alone.

**Section:** 7.7 New Section: Population PK (Chinese Subjects Only) and New Appendix: Appendix 7: Population PK (Chinese Subjects Only).

**Action:** Addition of new assessements, applicable to men of Chinese origin, living in China, who are required to provide blood samples for PPK analysis.

**Rationale:** To comply with a request from the Regulatory Authority in China.

**Original Text:** Not applicable.

**Updated Text:** (Section 7.7) A population pharmacokinetics (PPK) substudy will be performed only in subjects of Chinese origin, living in China, and participation in this substudy will be mandatory for these subjects. This substudy will estimate the PK parameters of dutasteride when dosed orally in combination (dutasteride 0.5 mg once daily and tamsulosin 0.2 mg once daily) in Chinese men with BPH. See Appendix 7 for more details on the PPK substudy.

Serum PK samples will be collected as indicated in Table 1. The actual date and time of each blood sample collection will be recorded. Details of blood sample collection (including volume to be collected), processing, storage, and shipping procedures are provided in the SPM.

**Section:** 9.3.3 PPK Population.

**Action:** Addition of new section for PPK.

**Rationale:** To describe the population to be used for the PPK analysis.

**Original Text:** Not applicable.

**Updated Text:** The PPK population wil comprise all ITT subjects of Chinese origin, recuited in China, randomized to receive the combination (0.5mg dutasteride and 0.2mg tamsulosin) who have available PPK samples.

**Section:** 9.3.4 Analysis Data Sets.

**Action:** Section re-numbered to account for addition of Section 9.3.3 regarding PPK population and information added on analysis of suicidality.

**Rationale:** Consistency with other sections of the protocol.

**Original Text:** Endpoints measured at specific visits and analysed in terms of visit numbers include: IPSS, Qmax, prostate volume, PSA, post void residual volume, and health outcomes. Analysis of the data collected in terms of visit numbers will be performed using two different approaches to account for missing data.

**Updated Text:** Endpoints measured at specific visits and analysed in terms of visit numbers include: IPSS, Qmax, prostate volume, PSA, post void residual volume, suicidality and health outcomes. Analysis of the data collected in terms of visit numbers will be performed using two different approaches to account for missing data.

**Section:** 9.3.7.2.1 New Section: Suicidality.

**Action:** Addition of new section for suicidality.

**Rationale:** To describe the how c-SSRS scores will be analyzed.

**Original Text:** Not applicable.

**Updated Text: Suicidality**

To protect subjects in the study, scores from C-SSRS tests will be reviewed in real time by the investigator and appropriate advice given to participants.

The C-SSRS scale has 10 outcomes, with binary (yes/no) responses. At the end of study, results will be assessed as follows:

- Suicidal ideation will be defined as a positive response at any time during treatment to any one of the five suicidal ideation questions (Categories 1-5) on the C-SSRS.
- Suicidal behavior will be defined as a positive response at any time during treatment to any one of the five suicidal behaviour questions (Categories 6-10) on the C-SSRS.
- Suicidal ideation or behavior will be defined as a positive response at any time during treatment to any one of the ten suicidal ideation and behaviour questions (Categories 1-10) on the C-SSRS.

The numbers of subjects with a positive response for suicidal ideation or suicidal behaviour will be reported at baseline and during study treatment at Visits 4, 6 and 10 (6, 12 and 24 months post randomization respectively). Scores on treatment will be compared with baseline scores and, for Visits 6 and 10, with scores at last visit to

determine the incidence of treatment-emergent suicidality. An increase in C-SSRS total score to 4 or 5 will be considered as serious treatment-emergent suicidality. Due to the low numbers of subjects expected to exhibit suicidal behaviours, formal statistical testing will not be performed.

**Section:** 9.3.10 New Section: Population Pharmacokinetic Analyses.

**Action:** Addition of new section for PPK.

**Rationale:** To describe the how PPK data will be analyzed.

**Original Text:** Not applicable.

**Updated Text:** Population Pharmacokinetic Analyses.

Details on PPK analyses will be addressed in Appendix 7 and the RAP

**Section:** 10.1 Posting of information.

**Action:** Changed specific reference to clintrials.gov to a more general reference to publicly available clinical trial registries.

**Rationale:** To cover the requirement to post study information on publicly-avaiable databases other than clintrials.gov

**Original Text:** Study information from this protocol will be posted on clinicaltrials.gov before enrolment of subjects begins.

**Updated Text:** Study information from this protocol will be posted on publicly available clinical trial registers before enrolment of subjects begins.

***Amendments to Study Appendices***

**Section:** Appendix 1: PGx.

**Action:** Volume of whole blood sample drawn for PGx research reduced from ~10 mL to ~6 mL.

**Rationale:** The reduced volume is sufficient for the PGx analyses.

**Section:** Appendix 2: Study Assessment Schedule In Order of Performance.

**Action:** Addition of relevant information for PPK and suicidality assessements.

**Rationale:** Consistency with the main text of the protocol.

**Section:** New Appendix: Appendix 7: Population PK (Chinese Subjects Only).

**Action:** Addition of new assessements, applicable to men of Chinese origin, living in China, who are required to provide blood samples for PPK analysis.

**Rationale:** To comply with a request from the Regulatory Authority in China.

**Section:** New Appendix : Appendix 8 Protocol Changes (previously Appendix 7).

**Action:** Appendix for Protocol Changes re-numbered.

**Rationale:** To accommodate new Appendix 7 for PPK monitoring.

## Protocol Amendment 3 Changes are listed below:

**Rationale**

To clarify that subjects who have received PDE-5 inhibitors in the past are eligible for enrolment into the study. Subjects must stop taking PDE-5 inhibitors as described in the prohibited medication Section 6.2.

**Section 4.1.3. Exclusion Criteria**

10. Current or Previous Use of the following medications*:*

**Text deleted**

f. Phosphodiesterase-5 (PDE-5) inhibitors for Erectile Dysfunction.

**Appendix 7 Population Pharmacokinetic Substudy (Chinese Subjects Only)**

**Rationale**

Amended to ensure consistency between Appendix 7 and Table 1 with respect to population PK sample collection.

**Original text**

Serum PK samples will be obtained on Visits 3, 5 and 5 (Table 1).

**Revised text**

Serum PK samples will be obtained on Visits 3, 4 and 5 (Table 1).

## Protocol Amendment 4 Changes are listed below:

**Section: Sponsor Information Page**

**Action:** Insertion of details of Secondary Medical Monitor.

**Rationale:** Current GSK procedures recommend a secondary medical monitor for global studies.

**Revised text:**

PPD MD
980 Great West Road, Brentford, Middlesex,
TW8 9GS, United Kingdom
Mobile: PPD

**Section: Sponsor Information Page**

**Action:** Change of e-mail and fax details for SAE reports.

**Rationale:** Current fax number and e-mail details in the protocol are incorrect.

**Original text:**

Reports from countries other than North or South America (eg, Japan, Thailand, Taiwan, Philippines and Russia)
E-mail (preferred method): PPD Fax: PPD

**Revised text:**

Paper SAE: PPD or via e-mail to PPD

**Section 4.1.3 Exclusion Criteria**

**Action:** Insertion of exclusion criteria for use of selective ß3-adrenoceptor agonist (mirabegron) within 2 weeks prior to all uroflowmetry assessments.

**Rationale:** As mirabegron is used to treat overactive bladder and therefore improves the storage capacity of the bladder, a restriction on its use has been placed before each IPSS or peak flow assessment. Fourteen days washout has been selected as Mirabegron has a half life of approximately 50 hours.

**Revised text:**

f. Use of selective beta 3-adrenoceptor agonist (mirabegron) within 2 weeks prior to all uroflowmetry assessments.

**Section 6.2 Prohibited Medications and Non-Drug Therapies**

**Action:** Insertion of restriction of ginseng for the treatment of BPH or sexual dysfunction.

**Rationale :** Ginseng is widely taken in the countries that are participating in the trial. Whist the use of ginseng is not advised, the use specifically for the treatment of BPH or sexual dysfunction is prohibited.

**Revised Text:**

Addition of:

a. Not permitted at any time:
    - Ginseng utilised for the treatment of BPH or sexual dysfunction

**Section 6.2 Prohibited Medications and Non-Drug Therapies**

**Action:** Correction of spelling of darifenacin

**Rationale :** To correct the spelling of darifenacin

**Original text:**

- Anticholinergics (e.g. oxybutynin, propantheline, danifenacin, solifenacin, tolterodine)

**Revised Text:**

- Anticholinergics (e.g. oxybutynin, propantheline, darifenacin, solifenacin, tolterodine)

**Section 6.2 Prohibited Medications and Non-Drug Therapies**

**Action:** Insertion of 14 day restriction of ß3 adrenergic receptor agonist for over-active bladder syndrome (e.g. Mirabegron) prior to each IPSS or peak flow assessment.

**Rationale :** As Mirabegron is used to treat overactive bladder and therefore improves the storage capacity of the bladder, a restriction on its use has been placed before each IPSS

or peak flow assessment. Fourteen days washout has been selected as Mirabegron has a half life of approximately 50 hours.

**Revised Text:**

b. Not permitted within two weeks prior to each IPSS or peak flow assessment:

- Selective beta 3-adrenoceptor agonist (mirabegron)

**Section 7.1 Critical Baseline Assessments**

**Action:** Insertion of C-SSRS in critical baseline assessment.

**Rationale:** The assessment is present on the Time and Events schedule but missing from the critical baseline assessments.

**Original Text:**

A 12-lead ECG, vital signs; clinical laboratory including hematology, clinical chemistry; total PSA; prostate volume*; post void residual volume (PVR); peak urinary flow (Qmax) and health outcomes questionnaires: IPSS, BHS, BII and PAS SFI.

**Revised Text:**

A 12-lead ECG, vital signs; clinical laboratory including hematology, clinical chemistry; total PSA; prostate volume*; post void residual volume (PVR); peak urinary flow (Qmax) and health outcomes questionnaires: IPSS, BHS, BII and PAS SFI and C-SSRS questionnaire.

**Section 7.2.2.1 International Prostate Symptom Score (IPSS)**

**Action:** To insert that if s subjects has taken the following medications prior to each IPSS, that the visit should be rescheduled. a) alpha adrenergic agonist, cholinergic or anticholinergic agents including anti-histamines or decongestants within 48 hours or b) ß3 adrenergic receptor agonist for over-active bladder syndrome within 14days

**Rationale:** The above medications have an affect on urinary flow. The restriction of 48 hours and 14 days respectively allows for a sufficient washout period before measurement of IPSS.

**Revised Text:**

Also, subjects must be instructed to abstain from using any alpha adrenergic agonist, cholinergic or anticholinergic agents including anti-histamines or decongestants within 48 hours prior to conducting each IPSS. In addition subjects must also abstain from taking selective beta 3-adrenoceptor agonist (mirabegron) for over-active bladder syndrome two weeks prior to each IPSS. If the subject did not adhere to these guidelines, study procedures should not be performed and the visit should be rescheduled.

**Section: 7.2.2.2 Prostate Volume**

**Action:** Insertion of text that use of a prostate volume calculator is acceptable.

**Rationale:** In assessing prostate volume, the standard clinical practice is that the prostate volume calculator inbuilt into the machine is utilised. Therefore for ease of use at the site, the prostate volume calculator will be allowed.

**Original text:**

Prostate volume calculated by pre-programmed equipment will not be accepted.

**Revised text:**

Prostate volume calculated by pre-programmed equipment will be accepted if the anteroposterior, cephalocaudal and transverse are also outputted and recorded in the eCRF. If the prostate volume calculated by pre-programmed equipment is utilised for a subject, then the same equipment and hence calculator, must be used for the duration of the subject's participation in the study.

**Section: 7.2.2.3 Urinary Flow Measurement**

**Action:** To amend the text to allow less frequent calibration of the uroflow device.

**Rationale:** As the visits are every three months during the treatment phase, there may be long periods of inactivity for the uroflowmeter. Weekly calibration is therefore considered to frequent and site resource heavy when there is not constant use.

**Original Text:**

The correct functioning of the uroflow meter will be checked once a week (especially if moved) and appropriate actions taken to ensure good maintenance of the machine.

**Revised text:**

During constant use, the correct functioning of the uroflow meter should be checked once a week (especially if moved) and appropriate actions taken to ensure good maintenance of the machine.

**Section: 7.2.2.3 Urinary Flow Measurement**

**Action:** To add that subjects must abstain from selective beta 3-adrenoceptor agonist (mirabegron) for over-active bladder syndrome for two weeks prior to this test.

**Rationale:** A restriction for mirabegron has been added to the protocol.

**Original text:**

Also, subjects must be instructed to abstain from using any alpha adrenergic agonist, cholinergic or anticholinergic agents including anti-histamines or decongestants within 48 hours prior to conducting this test. If the subject did not adhere to these guidelines, study procedures should not be performed and the visits should be rescheduled.

**Revised text:**

Also, subjects must be instructed to abstain from using any alpha adrenergic agonist, cholinergic or anticholinergic agents including anti-histamines or decongestants within 48 hours prior to conducting this test. . In addition subjects must also abstain from taking selective beta 3-adrenoceptor agonist (mirabegron) for over-active bladder syndrome for two weeks prior to this test. If the subject did not adhere to these guidelines, study procedures should not be performed and the visits should be rescheduled.

**Section 7.2.2.5 End of Study Treatment Assessments**

**Action:** Insertion of C-SSRS in End of Treatment Study Assessments.

**Rationale:** The assessment is present on the time and events schedule but missing from the critical baseline assessments.

**Revised text:**.

- Administration of C-SSRS questionnaire.

**Section 7.3.2 Medical History, Concomitant Medications, ECG, Physical Examination**

**Action:** Revision of text with regards generation of 30 second rhythm strip.

**Rationale:** To allow flexibility in duration of rhythm strip obtained.

**Original Text**: The subject should rest supine for 5 minutes before the 12-lead ECG is recorded. A 30-second rhythm strip will be obtained.

**Revised text:**. The subject should rest supine for 5 minutes before the 12-lead ECG is recorded. Additionally a rhythm strip will be obtained to assess for presence of arrhythmias.

**Section: 7.4.2.4 Sentinel Events**

**Action:** Insertion of standard text on GSK adverse events

**Rationale:** The current protocol is missing the standard GSK wording on sentinel events

**Revised text:**

A Sentinel Event is a GSK-defined SAE that is not necessarily drug-related but has been associated historically with adverse reactions for other drugs and is therefore worthy of heightened pharmacovigilance. Medical monitor review of all SAEs for possible Sentinel Events is mandated at GSK. The GSK medical monitor may request additional clinical information on an urgent basis if a possible Sentinel Event is identified on SAE review. The current GSK-defined Sentinel Events are listed below:

- Acquired Long QT Syndrome
- Agranulocytosis/Severe Neutropenia
- Anaphylaxis & Anaphylactoid Reactions
- Hepatotoxicity
- Acute Renal Failure
- Seizure
- Stevens Johnson syndrome/Toxic epidermal necrosis

**Section: 7.4.6 Suicidality Monitoring**

**Action:** To correct that the C-SSRS will be completed by the subject.

**Rationale:** The C-SSRS needs to be administered by a trained rater rather than the subject.

**Original text:**

The subject will complete the self-administered C-SSRS questionnaires according to the schedule detailed in Table 1. The investigator will ask the study subject to complete the C-SSRS questionnaire during the clinical visit separately from the medical history and the standard adverse event questions.

**Revised text:**

A trained rater will administer the C-SSRS questionnaires according to the schedule detailed in Table 1. The C-SSRS questionnaire will be completed during the clinical visit separately from the medical history and the standard adverse event questions.

**Section: 7.5.3.1 Collection and Storage**

**Action:** To correct that the original of the C-SSRS will be stored with the subject's source notes rather than a copy.

**Rationale:** To allow the original to the source record in the subject's notes.

**Original text:**

The investigator (or qualified designated member of their staff) will use the subject completed questionnaires to enter the recorded data into the appropriate section of the eCRF. A copy of the completed questionnaires will stay with the subject's source notes.

**Revised text:**

The investigator (or qualified designated member of their staff) will use the subject completed questionnaires to enter the recorded data into the appropriate section of the eCRF. A copy of the completed questionnaires will stay with the subject's source notes.

**Section: Appendix 2**

**Action:** Insertion of pre-screening Visit 1a and screening Visit 1b.

**Rationale:** To ensure consistency between main text of protocol and time and events schedule.

**Original text:**

Visit 1 (Screening)

**Revised text:**

Visit 1 (Pre-Screening Visit 1a and Screening Visit 1b)

**Section: Appendix 2 Visit 1b (Placebo-run-in)**

**Action:** To insert that SAEs will be assessed at Visit 1b.

**Rationale:** This change is to ensure consistency with the Time and Events schedule i.e Only Serious AEs (related to study participation) occurring between Screening (Visit 1a) and the start of placebo run-in medication need to be recorded

**Revised Text:**

Addition of:

5. Assess SAEs

**Section: Appendix 2 Visit1 1, Visit 4, Visit 6 and Visit 10**

**Action:** To correct that the C-SSRS will not be a patient self administered questionnaire

**Rationale:** The protocol states that the C-SSRS questionnaires will be patient self administered questionnaire. The C-SSRS can only be administered by a trained rater.

**Original text:**

Administer patient self-assessment questionnaires: International Prostate Symptom Score [IPSS], BHS Q8 BPH Impact Index [BII] and suicidality [C-SSRS]

**Revised:**

Administer patient self-assessment questionnaires: International Prostate Symptom Score [IPSS], BHS Q8 BPH Impact Index [BII]

Administer suicidality questionnaire [C-SSRS]

**Section: Appendix 2 Visit 4 and Visit 10**

**Action:** Removal of transition zone volume

**Rationale:** Transition zone volume will not be measured within this protocol as not required.

**Original text:** Measure prostate volume (and at selected sites, transition zone volume) by transrectal ultrasound (TRUS)

**Revised text:**

Measure prostate volume by transrectal ultrasound (TRUS)

**Section: Time and Events Schedule**

**Action:** Insertion of text to show that if there is a positive Hepatitis C sample, rather than a immunoblot RIBA immunoblot assay, a hepatitis C RNA test will be reflexively performed to confirm the result.

**Rationale:** The change is reflective of the procedures at the central lab and consistent with the laboratory manual.

**Original text:**

g. Hepatitis B surface antigen and hepatitis C antibody (if hepatitis C antibody positive, a hepatitis C RIBA immunoblot assay should be reflexively performed on the same sample to confirm the result.

**Revised text:**

g. Hepatitis B surface antigen and hepatitis C antibody (if hepatitis C antibody positive, a hepatitis C RNA test should be reflexively performed to confirm the result.