

## TITLE PAGE

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

|               |   |
|---------------|---|
| <b>Title:</b> | Implementation of a screening tool for subjects with benign prostatic enlargement/obstruction to identify men $\geq 50$ years presenting in General Practice with other co-morbidities who should be assessed for BPH |
|---------------|---|

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**Author (s):**

PPD

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| <ul style="list-style-type: none"><li>• Deletion of compound numbers on the title page and the entering of “None”.</li><li>• Deletion of the development status on the title page and entering “NA”.</li><li>• Changing the study to an interventional study from non-interventional (Section 4).</li><li>• Deletion of the collection of race and ethnicity (Section 6.2).</li></ul>   |             |                 |
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| <ul style="list-style-type: none"><li>• Clarification of digital rectal exam throughout the protocol.</li><li>• Addition of criteria for probable BPH (Study 4).</li><li>• Addition to concomitant medications - exclusion criteria (Section 5.2.).</li><li>• Addition of footnotes to Time and Events Table. (Section 6.1.).</li><li>• Deletion of text referring to GSK product. (Section 6.3.1.1. and Section 6.3.1.3.).</li></ul> |             |                 |

**SPONSOR SIGNATORY**

PPD



1/18/2016

Michael J. Manyak, MD, FACS  
Director, Global Medical Affairs

Date

**MEDICAL MONITOR/SPONSOR INFORMATION PAGE****Medical Monitor/SAE Contact Information:**

| Role                      | Name                                   | Day Time Phone Number and email address | After-hours Phone/Mobile/ Pager Number | Fax Number | Site Address  |
|---------------------------|--|---|--|------------|---|
| Primary Medical Monitor   | PPD<br>MD                              | Mobile: PPD<br>Email: PPD               | Mobile: PPD                            | N/A        | GlaxoSmithKline (GSK)<br>5 Moore Drive, PO Box 13398, RTP, NC 27709-3398, United States |
| Secondary Medical Monitor | PPD                                    | Mobile: PPD<br>Phone: PPD<br>Email: PPD | Mobile: PPD                            | N/A        | Istanbul, Turkey  |
| SAE contact information   | Medical monitor as above:<br>PPD<br>MD | Mobile: PPD<br>Email: PPD               | Mobile: PPD<br>PPD                     | N/A        | GSK<br>5 Moore Drive, PO Box 13398, RTP, NC 27709-3398, United States                   |

**Sponsor Legal Registered Address:**

GlaxoSmithKline Research & Development Limited  
 980 Great West Road  
 Brentford  
 Middlesex, TW8 9GS  
 UK

In some countries, the clinical trial sponsor may be the local GlaxoSmithKline Affiliate Company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

**INVESTIGATOR PROTOCOL AGREEMENT PAGE**

For protocol number FDC116114

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 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 Address:      |      |
| Investigator Phone Number: |      |
|                            |      |
| Investigator Signature     | Date |



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# 1. PROTOCOL SYNOPSIS FOR STUDY FDC116114

## Rationale

The rationale for developing an instrument to screen populations of men for lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) is that it may help a General Practitioners (GP) to identify patients who may have BPH for further tests and improve the speed of referrals to specialists when this is appropriate. Symptomatic BPH is present in 40 – 60% of men over the age of 50 and prevalence rises with age. It is known that men with LUTS may be reluctant to discuss these symptoms with their GP, and that GPs do not routinely proactively ask about LUTS when men present for other complaints. As a result, many men with BPH present late with more severe symptoms. As a result up to 70% of men may have moderate to severe BPH at their initial diagnosis. The recent D-IMPACT study confirmed that GPs can accurately diagnose BPH in around 75% of men presenting with LUTS, using simple tests. A Benign Prostatic Enlargement (BPE)/Benign Prostatic Obstruction (BPO) screening tool which identifies LUTS probably due to BPH in men not yet presenting with LUTS would provide an opportunity to proactively assess men who do not present with LUTS. BPH is a progressive condition and identifying men at risk of progression is important to allow their treatment to be optimised. Furthermore the utility of the screening tool will be compared to the validated tool in wide clinical use, the International Prostate Symptom Score (IPSS).

## Objective(s)/Endpoint(s)

| Objectives  | Endpoints   |
|---|---|
| <b>Primary</b>  |   |
| To assess the utility of a BPE/BPO screening tool in conjunction with serum prostate specific antigen (PSA) in finding men confirmed to have BPH on full urologist assessment of diagnostic test results.   | Proportion of men that are confirmed to have BPH based on full urologist assessment of diagnostic test results among men with a positive result on the BPE/BPO screening tool (score $\geq 3$ ) and serum PSA $\geq 2$ ng/mL.   |
| <b>Secondary</b>  |   |
| <ul style="list-style-type: none"> <li>To assess the utility of a BPE/BPO screening tool in conjunction with serum PSA in finding men with risk of BPH Progression on full urologist assessment of diagnostic test results.</li> <li>To assess the utility of a BPE/BPO screening tool in finding men diagnosed with probable BPH as assessed by the GP.</li> <li>Compare the utility of the BPE/BPO screening tool with the International Prostate Symptom Score (IPSS) screening tool.</li> </ul> | <ul style="list-style-type: none"> <li>Proportion of men that are confirmed to be a risk for BPH progression based upon full urologist assessment among men with a positive result on the BPE/BPO screening tool (score <math>\geq 3</math>) and serum PSA <math>\geq 2</math> ng/mL.</li> <li>Proportion of men that are diagnosed with probable BPH<sup>1</sup> as assessed by the GP among men with a positive result on the BPE/BPO screening tool (score <math>\geq 3</math>).</li> <li>Agreement (using Kappa statistic for categories) between the BPE/BPO screening tool assessment (score <math>\geq 3</math>) and an IPSS score approach (score <math>\geq 8</math>) in selecting men to investigate for BPH).</li> </ul> |
| <sup>1</sup> Probable BPH is the presumptive diagnosis of urinary tract obstruction from an enlarged prostate based on clinical symptoms and findings where urinary symptoms are not apparently related to any other cause.   |   |



## Overall Design

- This study will evaluate the utility of the Benign Prostatic Enlargement (BPE)/ Benign Prostatic Obstruction (BPO) screening tool in a general practice setting where the results of this screening tool will be used for further investigation. Therefore in this study, all men testing positive on the BPE/BPO screening tool (score  $\geq 3$ ) tool or on the IPSS (score  $\geq 8$ ) will be enrolled and offered a prostate specific antigen (PSA) test and urinalysis to establish a diagnosis of probable benign prostatic hyperplasia (BPH) (Part I – Visit 1). The General Practitioner (GP) may perform a DRE (digital rectal examination), however the DRE will be repeated by the urologist to confirm the diagnosis and to rule out an abnormality suggesting prostate cancer. The GP will make a diagnosis of probable BPH based upon screening results and lab tests which suggest that they are related to BPH and not other causes of such symptoms.
- The GP will phone the subject to report yes or no for probable BPH Part II (Visit 2). If the subject has probable BPH, the GP will schedule the subject for Visit 3 with a urologist. If the subject does not have probable BPH, then the subject has completed the study.
- Subjects that proceed to Part II (Visit 3) will be scheduled for a urology assessment performed by a urologist. This assessment includes a DRE and a brief physical exam and review of the PSA test, for a confirmatory diagnosis of BPH and estimation of risk of progression of BPH.

## Treatment Arms and Duration

- Approximately 1,500 males presenting to a GP with a primary complaint other than LUTS will be screened for probable BPH to yield 500 subjects being referred to a urologist.
- The duration of the study will be 1 week ( $\pm 4$  days) and up to 6 weeks to allow for GP and urologist visit scheduling.
- There is no study drug in this study.

## Type and Number of Subjects

- Approximately 1,500 males  $\geq 50$  years presenting to a GP for reasons unrelated to this study will be screened for probable BPH to yield 500 subjects being referred to a urologist.

## Analysis

- The primary endpoint is defined as the proportion of men that are confirmed to have BPH based on full urologist assessment of diagnostic test results among men with a positive result on the BPE/BPO screening tool and probable BPH diagnosis as assessed by the GP. For this proportion, the numerator is number of subjects diagnosed with BPH by a urologist; denominator is number of subjects with a positive result on the BPE/BPO screening tool and a probable BPH assessment by

the GP and a BPH assessment by the urologist. The 95% confidence interval for this proportion will be presented.

- Sufficient general practice centres (50 consecutive men per centre) in various markets will be recruited to administer the BPE/BPO screening tool to 1,500 men (using protocol defined criteria) presenting to clinic for reasons unrelated to the study. It is expected that 33% of the 1,500 presenting (or approximately 500) will have a positive result on the BPE/BPO screening tool and a probable BPH assessment by GP and thus will be assessed by a urologist.
- Due to the design of the study and types of endpoints incorporated, ‘observed cases’ will be summarized for a subset of subjects in study Parts I and II. There will be no imputations for missing data or for discontinued subjects.
- An interim analysis is not planned for this study.

## 2. INTRODUCTION

- This study will evaluate the utility of the Benign Prostatic Enlargement (BPE)/ Benign Prostatic Obstruction (BPO) screening tool in a general practice setting where the results of the BPE/BPO screening tool will be used for further investigation. Therefore in this study, all men testing positive with the BPE/BPO tool (score  $\geq 3$ ) and/or on the IPSS (score  $\geq 8$ ) will be enrolled and offered a prostate specific antigen (PSA) test and urinalysis to help establish a diagnosis of probable benign prostatic hyperplasia (BPH) (Part I – Visit 1). The GP may perform a DRE, however the DRE will be repeated by the urologist to confirm the diagnosis and to rule out an abnormality suggesting prostate cancer.
- The GP will phone the subject to report yes or no for probable benign prostatic hyperplasia (BPH) Part II (Visit 2). If the subject has probable BPH, the GP will schedule the subject for Visit 3 with a urologist. If the subject does not have probable BPH, then the subject has completed the study.
- For those subjects that proceed to Part II (Visit 3) they will be scheduled for a urology assessment performed by a urologist. This assessment includes DRE and a brief physical exam with review of the PSA test, for a confirmatory diagnosis of BPH and estimation of risk of progression of BPH.

### 2.1. Study Rationale

The rationale for developing an instrument to screen populations of men for lower urinary tract symptoms (LUTS) due to BPH is that it may help a GP to identify patients who may have BPH for further tests and improve the speed of referrals to specialists when this is appropriate. Symptomatic BPH is present in 40 – 60% of men over the age of 50 and prevalence rises with age (Emberton, 2003). It is known that men with lower urinary tract symptoms (LUTS) may be reluctant to discuss these symptoms with their GP, and that GPs do not routinely proactively ask about LUTS when men present for other complaints. As a result, many men with BPH present late with more severe symptoms. As a result, up to 70% of men may have moderate to severe BPH at their initial diagnosis. The recent D-IMPACT study confirmed that GPs can accurately

diagnose BPH in around 75% of men presenting with LUTS, using simple tests (Carballido, 2011). A simple screening tool which identifies LUTS probably due to BPH in men not yet presenting with LUTS would provide an opportunity to proactively identify and potentially treat men who do not present with LUTS as their primary complaint. It is important to identify BPH early. BPH is a progressive condition and identifying men at risk of progression is important to allow their treatment to be optimised (Fitzpatrick, 2006). Furthermore the utility of screening tool will be compared to a validated tool in wide clinical use, the International Prostate Symptom Score (IPSS).

## 2.2. Brief Background

Symptomatic BPH is present in 40 – 60% of men over the age of 50 and prevalence rises with age (Emberton, 2003). It is known that men with LUTS may be reluctant to consult, and that GPs do not proactively ask about LUTS when men present for other co-morbidities. As a result many men present late, and up to 70% of men may have moderate to severe BPH at diagnosis. Some of these men may have an increased prostate volume (>30 cc) and a prostate specific antigen (PSA)  $\geq 1.5$  ng/mL, and therefore be at risk of progression (Roehrborn, 2007). Under European Association of Urology (EAU) guidelines, these men may be suitable for treatments targeted to the underlying cause of the disease.

The International Prostate Symptom Score (IPSS) score is well validated as a tool to assess the severity of LUTS symptoms, and has similarly been used for assessing symptomatic efficacy of treatments for BPH (Roehrborn, 2008). Nevertheless this tool was not developed as a diagnostic tool for BPH. Furthermore, GPs are reluctant to use the IPSS because it takes time away from other problems and extends the patient visit time and may require other staff to implement. An abbreviated diagnostic tool would therefore assist the GP in diagnosis and timely referral to a urologist.

A screening tool which identifies LUTS probably due to BPH in men presenting for reasons unrelated to the study would provide an opportunity to proactively assess men who may not consider presenting with these symptoms. BPH is a progressive condition and identifying men at risk of progression is important to allow their treatment to be optimised (Fitzpatrick, 2006).

### 3. OBJECTIVE(S) AND ENDPOINT(S)

| Objectives   | Endpoints  |
|--|--|
| <b>Primary</b>   |  |
| To assess the utility of a BPE/BPO screening tool in conjunction with PSA in finding men confirmed to have BPH on full urologist assessment of diagnostic test results.  | Proportion of men that are confirmed to have BPH based on full urologist assessment of diagnostic test results among men with a positive result on the BPE/BPO screening tool and tool (score $\geq 3$ ) and serum PSA $\geq 2$ ng/mL.   |
| <b>Secondary</b>   |  |
| <ul style="list-style-type: none"> <li>• To assess the utility of a BPE/BPO screening tool in conjunction with PSA in finding men with risk of BPH Progression on full urologist assessment of diagnostic test results.</li> <li>• To assess the utility of a BPE/BPO screening tool in finding men diagnosed with probable BPH as assessed by the GP.</li> <li>• Compare the utility of the BPE/BPO screening tool with the IPSS screening tool.</li> </ul> | <ul style="list-style-type: none"> <li>• Proportion of men that are confirmed to be a risk for BPH progression based upon full urologist assessment among men with a positive result on the BPE/BPO screening tool and probable GP BPH diagnosis.</li> <li>• Proportion of men that are diagnosed with probable BPH<sup>1</sup> as assessed by the GP among men with a positive result on the BPE/BPO screening tool (score <math>\geq 3</math>).</li> <li>• Agreement (using Kappa statistic for categories) between the BPE/BPO screening tool assessment (score <math>\geq 3</math>) and an IPSS score approach (score <math>\geq 8</math>) in selecting men to investigate for BPH.</li> </ul> |
| <sup>1</sup> Probable BPH is the presumptive diagnosis of urinary tract obstruction from an enlarged prostate based on clinical symptoms and findings where urinary symptoms are not apparently related to any other cause.  |  |

### 4. STUDY DESIGN

This non-randomized, interventional study utilizing a questionnaire-based assessment of men in General Practice. Validation of the tool was performed in a previous GlaxoSmithKline (GSK) study (FDC116700: Quick Question Tool Development and Linguistic Validation). Men who sign the informed consent form and meet the eligibility criteria will be enrolled and complete the Part I diagnostic tests at the GP clinic. If the GP determines that the subject has probable BPH (IPSS  $\geq 8$  and/or BPE/BPO questionnaire  $\geq 3$  with a PSA  $\geq 2$  ng/ml), the subject proceeds to Part II and is scheduled for a urologist assessment and diagnostic tests to confirm or refute a BPH diagnosis and to assess risk of progression of BPH.

#### 4.1. Overall Design

This study is intended to reproduce the circumstances in which the BPH quick tool will be used in General Practice, i.e., in men that may have ‘hidden’ LUTS symptoms. To reproduce these circumstances of opportunistic screening, men will not be invited to attend their GP but **must attend spontaneously with for reasons that are not related to this study**. At this point they will be invited to participate in the study.

GPs participating in the study will recruit men  $\geq 50$  years that present in their clinic for reasons that are not related to this study.

After obtaining informed consent, the GP will initially assess all inclusion and exclusion criteria except for the questionnaire inclusion criterion. If the subject meets those eligibility requirements, the GP administers the BPE/BPO and IPSS screening tools. Subjects who have a positive score on the BPE/BPO screening tool (total score  $\geq 3$ ) and/or the IPSS tool (score  $\geq 8$ ) and meet all other eligibility requirements will be enrolled in Part I of the study. The GP then performs the following diagnostic tests for Part I of the study: urinalysis (sample sent to local lab if the strip test is positive) and Prostate Specific Antigen (PSA) blood test. If the serum PSA result is  $\geq 2$  ng/mL, the GP will make a diagnosis of ‘probable BPH (subjects with symptoms likely to be related to BPH)’ or not. All men with ‘probable BPH’ will proceed to Part II and will be scheduled for Visit 3 with a urologist for confirmation of the GP’s findings plus a brief physical exam and DRE. Additional testing may be performed as per standard of care to assist with a confirmatory diagnosis such as a DRE, however this is not required by the protocol.

The urologist is to:

1) Establish a clinical diagnosis of BPH

AND

2) Estimate whether the patient is at risk of progression of BPH (PSA  $\geq 2.0$  ng/mL and other testing).

For the purposes of this study the diagnosis of the urologist (BPH yes/no) is the operational definition of confirmed BPH. Those men refusing referral to the urologist, but considered by a GP to have BPH (after the tests specified above) will be classified as ‘probable BPH’.

## Description of Visits:

## VISIT 1 (primary care clinic)

- Males  $\geq 50$  years visiting GP for reasons unrelated to the study
- Patient provides informed consent



Eligible to participate

- Inclusion/exclusion criteria confirmation
- Medical history and demography
- BPE/BPO and IPSS screening tools

If subject meets entry criteria, including a positive IPSS (score  $\geq 8$ ) and/or BPE/BPO (score  $\geq 3$ ).



ENROLLED: Subject is enrolled and proceeds to Part I (GP Assessment) of the study. If the GP diagnoses probable BPH, the subject will proceed to Part II (urologist assessment).

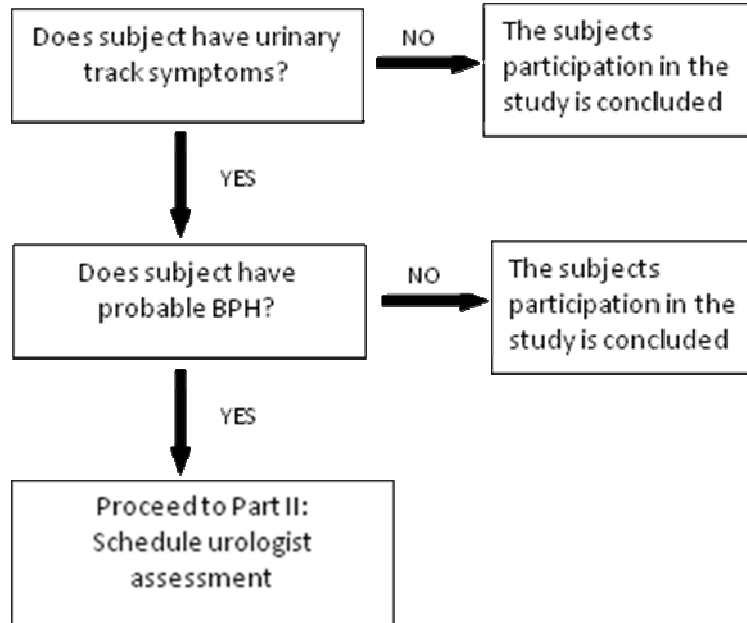
## PART I: GP Assessment

After being enrolled, complete the following at Visit 1:

- Urinalysis strip test.
  - If strip test is positive, send urine sample to local lab urinalysis.
- PSA blood test
- Additional testing may be performed as per standard of care to assist with a confirmatory diagnosis such as a DRE, however this is not required.

## VISIT 2 (telephone call)

- GP reviews urinalysis and PSA lab results.
- Call subject: If lab results show NO probable BPH, then subject will not continue in the study. If PSA lab results show PROBABLE BPH ( $\geq 2$  ng/mL), subject proceeds to Part II and Visit 3 is scheduled for the urologist assessment.



**VISIT 3 (Part II – urologist clinic visit)**

- Urologist reviews medical history and symptoms
- Brief physical examination
- DRE
- Review previous tests (BPE/BPO screening tool, IPSS screening tool, urinalysis, PSA)

**Urologist provides:**

- Confirmation of clinical diagnosis of BPH (or confirmation the subject does NOT have BPH).
- Estimate whether the patient is at risk of progression of BPH (PSA  $\geq$  2.0ng/mL and other tests).

- NOTE: Urologist may need to perform additional diagnostic testing as per standard of care and as needed to assess the BPH diagnosis. This follow-up is not prescribed by this protocol, however, any data collected that is used for the final diagnosis will be entered in the study case report form (CRF). Advice or treatment post study will be discretion of the GP or Urologist.

**4.2. Treatment Arms and Duration**

- Approximately 1,500 males presenting to a GP for a reason that is not related to this study will be screened for probable BPH to yield 500 subjects being referred to a urologist.
- The duration of the study will be 1 week ( $\pm$  4 days) and up to 6 weeks to allow for GP and urologist visit scheduling.

There is no study drug in this study.



### **4.3. Type and Number of Subjects**

Approximately 1,500 males presenting to a GP for reasons unrelated to this study will be screened for probable BPH to yield 500 subjects being referred to a urologist.

### **4.4. Design Justification**

The BPE/BPO screening tool has been developed using the currently recommended FDA guidelines ([Food and Drug Administration](#), 2009) for developing patient-completed questionnaires such as Patient Reported Outcomes. The tool to be used in this study in the General Practice setting has undergone validation in a urology setting to demonstrate the validity of the tool in populations with and without a definite diagnosis of BPH (GSK Study FDC116700). The FDC116700 study demonstrated that the most effective have been observed by screening patients with BPE/BPO items with a threshold score  $\geq 3$  and then testing such patients with PSA. With total PSA greater than or equal to 2 the combination screener/PSA shows a sensitivity of 83.8% and a specificity of 74.0%, with an accuracy of 80.1%.

### **4.5. Dose Justification**

No investigational study drug will be used in this study.

### **4.6. Benefit:Risk Assessment**

The following section outlines the risk assessment and mitigation strategy for this protocol:

**4.6.1. Risk Assessment**

| Potential Risk of Clinical Significance   | Summary of Data/Rationale for Risk                              | Mitigation Strategy   |
|---|---|---|
| <b>Study Procedures</b>   |   |   |
| Urine strip test  | Routine and minimal risk  | Serious adverse events (SAEs) are monitored via automated emails and adverse events (AEs) are reviewed on a routine basis to identify any procedure related events. |
| PSA blood test:<br><br>The risks of taking blood include pain, a bruise at the point where the blood is taken, redness and swelling of the vein and infection, and a rare risk of fainting. | Routine and minimal risk  | SAEs are monitored via automated emails and AEs are reviewed on a routine basis to identify any procedure related events.   |
| DRE:  | Routine and minimal risk. Procedure used in evaluation for BPH. | SAEs are monitored via automated emails and AEs are reviewed on a routine basis to identify any procedure related events.   |
| Urologist physical examination  | Routine and minimal risk. Procedure used in evaluation for BPH. | Performed by a urologist.<br><br>SAEs are monitored via automated emails and AEs are reviewed on a routine basis to identify any procedure related events.          |

#### 4.6.2. Benefit Assessment

Subjects could benefit from this study by having the protocol-specified assessments and procedures performed. It is possible that undiagnosed BPH could be identified.

#### 4.6.3. Overall Benefit:Risk Conclusion

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with the procedures to be performed in this study are justified by the anticipated benefits that may be afforded to subjects who may have undiagnosed BPH.

### 5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the Informed Consent Form.

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. Therefore, adherence to the criteria as specified in the protocol is essential.

#### 5.1. Inclusion Criteria

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

|  |
|--|
| AGE  |
| 1. Greater than or equal to 50 ( $\geq 50$ ) years of age at the time of signing the informed consent form.  |
| SEX  |
| 2. Male  |
| INFORMED CONSENT   |
| 3. Capable of giving signed informed consent as described in Section 9.2 which includes compliance with the requirements and restrictions listed in the consent form and in this protocol. |
| OTHER  |
| 4. Present in a General Practice setting for a reason unrelated to this study.   |
| 5. Positive IPSS score ( $\geq 8$ ) and/or positive BPE/BPO screening tool score ( $\geq 3$ ).   |

## 5.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

### CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)

1. History of BPH for which they have received test procedures, medical intervention and/or medicine.
2. History of prostate-related LUTS for which they have received test procedures, medical intervention and/or medicine.
3. History of prostatic surgery (including transurethral resection of the prostate [TURP], balloon dilatation, thermotherapy, and/or stent replacement) or other invasive or minimally invasive procedures to treat BPH.
4. Has other conditions that may cause urinary symptoms (e.g., neurogenic bladder, bladder neck contracture, urethral stricture, bladder malignancy, acute or chronic prostatitis, or acute or chronic urinary tract infections, etc.).
5. History or evidence of prostate cancer (e.g., positive biopsy or ultrasound, suspicious DRE and/or rising PSA).

### CONCOMITANT MEDICATIONS

6. Current or prior use of the following:
  - a. 5 $\alpha$ -reductase inhibitors (finasteride or dutasteride),
  - b. anti-cholinergics (e.g. oxybutynin, propantheline, tolterodine, solifenacin, darifenacin, mirabegron) alpha-adrenoreceptor blockers (i.e., indoramin, prazosin, terazosin, tamsulosin, alfuzosin, doxazosin and silodosin), herbal products for urinary symptoms.
  - c. Use of any investigational study drug within 30 days or 5 half-lives of the drug in question, (whichever is longer), preceding the first study visit.
7. Use within previous 30 days at Visit 1 of:
  - a. PDE-5 inhibitors for erectile dysfunction
  - b. anabolic steroids

## 5.3. Screening/Baseline/Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but do not meet eligibility criteria and are not subsequently enrolled. In order to ensure transparent reporting of screen failure subjects, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure details, Eligibility Criteria, and Serious Adverse Events (see Section 6.3.1.3). Data for screen failures will be collected in source information at the site and will be transmitted to GSK.

Subjects will be screen failures if they do not meet inclusion/exclusion criteria and do not have a qualifying score on at least one of the two questionnaires (BPE/BPO and/or IPSS screening tools).

#### **5.4. Withdrawal/Stopping Criteria**

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed ‘lost to follow up’, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject’s last known mailing address or local equivalent methods). These contact attempts should be documented in the subject’s medical record.
- Should the subject continue to be unreachable, only then will he be considered to have withdrawn from the study with a primary reason of “Lost to Follow-up”.

A subject may withdraw from study treatment at any time at his own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. If a subject withdraws from the study, he may request destruction of any samples taken, and the investigator must document this in the site study records.

#### **5.5. Subject and Study Completion**

A completed subject is one who has completed all study visits.

The end of the study is defined as the last subject’s last visit.

#### **5.6. Concomitant Medications and Non-Drug Therapies**

##### **5.6.1. Permitted Medications and Non-Drug Therapies**

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

##### **5.6.2. Prohibited Medications and Non-Drug Therapies**

Use of prohibited medications, as stated in the exclusion criteria, could potentially affect the value of the data collected. If there is no option other than to administer a prohibited medication, please if possible discuss the procedure with your monitor before administration.

Prohibited medications:

- $5\alpha$ -reductase inhibitors (finasteride or dutasteride),
- anti-cholinergics (e.g. oxybutynin, propantheline, tolterodine, solifenacin, darifenacin, mirabegron) alpha-adrenoreceptor blockers (i.e., indoramin, prazosin, terazosin, tamsulosin, alfuzosin, doxazosin and silodosin), herbal products for urinary symptoms.
- PDE-5 inhibitors for erectile dysfunction
- anabolic steroids

## **6. STUDY ASSESSMENTS AND PROCEDURES**

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.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section [6.1](#)

## 6.1. Time and Events Table

| Procedure   | VISIT 1:<br>Screening/<br>Enrolment at GP Clinic | Study Period<br>(1 week $\pm$ 4 days to 6 weeks) |   |
|---|--|--|---|
|   |  | VISIT 2 (phone call):<br>GP                      | VISIT 3: Urologist <sup>6</sup><br>(up to 6 weeks after V1) |
| Informed consent  | X  |  |   |
| Inclusion and exclusion criteria  | X  |  |   |
| Demography  | X  |  |   |
| Medical history   | X  |  |   |
| Concomitant medications (all ongoing and within 30 days prior to Visit 1)       | X  |  |   |
| IPSS screening tool   | X  |  |   |
| BPE/BPO screening tool  | X  |  |   |
| <b>PROCEDURES AFTER SUBJECT IS ENROLLED<sup>1</sup>:</b>                        |  |  |   |
| Urine strip test <sup>2</sup>   | X  |  |   |
| Urinalysis (only if urine strip test is positive) <sup>2</sup>                  | X  |  |   |
| PSA blood test <sup>3</sup>   | X  |  |   |
| Results phone call to subject <sup>4</sup>                                      |  | X  |   |
| Digital rectal exam (DRE) <sup>5</sup>  | X  |  | X   |
| Brief physical examination  |  |  | X   |
| Enter prostate-related results in the CRF from non-protocol required procedures |  |  | X   |
| AE/SAE review (related to study procedures and/or participation)                |  | ←=====→  |   |
| Concomitant medication review   |  | ←=====→  |   |

1. Subject is enrolled after meeting eligibility requirements, which includes a positive BPE/BPO screening tool and/or positive IPSS screening tool.
2. Urinalysis sent to local laboratory only if urine strip test is positive.
3. PSA blood test sent to local lab. Local lab results and reference ranges are entered in the CRF.
4. For Visit 2, the GP calls the subject to report yes or no for probable BPH. If the subject has probable BPH, the GP schedules the subject for Visit 3 with the urologist. If the subject does not have probable BPH, then the subject has completed the study.
5. DRE is performed by the urologist. The GP may conduct a DRE at visit 1 however the DRE will be repeated by the urologist to confirm the diagnosis and to rule out an abnormality suggesting prostate cancer..
6. Information collected during visit 3 will be entered into the eCRF by the Principal Investigator.

## 6.2. Screening and Critical Baseline Assessments

The following demographic parameters will be captured: year of birth, and sex.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.

Patient Reported Outcomes questionnaires should be completed by subjects before any other assessment at a clinic visit, in the order specified.

## 6.3. Safety

### 6.3.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in Section 11.2.

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

#### 6.3.1.1. Time period and Frequency for collecting AE and SAE information

- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- Medical occurrences that begin after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Section 11.2.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Section 11.2.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- “How are you feeling?”
- “Have you had any (other) medical problems since your last visit/contact?”
- “Have you taken any new medicines, other than those provided in this study, since your last visit/contact?”



### **6.3.1.2. Follow-up of AEs and SAEs**

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs (as defined in Section 6.3.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.4). Further information on follow-up procedures is given in Section 11.2.

### **6.3.1.3. Regulatory Reporting Requirements for SAEs**

Prompt notification by the investigator to GSK or designee of SAEs related to study treatment or related to a GSK product 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.

### **6.3.2. Physical Exams**

- The urologist will perform a brief physical exam.
- Investigators should pay special attention to clinical signs related to previous serious illnesses

### **6.3.3. Clinical Safety Laboratory Assessments**

All protocol required laboratory assessments, must be conducted in accordance with the local laboratory requirements and Protocol Time and Events Schedule.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification) the results must be recorded in the CRF.

Refer to the study reference manual (SRM) for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

All study-required laboratory assessments will be performed by a local laboratory, apart from:

- Urinalysis strip test

If the urinalysis test strip is positive, then the sample is sent to a local lab for urinalysis.

The results of each test and reference ranges must be entered in the CRF.

PSA chemistry and urinalysis are listed in [Table 1](#).

**Table 1 Protocol Required Safety Laboratory Assessments**

| Laboratory Assessments | Parameters  |
|------------------------|---|
| Routine Urinalysis     | <ul style="list-style-type: none"> <li>• Urinalysis strip test</li> <li>• If strip test is positive, send sample to local lab for urinalysis</li> </ul> |
| PSA Chemistry          | <ul style="list-style-type: none"> <li>• Submit blood sample to local lab for PSA analysis.</li> </ul>  |

### 6.3.4. Urine Sample Collection

A urine strip test will be performed at screening. If the dipstick is positive, a urine sample will be submitted to the local laboratory for urinalysis. Please see the time points listed in Section [6.1 Time and Events Table](#). Results and reference ranges will be entered in the CRF.

## 7. DATA MANAGEMENT

- For this study, subject data will be entered into GSK defined electronic CRFs, transmitted electronically to GSK or designee, 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 terms and concomitant medications will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.
- CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

## 8. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

### 8.1. Hypotheses

The primary endpoint is defined as the proportion of men confirmed to have BPH based on full urologist diagnostic testing in men with a positive result on the BPE/BPO screening tool and a probable BPH assessment by GP. Primary endpoint summaries will be descriptively presented in terms of the calculated proportion, described below, and 95% confidence interval on the proportion. Formal hypothesis testing will not be conducted in terms of the primary and secondary endpoint proportions.

### 8.2. Sample Size Considerations

Sufficient general practice centres (approximately 50 subjects per centre) in the various markets will be recruited to administer the BPE/BPO screening tool to 1,500 men using protocol defined criteria presenting to clinic. It is expected that 33% of the 1,500 presenting (or approximately 500) will have a positive result on the BPE/BPO and/or IPSS screening tools and a probable BPH assessment by GP and thus will be assessed by a urologist.

Evaluation of 500 subjects by a urologist will allow estimation of a 95% confidence interval on the primary endpoint proportion with a maximum width of  $\pm 0.044$ . Sample size assumptions are in terms of the binominal distribution with the proportion of urologist confirmed BPH diagnosis most conservatively assigned at 0.50. Using these assumptions, the following provides an overview of other possible sample sizes along with projected 95% confidence interval maximum width.

| Number of Subjects Evaluated by Urologist | Maximum Width of a 95% Confidence Interval |
|---|--|
| 300                                       | $\pm 0.057$                                |
| 500                                       | $\pm 0.044$                                |
| 700                                       | $\pm 0.037$                                |

Sample size re-estimation is not planned.

### 8.3. Data Analysis Considerations

#### 8.3.1. Analysis Populations

Subjects are not randomized or dispensed study treatment. As designed in the protocol, the number of subjects will decrease from the screening period to GP Assessment (Part I) and then again in the subsequent Urologist Assessment (Part II) either due to not qualifying for progression to the next part of the study or due to any withdrawal.

The decreases, along with planned multiple summary and analysis types, will impact and restrict the evaluable population for a given endpoint. Therefore, populations are not defined in the traditional sense. Rather, for each reported summary statistic and analyses,

the subset of subjects and/or denominators will be clearly defined in the Reporting and Analysis Plan (RAP).

- Due to the design of the study and types of endpoints incorporated, ‘observed cases’ will be summarized. For the primary analyses, there will be no imputations for missing data, no imputations for missing responses within the BPE/BPO or IPSS screening tools, and no imputations for subjects withdrawing from the study or not qualifying for a subsequent part of the study.

Any pre-planned exclusions from analysis, such as for protocol deviations, will be defined in the RAP.

### **8.3.2. Interim Analysis**

An interim analysis is not planned for this study.

### **8.3.3. Multiplicity**

All pre-planned summary statistics and hypothesis testing results will be presented. There are no established controls for interpretation of the multiple outputs.

## **8.4. Key Elements of Analysis Plan**

Data will be listed and summarized according to 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 the protocol will be documented in the RAP and final study report.

### **8.4.1. Population Descriptive Statistics**

Numbers of subjects participating in the study will be summarized for each study period: Screening, GP Assessment (Part I), and Urologist Assessment (Part II). Numbers of subjects who do not continue to a subsequent study period, along with reason, will be summarized.

Summary statistics for CRF collected demography, medical history, and medical evaluations collected by the GP and urologist will be summarized, as applicable, for each study period.

### **8.4.2. Primary Analyses**

The primary endpoint is defined as the proportion of men confirmed to have BPH based on full urologist diagnostic testing among men with a positive result on the BPE/BPO screening tool (score  $\geq 3$ ) and serum PSA  $\geq 2$  ng/mL. Primary endpoint summaries will be descriptively presented in terms of the calculated proportion, described below, and 95% confidence interval on the proportion. Formal hypothesis testing will not be conducted.

| Tool        | Proportion  | Numerator  | Denominator  |
|-------------|---|--|--|
| BPE/<br>BPO | BPH Diagnosis by Urologist based upon BPE/BPO screening tool (score $\geq 3$ ) and serum PSA $\geq 2$ ng/mL | Number of subjects diagnosed with BPH based on full urologist diagnostic testing | Number of subjects with a positive result on the BPE/BPO screening tool (score $\geq 3$ ) and serum PSA $\geq 2$ ng/mL and a BPH assessment by urologist |

### 8.4.3. Secondary Analyses

Secondary endpoints and other measures of interest are defined in terms of proportions for each: probable BPH diagnosis by GP, BPH diagnosis by urologist, and BPH progression risk by urologist along with use of 1) BPE/BPO screening tool and 2) IPSS screening tool. These proportions will be calculated in terms of the numerators and denominators shown below; the 95% confidence intervals for these proportions will be presented.

| Secondary Endpoints: Proportions only in terms of the BPE/BPO tool |  |   |   |
|--|--|---|---|
| Tool   | Proportion   | Numerator   | Denominator   |
| BPE/<br>BPO  | BPH Progression Risk by Urologist based upon BPE/BPO screening tool (score $\geq 3$ ) and serum PSA $\geq 2$ ng/mL | Number of subjects diagnosed with BPH progression risk by urologist | Number of subjects with a positive result on the BPE/BPO screening tool (score $\geq 3$ ) and serum PSA $\geq 2$ ng/mL and a BPH progression risk assessment by urologist |
| BPE/<br>BPO  | Probable BPH Diagnosis by GP based upon BPE/BPO screening tool (score $\geq 3$ )                                   | Number of subjects diagnosed with 'probable BPH' by GP              | Number of subjects with a positive result on the BPE/BPO screening tool (score $\geq 3$ ) and a BPH assessment by GP  |

| Secondary Endpoints: Proportions only in terms of the IPSS screening tool |  |  |   |
|---|--|--|---|
| Tool  | Proportion   | Numerator  | Denominator   |
| IPSS  | BPH Diagnosis by urologist based upon IPSS (score $\geq 8$ ) and serum PSA $\geq 2$ ng/mL        | Number of subjects diagnosed with BPH based on full urologist diagnostic testing | Number of subjects with a positive result on the IPSS (score $\geq 8$ ) and serum PSA $\geq 2$ ng/mL and a BPH assessment by urologist                  |
| IPSS  | BPH Progression Risk by urologist based upon IPSS (score $\geq 8$ ) and serum PSA $\geq 2$ ng/mL | Number of subjects diagnosed with BPH progression risk by urologist              | Number of subjects with a positive result on the IPSS (score $\geq 8$ ) and serum PSA $\geq 2$ ng/mL and a BPH progression risk assessment by urologist |
| IPSS  | Probable BPH Diagnosis by GP based upon IPSS (score $\geq 8$ )                                   | Number of subjects diagnosed with 'probable BPH' by GP                           | Number of subjects with a positive result on the IPSS (score $\geq 8$ ) and a BPH assessment by GP  |

Additional summaries, proportions and related 95% confidence intervals, will be generated as outlined above, but in terms of a positive result for both the BPE/BPO and the IPSS screening tools.

Another secondary endpoint of this study is to assess the level of agreement between the BPE/BPO and/or IPSS screening tools for selecting men to investigate for BPH. The number and proportion of subjects with a positive or with a negative response to both the BPE/BPO and IPSS screening tools at screening will be summarized.

Agreement of the BPE/BPO and the IPSS screening tools will be assessed using the kappa coefficient. The simple kappa coefficient along with the 95% confidence interval will be generated using SAS along with hypothesis testing. The associated null hypothesis is that the two measures (BPE/BPO and IPSS screening tools) are independent, i.e.,  $\kappa = 0$ . The alternative hypothesis is that the agreement of the two measures is better than one would expect by chance. Two-sided tests of the null hypothesis will be conducted at the 0.05 level of significance.

The above defined kappa coefficient will be characterized as proposed by Landis and Koch (Landis, 1977) with  $<0$  indicating no agreement, 0-0.20 as slight, 0.21-0.40 as fair, 0.41-0.60 as moderate, 0.61-0.80 as substantial, and 0.81 – 1 as almost perfect agreement.

The proportion of men refusing further GP investigation among subjects with a positive BPE/BPO screening tool will be summarized. The proportion of subjects refusing referral to an urologist among subjects with a positive BPE/BPO screening tool and probable GP BPH diagnosis will be summarized.

The above described proportions, for both primary and secondary endpoints, will also be summarized by country.

## **9. STUDY GOVERNANCE CONSIDERATIONS**

### **9.1. Posting of Information on Publicly Available Clinical Trial Registers**

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

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

Prior to initiation of a site, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable

- Obtaining signed informed consent
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GPs and Urologists will be selected based on their medical qualifications and the capacity to perform study procedures per the protocol. No bias is expected as a result of this selection.
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study
- As a non-randomized study, subjects will be selected by the inclusion/exclusion criteria. No bias is expected as a result of this selection.

### **9.3. Quality Control (Study Monitoring)**

- In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site 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 also include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK will monitor the study and site activity to verify 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, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents

### **9.4. Quality Assurance**

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

## 9.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

## 9.6. Records Retention

- Following closure of the study, the investigator or the 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 maintained to allow easy and timely retrieval, 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 these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to 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 and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.
- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any



institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.

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

### **9.7. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers 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.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

## 10. REFERENCES

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## 11. APPENDICES

### 11.1. Appendix 1 – Abbreviations and Trademarks

#### Abbreviations

|         |  |
|---------|--|
| AE      | Adverse Event  |
| BPH     | Benign prostatic hyperplasia                             |
| BPE     | Benign prostatic enlargement                             |
| BPO     | Benign prostatic obstruction                             |
| CONSORT | Consolidated Standards of Reporting Trials               |
| CRF     | Case report form   |
| DRE     | Digital rectal examination                               |
| EAU     | European Association of Urology                          |
| GSK     | GlaxoSmithKline  |
| GP      | General Practitioner                                     |
| IPSS    | International Prostate Symptom Score (Version 2), I-PSS2 |
| LUTS    | Lower urinary tract symptoms                             |
| PSA     | Prostate specific antigen                                |
| RAP     | Reporting and analysis plan                              |
| SAE     | Serious adverse event                                    |
| SRM     | Study reference manual                                   |
| TURP    | Transurethral resection of the prostate                  |

|   |
|---|
| <b>Trademarks of the GlaxoSmithKline<br/>group of companies</b> |
| NONE  |

|   |
|---|
| <b>Trademarks not owned by the<br/>GlaxoSmithKline group of companies</b> |
| SAS   |

## 11.2. Appendix 2: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

### 11.2.1. Definition of Adverse Events

#### Adverse Event Definition:

- An AE is any untoward medical occurrence in a patient 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.

#### Events meeting AE definition 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 intensity 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).
- The signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

#### Events NOT meeting definition of an AE include:

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

**Events NOT meeting definition of an AE include:**

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.

**11.2.2. Definition of Serious Adverse Events**

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

**Serious Adverse Event (SAE) is defined as 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-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills 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**

NOTE:

- The term disability means a substantial disruption of a person's ability to conduct

|   |
|---|
| <b>Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:</b>   |
| <p>normal life functions.</p> <ul style="list-style-type: none"> <li>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</li> </ul>  |
| <b>e. Is a congenital anomaly/birth defect</b>  |
| <b>f. Other situations:</b>   |
| <ul style="list-style-type: none"> <li>Medical or scientific judgment 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.</li> <li>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</li> </ul> |
| <b>g. Is associated with liver injury <u>and</u> impaired liver function defined as:</b>  |
| <ul style="list-style-type: none"> <li>ALT <math>\geq</math> 3xULN and total bilirubin* <math>\geq</math> 2xULN (&gt;35% direct), <b>or</b></li> <li>ALT <math>\geq</math> 3xULN and INR** <math>&gt;</math> 1.5.</li> </ul> <p>* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT <math>\geq</math> 3xULN and total bilirubin <math>\geq</math> 2xULN, then the event is still to be reported as an SAE.</p> <p>** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.</p>                 |

### 11.2.3. Recording of AEs and SAEs

|   |
|---|
| <b>AEs and SAE Recording:</b>   |
| <ul style="list-style-type: none"> <li>When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.</li> <li>The investigator will then record all relevant information regarding an AE/SAE in the CRF</li> <li>It is <b>not</b> acceptable for the investigator to send photocopies of the subject's medical</li> </ul> |

**AEs and SAE Recording:**

records to GSK in lieu of completion of the GSK, AE/SAE CRF page.

- There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.
- Subject-completed Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study.
- Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer.
- The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

**11.2.4. Evaluating AEs and SAEs****Assessment of Intensity**

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

**Assessment of Causality**

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled

### Assessment of Causality

out.

- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his assessment.
- For each AE/SAE the investigator **must** document in the medical notes that he has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

### Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

#### 11.2.5. Reporting of SAEs to GSK

##### SAE reporting to GSK via electronic data collection tool

- Primary mechanism for reporting SAEs to GSK will be the electronic data collection



**SAE reporting to GSK via electronic data collection tool**

tool

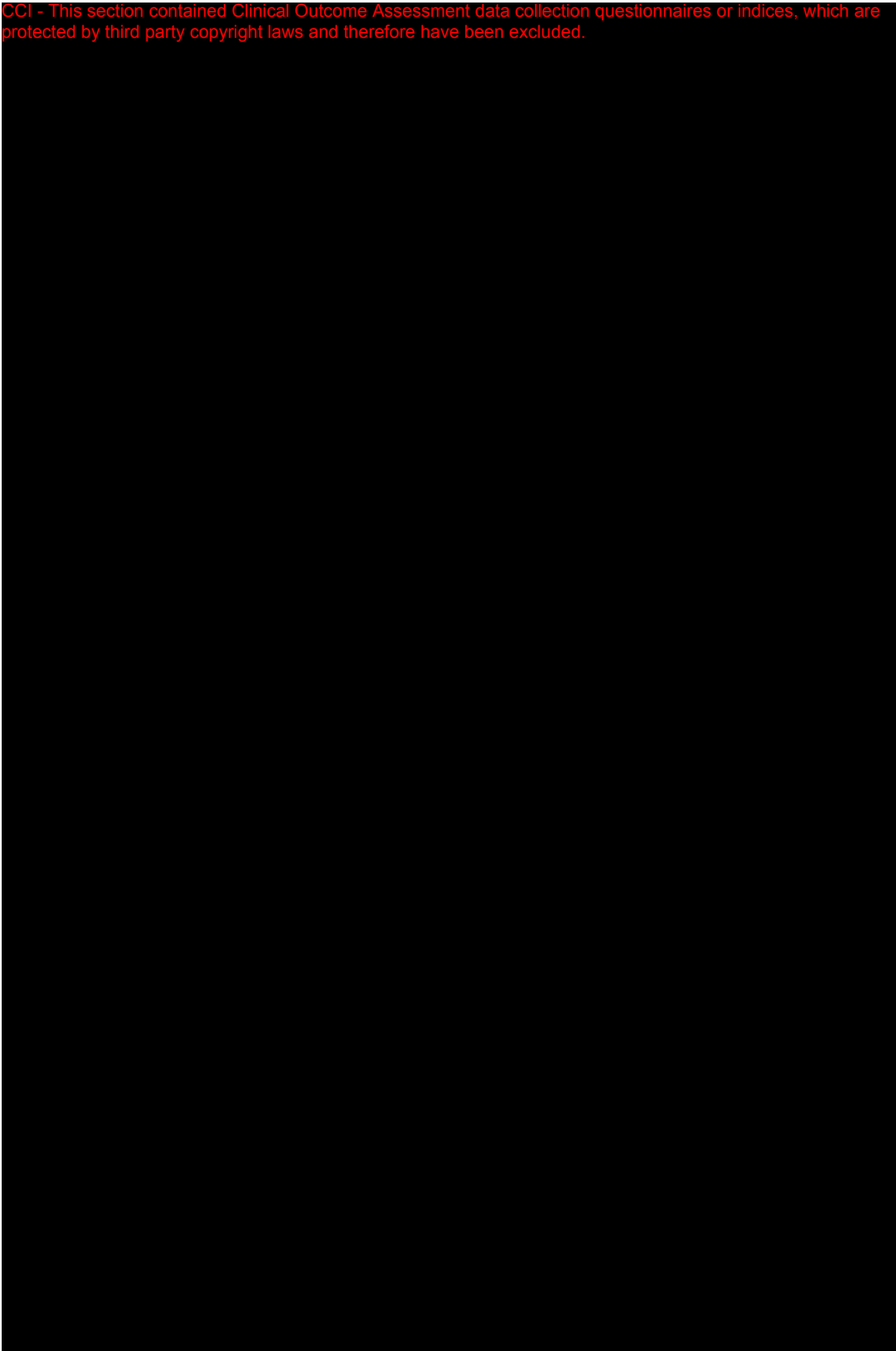
- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the SAE coordinator.
- Site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the CRF page within 72 hours of submission of the SAE.
- After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the SAE coordinator by telephone.
- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

### **11.3. Appendix 3 - Country Specific Requirements**

No country-specific requirements exist.

## 11.4. Appendix 4 – IPSS SCREENING TOOL

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.



## 11.5. Appendix 5 – SCREENER FOR PATIENTS WITH BENIGN PROSTATIC ENLARGEMENT/OBSTRUCTION (BPE/BPO)

### BPE/BPO-S (Version 1.0)

Screening questions for patients with benign prostatic enlargement/benign prostatic obstruction (BPE/BPO)

|                  |
|------------------|
| MAINSTREAM ITEMS |
|------------------|

Please ask the patient the following questions:

| In the last month HOW OFTEN... |   | Never | Rarely | Less than half of the time | About half of the time | More than half of the time | Always or almost always |
|--------------------------------|---|-------|--------|----------------------------|------------------------|----------------------------|-------------------------|
| 1                              | Have you found it difficult to start urinating if you held on for too long? | 0     | 1      | 2                          | 3                      | 4                          | 5                       |
| 2                              | Have you found it difficult to start urinating during the night?            | 0     | 1      | 2                          | 3                      | 4                          | 5                       |
| 3                              | Has your urinary stream been weaker at night?                               | 0     | 1      | 2                          | 3                      | 4                          | 5                       |

a) Please add the scores obtained on items 1, 2, 3 and write the total score in the box below

|               |             |
|---------------|-------------|
| Total BPE/BPO | Score _____ |
|---------------|-------------|

If the Score is 3 or more, test the patient for PSA

**11.6. Appendix 6 - Protocol Changes****AMENDMENT 1****Where the Amendment Applies**

This amendment applies to all sites participating in this study.

**Summary of Changes with Rationale**

- Deletion of compound numbers on the title page and the entering of “None”
- Deletion of the development status on the title page and entering “NA”
- Changing the study to an interventional study from non-interventional (Section 4)
- Deletion of the collection of race and ethnicity (Section 6.2)

**List of Specific Changes**

Changes are struck through and additions are underlined:

**TITLE PAGE**

PREVIOUS TEXT

**Compound Number:** GI198745+GI138525

**Development Phase:** IV

REVISED TEXT

**Compound Number:** ~~GI198745+GI138525~~ None

**Development Phase:** ~~IV~~ NA

Rationale for the changes: There are no compound numbers cited in the text, hence the value ‘None’ is used.

## Section 4 - Study Design

### PREVIOUS TEXT

This non-randomized, non-interventional study utilizing a questionnaire-based assessment of men in General Practice. Validation of the tool was performed in a previous GlaxoSmithKline (GSK) study (FDC116700: Quick Question Tool Development and Linguistic Validation).

### REVISED TEXT

This non-randomized, ~~non~~-interventional study utilizing a questionnaire-based assessment of men in General Practice. Validation of the tool was performed in a previous GlaxoSmithKline (GSK) study (FDC116700: Quick Question Tool Development and Linguistic Validation).

Rationale for the change: The study was changed from non-interventional to interventional based on the collection of urine and blood samples which is outside of normal medical practice for subjects presenting to their physician reasons that are not related to this study.

## Section 6.2 - Screening and Critical Baseline Assessments

### PREVIOUS TEXT

The following demographic parameters will be captured: year of birth, sex, race and ethnicity.

### REVISED TEXT

The following demographic parameters will be captured: year of birth, and sex. ~~, race and ethnicity.~~

Rationale for the change: Collection of this information is not required for the analysis of the study end points and therefore will not be collected.

## AMENDMENT 2

### Where the Amendment Applies

This amendment applies to all sites participating in this study.

### Summary of Changes with Rationale

- The study title has been revised to indicate the specific age criteria for men to be involved in the study.
- Deletion of phase IV to maintain consistency with title page.
- Included the DRE at all applicable sections of the protocol to confirm the diagnosis and to rule out an abnormality suggesting prostate cancer by urologist.
- Included the probable BPH criteria for clarity and to maintain consistency with other sections of protocol.
- Addition of herbal products for urinary symptoms under prohibited medications to exclude subjects that are receiving treatment of BPH symptoms.
- Modified the regulatory reporting requirements for SAEs to exclude GSK product as no product is to be investigated.
- Minor corrections and edits have been made throughout the protocol.

### List of Specific Changes

Changes are noted below with ~~strikethrough~~ to identify deleted text and underlining to identify new or replacement text.

#### TITLE PAGE

#### PREVIOUS TEXT

|               |  |
|---------------|--|
| <b>Title:</b> | Implementation of a screening tool for subjects with benign prostatic enlargement/obstruction to identify men 50 years presenting in General Practice with other co-morbidities who should be assessed for BPH |
|---------------|--|

#### REVISED TEXT

|               |   |
|---------------|---|
| <b>Title:</b> | Implementation of a screening tool for subjects with benign prostatic enlargement/obstruction to identify men <u>≥</u> 50 years presenting in General Practice with other co-morbidities who should be assessed for BPH |
|---------------|---|

Rationale for the changes: The change has been made for clarification of men age criteria.

## Protocol Synopsis

### Rationale

#### PREVIOUS TEXT

The rationale for developing an instrument to screen populations of men for lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) is that it may help General Practitioners (GPs) identify patients who may have BPH for further tests and improve the speed of referrals to specialists when this is appropriate.

#### REVISED TEXT

The rationale for developing an instrument to screen populations of men for lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) is that it may help a General Practitioners (GPs) to identify patients who may have BPH for further tests and improve the speed of referrals to specialists when this is appropriate.

### Overall Design

#### PREVIOUS TEXT

- This is a Phase IV study that will test the utility of the Benign Prostatic Enlargement (BPE)/ Benign Prostatic Obstruction (BPO) screening tool in a general practice setting where the results of this screening tool will be used for further investigation. Therefore in this study, all men testing positive on the BPE/BPO screening tool (score  $\geq 3$ ) tool or on the IPSS (score  $\geq 8$ ) will be enrolled and offered a prostate specific antigen (PSA) test and urinalysis to establish a diagnosis of probable benign prostatic hyperplasia (BPH) (Part I – Visit 1). A GP makes a diagnosis of probable BPH based upon screening results and lab tests which suggest that they are related to BPH and not other causes of such symptoms.
- The General Practitioners (GPs) will phone the subject to report yes or no for probable BPH Part II (Visit 2). If the subject has probable BPH, the GP schedules the subject for Visit 3 with a urologist. If the subject does not have probable BPH, then the subject has completed the study.
- Subjects that proceed to Part II (Visit 3) will be scheduled for a urology assessment performed by a urologist. This assessment includes digital rectal examination (DRE) and a brief physical exam and review of the PSA test, for a confirmatory diagnosis of BPH and estimation of risk of progression of BPH.

#### REVISED TEXT

- This is a Phase IV study that will test evaluate the utility of the Benign Prostatic Enlargement (BPE)/ Benign Prostatic Obstruction (BPO) screening tool in a general practice setting where the results of this screening tool will be used for further investigation. Therefore in this study, all men testing positive on the BPE/BPO



screening tool (score  $\geq 3$ ) tool or on the IPSS (score  $\geq 8$ ) will be enrolled and offered a prostate specific antigen (PSA) test and urinalysis to establish a diagnosis of probable benign prostatic hyperplasia (BPH) (Part I – Visit 1). The General Practitioner (GP) may perform a DRE (digital rectal examination), however the DRE will be repeated by the urologist to confirm the diagnosis and to rule out an abnormality suggesting prostate cancer. ~~A~~ The GP will makes a diagnosis of probable BPH based upon screening results and lab tests which suggest that they are related to BPH and not other causes of such symptoms.

- The ~~General Practitioners (GPs)~~ will phone the subject to report yes or no for probable BPH Part II (Visit 2). If the subject has probable BPH, the GP will schedules the subject for Visit 3 with a urologist. If the subject does not have probable BPH, then the subject has completed the study.
- Subjects that proceed to Part II (Visit 3) will be scheduled for a urology assessment performed by a urologist. This assessment includes ~~a digital rectal examination (DRE)~~ and a brief physical exam and review of the PSA test, for a confirmatory diagnosis of BPH and estimation of risk of progression of BPH.

## Analysis

### PREVIOUS TEXT

- The primary endpoint is defined as the proportion of men that are confirmed to have BPH based on full urologist assessment of diagnostic test results among men with a positive result on the BPE/BPO screening tool and probable GP BPH diagnosis. For this proportion, the numerator is number of subjects diagnosed with BPH by a urologist; denominator is number of subjects with a positive result on the BPE/BPO screening tool and a probable BPH assessment by the GP and a BPH assessment by the urologist. The 95% confidence interval for this proportion will be presented.
- Sufficient general practice centres (50 consecutive men per centre) in the top 5 European markets will be recruited to administer the BPE/BPO screening tool to 1,500 men (using protocol defined criteria) presenting to clinic for reasons unrelated to the study. It is expected that 33% of the 1,500 presenting (or approximately 500) will have a positive result on the BPE/BPO screening tool and a probable BPH assessment by GP and thus will be assessed by a urologist.

### REVISED TEXT

- The primary endpoint is defined as the proportion of men that are confirmed to have BPH based on full urologist assessment of diagnostic test results among men with a positive result on the BPE/BPO screening tool and probable ~~GP~~ BPH diagnosis as assessed by the GP. For this proportion, the numerator is number of subjects diagnosed with BPH by a urologist; denominator is number of subjects with a positive result on the BPE/BPO screening tool and a probable BPH assessment by the GP and a BPH assessment by the urologist. The 95% confidence interval for this proportion will be presented.
- Sufficient general practice centres (50 consecutive men per centre) in ~~the top~~ various ~~5 European~~ markets will be recruited to administer the BPE/BPO screening tool to

1,500 men (using protocol defined criteria) presenting to clinic for reasons unrelated to the study. It is expected that 33% of the 1,500 presenting (or approximately 500) will have a positive result on the BPE/BPO screening tool and a probable BPH assessment by GP and thus will be assessed by a urologist.

Rationale for the changes: The changes have been made to maintained consistency with other sections of protocol.

## 2. INTRODUCTION

### PREVIOUS TEXT

- This Phase IV study will test the utility of the Benign Prostatic Enlargement (BPE)/ Benign Prostatic Obstruction (BPO) screening tool in a general practice setting where the results of the BPE/BPO screening tool will be used for further investigation. Therefore in this study, all men testing positive with the BPE/BPO tool (score  $\geq 3$ ) and/or on the IPSS (score  $\geq 8$ ) will be enrolled and offered a prostate specific antigen (PSA) test and urinalysis to help establish a diagnosis of probable benign prostatic hyperplasia (BPH) (Part I – Visit 1).
- The General Practitioners (GPs) will phone the subject to report yes or no for probable benign prostatic hyperplasia (BPH) Part II (Visit 2). If the subject has probable BPH, the GP schedules the subject for Visit 3 with a urologist. If the subject does not have probable BPH, then the subject has completed the study.
- For those subjects that proceed to Part II (Visit 3) they will be scheduled for a urology assessment performed by a urologist. This assessment includes digital rectal examination (DRE) and a brief physical exam with review of the PSA test, for a confirmatory diagnosis of BPH and estimation of risk of progression of BPH.

### REVISED TEXT

- This ~~Phase IV~~ study will ~~test~~ evaluate the utility of the Benign Prostatic Enlargement (BPE)/ Benign Prostatic Obstruction (BPO) screening tool in a general practice setting where the results of the BPE/BPO screening tool will be used for further investigation. Therefore in this study, all men testing positive with the BPE/BPO tool (score  $\geq 3$ ) and/or on the IPSS (score  $\geq 8$ ) will be enrolled and offered a prostate specific antigen (PSA) test and urinalysis to help establish a diagnosis of probable benign prostatic hyperplasia (BPH) (Part I – Visit 1). The GP may perform a DRE, however the DRE will be repeated by the urologist to confirm the diagnosis and to rule out an abnormality suggesting prostate cancer.
- The ~~General Practitioners (GPs)~~ will phone the subject to report yes or no for probable benign prostatic hyperplasia (BPH) Part II (Visit 2). If the subject has probable BPH, the GP will schedules the subject for Visit 3 with a urologist. If the subject does not have probable BPH, then the subject has completed the study.
- For those subjects that proceed to Part II (Visit 3) they will be scheduled for a urology assessment performed by a urologist. This assessment includes ~~digital rectal examination (DRE)~~ and a brief physical exam with review of the PSA test, for a confirmatory diagnosis of BPH and estimation of risk of progression of BPH.

Rationale for the change: The phase of study is not applicable. Hence, phase IV has been deleted and DRE has been included to confirm the diagnosis and to rule out an abnormality suggesting prostate cancer by urologist.

## 2.1 Study Rationale

### PREVIOUS TEXT

The rationale for developing an instrument to screen populations of men for lower urinary tract symptoms (LUTS) due to BPH is that it may help GPs identify patients who may have BPH for further tests and improve the speed of referrals to specialists when this is appropriate.

### REVISED TEXT

The rationale for developing an instrument to screen populations of men for lower urinary tract symptoms (LUTS) due to BPH is that it may help a GPs to identify patients who may have BPH for further tests and improve the speed of referrals to specialists when this is appropriate.

Rationale for the change: The changes have been made to correct the typographical error.

## 4. STUDY DESIGN

### PREVIOUS TEXT

This non-randomized, interventional study utilizing a questionnaire-based assessment of men in General Practice. Validation of the tool was performed in a previous GlaxoSmithKline (GSK) study (FDC116700: Quick Question Tool Development and Linguistic Validation). Men who sign the informed consent form and meet the eligibility criteria will be enrolled and complete the Part I diagnostic tests at the GP clinic. If the GP determines that the subject has probable, the subject proceeds to Part II and is scheduled for a urologist assessment and diagnostic tests to confirm or refute a BPH diagnosis and to assess risk of progression of BPH.

### REVISED TEXT

This non-randomized, interventional study utilizing a questionnaire-based assessment of men in General Practice. Validation of the tool was performed in a previous GlaxoSmithKline (GSK) study (FDC116700: Quick Question Tool Development and Linguistic Validation). Men who sign the informed consent form and meet the eligibility criteria will be enrolled and complete the Part I diagnostic tests at the GP clinic. If the GP determines that the subject has probable BPH (IPSS  $\geq 8$  and/or BPE/BPO questionnaire  $\geq 3$  with a PSA  $\geq 2$  ng/ml), the subject proceeds to Part II and is scheduled for a urologist assessment and diagnostic tests to confirm or refute a BPH diagnosis and to assess risk of progression of BPH.

Rationale for the change: Included the probable BPH criteria for clarity and to maintain consistency with other sections of protocol.

#### 4.1 Overall Design

##### PREVIOUS TEXT

###### *First Paragraph:*

To reproduce these circumstances of opportunistic screening, men will not be invited to attend their GPs but **must attend spontaneously with for reasons that are not related to this study.**

###### *Third Paragraph:*

After obtaining informed consent, GPs will initially assess all inclusion and exclusion criteria except for the questionnaire inclusion criterion.

All men with ‘probable BPH’ will proceed to Part II and will be scheduled for Visit 3 with a urologist for confirmation of the GPs findings plus a brief physical exam and DRE. Additional testing may be performed as per standard of care to assist with a confirmatory diagnosis; however this is not required by the protocol.

2) Estimate whether the patient is at risk of progression of BPH (PSA  $\geq$ 2.0 ng/mL and/or other testing).

For the purposes of this study the diagnosis of the urologist (BPH yes/no) is the operational definition of confirmed BPH. Those men refusing referral to the urologist, but considered by the GPs to have BPH (after the tests specified above) will be classified as ‘probable BPH’.

##### Description of Visits:

###### VISIT 1 (primary care clinic)

- Males  $\geq$ 50 years visiting GP for reasons unrelated to the study
- Patient provides informed consent



Eligible to participate

- Inclusion/exclusion criteria confirmation
- Medical history and demography
- BPE/BPO and IPSS screening tools

If subject meets entry criteria, including a positive IPSS (score  $\geq 8$ ) and/or BPE/BPO (score  $\geq 3$ ).



ENROLLED: Subject is enrolled and proceeds to Part I (GP Assessment) of the study. If the GP diagnoses probable BPH, the subject will proceed to Part II (urologist assessment).

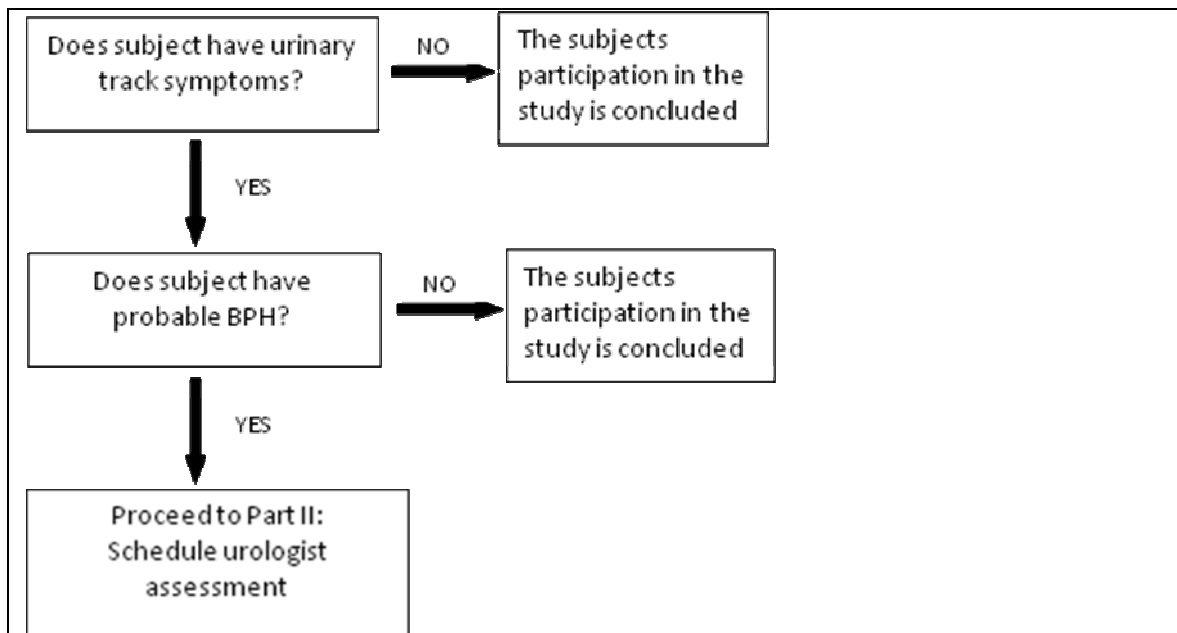
#### PART I: GP Assessment

After being enrolled, complete the following at Visit 1:

- Urinalysis strip test.
  - If strip test is positive, send urine sample to local lab urinalysis.
- PSA blood test

#### VISIT 2 (telephone call)

- GP reviews urinalysis and PSA lab results.
- Call subject: If lab results show NO probable BPH, then subject will not continue in the study. If PSA lab results show PROBABLE BPH ( $\geq 2$  ng/mL), subject proceeds to Part II and Visit 3 is scheduled for the urologist assessment.



### VISIT 3 (Part II – urologist clinic visit)

- Urologist reviews medical history and symptoms
- Brief physical examination
- DRE
- Review previous tests (BPE/BPO screening tool, IPSS screening tool, urinalysis, PSA)



#### Urologist provides:

- Confirmation of clinical diagnosis of BPH (or confirmation the subject does NOT have BPH).
- Estimate whether the patient is at risk of progression of BPH (PSA  $\geq$  2.0ng/mL and/or other tests).

- NOTE: Urologist may need to perform additional diagnostic testing as per standard of care and as needed to assess the BPH diagnosis. This follow-up is not prescribed by this protocol, however, any data collected that is used for the final diagnosis will be entered in the study case report form

(CRF). Advice or treatment post study will be discretion of the GP or Urologist.

#### REVISED TEXT

##### *First Paragraph:*

To reproduce these circumstances of opportunistic screening, men will not be invited to attend their GPs-but **must attend spontaneously with for reasons that are not related to this study.**

##### *Third Paragraph:*

After obtaining informed consent, the GPs will initially assess all inclusion and exclusion criteria except for the questionnaire inclusion criterion.

All men with 'probable BPH' will proceed to Part II and will be scheduled for Visit 3 with a urologist for confirmation of the GP's findings plus a brief physical exam and DRE. Additional testing may be performed as per standard of care to assist with a confirmatory diagnosis;—such as a DRE, however this is not required by the protocol.

2) Estimate whether the patient is at risk of progression of BPH (PSA  $\geq 2.0$  ng/mL and/or other testing).

For the purposes of this study the diagnosis of the urologist (BPH yes/no) is the operational definition of confirmed BPH. Those men refusing referral to the urologist, but considered by ~~the~~ a GPs to have BPH (after the tests specified above) will be classified as 'probable BPH'.

#### Description of Visits:

##### VISIT 1 (primary care clinic)


- Males  $\geq 50$  years visiting GP for reasons unrelated to the study
- Patient provides informed consent



Eligible to participate

- Inclusion/exclusion criteria confirmation
- Medical history and demography
- BPE/BPO and IPSS screening tools

If subject meets entry criteria, including a positive IPSS (score  $\geq 8$ ) and/or BPE/BPO (score  $\geq 3$ ).



ENROLLED: Subject is enrolled and proceeds to Part I (GP Assessment) of the study. If the GP diagnoses probable BPH, the subject will proceed to Part II (urologist assessment).

#### PART I: GP Assessment

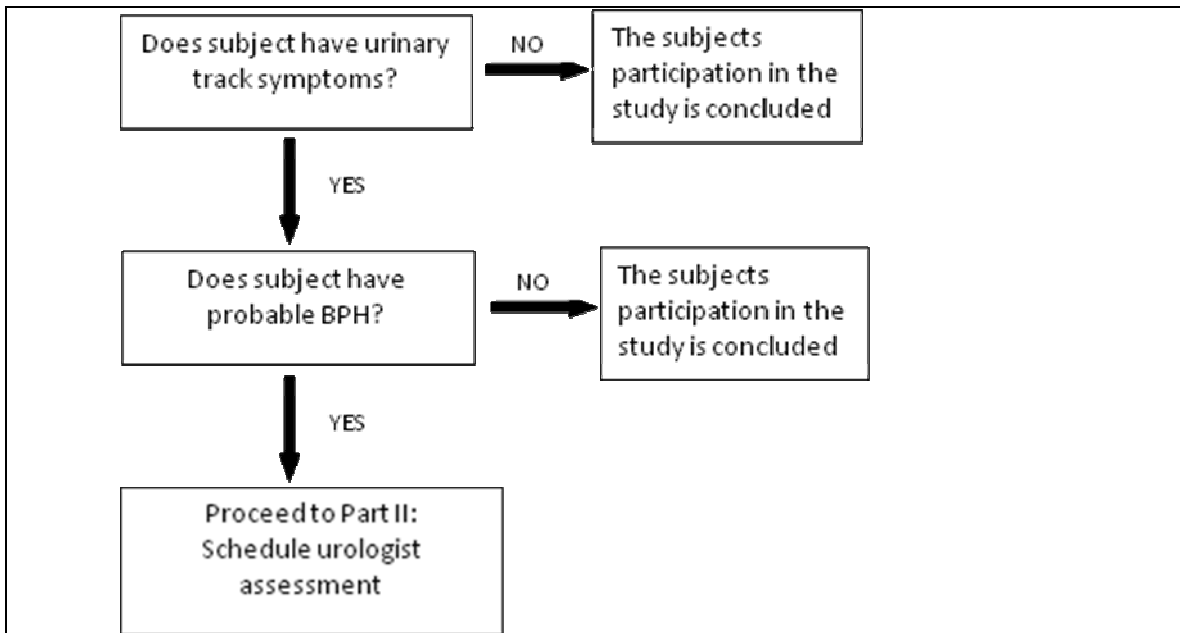
After being enrolled, complete the following at Visit 1:

- Urinalysis strip test.
  - If strip test is positive, send urine sample to local lab urinalysis.
- PSA blood test
- Additional testing may be performed as per standard of care to assist with a confirmatory diagnosis such as a DRE, however this is not required.

#### VISIT 2 (telephone call)

- GP reviews urinalysis and PSA lab results.
- Call subject: If lab results show NO probable BPH, then subject will not continue in the study. If PSA lab results show PROBABLE BPH ( $\geq 2$  ng/mL), subject proceeds to Part II and Visit 3 is scheduled for the urologist assessment.





### VISIT 3 (Part II – urologist clinic visit)

- Urologist reviews medical history and symptoms
- Brief physical examination
- DRE
- Review previous tests (BPE/BPO screening tool, IPSS screening tool, urinalysis, PSA)



Urologist provides:

- Confirmation of clinical diagnosis of BPH (or confirmation the subject does NOT have BPH).
- Estimate whether the patient is at risk of progression of BPH (PSA  $\geq$  2.0ng/mL and/or other tests).

- NOTE: Urologist may need to perform additional diagnostic testing as per standard of care and as needed to assess the BPH diagnosis. This follow-up is not prescribed by this protocol, however, any data collected that is used for the final diagnosis will be entered in the study case report form

(CRF). Advice or treatment post study will be discretion of the GP or Urologist.

Rationale for the change: Included the additional test such as a DRE to confirm the diagnosis and to maintain consistency with other sections of protocol.

## 5.2 Exclusion Criteria

PREVIOUS TEXT

### CONCOMITANT MEDICATIONS

6. Current or prior use of the following:
  - a. 5 $\alpha$ -reductase inhibitors (finasteride or dutasteride),
  - b. anti-cholinergics (e.g. oxybutynin, propantheline, tolterodine, solifenacin, darifenacin, miravegron) alpha-adrenoreceptor blockers (i.e., indoramin, prazosin, terazosin, tamsulosin, alfuzosin, doxazosin and silodosin).
  - c. Use of any investigational or marketed study drug within 30 days or 5 half-lives of the drug in question, (whichever is longer), preceding the first study visit.
7. Use within previous 30 days at Visit 1 of:
  - a. PDE-5 inhibitors for erectile dysfunction
  - b. anabolic steroids

REVISED TEXT

### CONCOMITANT MEDICATIONS

6. Current or prior use of the following:
  - a. 5 $\alpha$ -reductase inhibitors (finasteride or dutasteride),
  - b. anti-cholinergics (e.g. oxybutynin, propantheline, tolterodine, solifenacin, darifenacin, ~~miravegron~~ mirabegron) alpha-adrenoreceptor blockers (i.e., indoramin, prazosin, terazosin, tamsulosin, alfuzosin, doxazosin and silodosin), herbal products for urinary symptoms.
  - c. Use of any investigational ~~or marketed~~ study drug within 30 days or 5 half-lives of the drug in question, (whichever is longer), preceding the first study visit.
7. Use within previous 30 days at Visit 1 of:
  - a. PDE-5 inhibitors for erectile dysfunction
  - b. anabolic steroids

Rationale for the change: Herbal medications are used in several countries to treat BPH and therefore need to be excluded.

## 5.6.2 Prohibited Medications and Non-Drug Therapies

### PREVIOUS TEXT

Prohibited medications:

- 5 $\alpha$ -reductase inhibitors (finasteride or dutasteride),
- anti-cholinergics (e.g. oxybutynin, propantheline, tolterodine, solifenacin, darifenacin, miravegron) alpha-adrenoreceptor blockers (i.e., indoramin, prazosin, terazosin, tamsulosin, alfuzosin, doxazosin and silodosin).
- PDE-5 inhibitors for erectile dysfunction
- anabolic steroids

### REVISED TEXT

Prohibited medications:

- 5 $\alpha$ -reductase inhibitors (finasteride or dutasteride),
- anti-cholinergics (e.g. oxybutynin, propantheline, tolterodine, solifenacin, darifenacin, ~~miravegron~~ mirabegron) alpha-adrenoreceptor blockers (i.e., indoramin, prazosin, terazosin, tamsulosin, alfuzosin, doxazosin and silodosin), herbal products for urinary symptoms.
- PDE-5 inhibitors for erectile dysfunction
- anabolic steroids

Rationale for the change: Correction of spelling and rationale for the addition of herbal products to excluded products is that herbal products are commonly used to treat symptoms of BPH and therefore need to be excluded from the study.

## 6.1 Time and Events Table

## PREVIOUS TEXT

| Procedure   | VISIT 1:<br>Screening/<br>Enrolment at GP Clinic | Study Period<br>(1 week $\pm$ 4 days to 6 weeks) |  |
|---|--|--|--|
|   |  | VISIT 2 (phone call):<br>GP                      | VISIT 3: Urologist<br>(up to 6 weeks after V1) |
| Informed consent  | X  |  |  |
| Inclusion and exclusion criteria  | X  |  |  |
| Demography  | X  |  |  |
| Medical history   | X  |  |  |
| Concomitant medications (all ongoing and within 30 days prior to Visit 1)       | X  |  |  |
| IPSS screening tool   | X  |  |  |
| BPE/BPO screening tool  | X  |  |  |
| <b>PROCEDURES AFTER SUBJECT IS ENROLLED<sup>1</sup>:</b>                        |  |  |  |
| Urine strip test <sup>2</sup>   | X  |  |  |
| Urinalysis (only if urine strip test is positive) <sup>2</sup>                  | X  |  |  |
| PSA blood test <sup>3</sup>   | X  |  |  |
| Results phone call to subject <sup>4</sup>                                      |  | X  |  |
| Digital rectal exam (DRE) <sup>5</sup>  |  |  | X  |
| Brief physical examination  |  |  | X  |
| Enter prostate-related results in the CRF from non-protocol required procedures |  |  | X  |
| AE/SAE review (related to study procedures and/or participation)                | ←-----→  |  |  |
| Concomitant medication review   | ←-----→  |  |  |

1. Subject is enrolled after meeting eligibility requirements, which includes a positive BPE/BPO screening tool and/or positive IPSS screening tool.
2. Urinalysis sent to local laboratory only if urine strip test is positive.
3. PSA blood test sent to local lab. Local lab results and reference ranges are entered in the CRF.
4. For Visit 2, the GP calls the subject to report yes or no for probable BPH. If the subject has probable BPH, the GP schedules the subject for Visit 3 with the urologist. If the subject does not have probable BPH, then the subject has completed the study.
5. DRE is performed by the urologist.

REVISED TEXT

| Procedure   | VISIT 1:<br>Screening/<br>Enrolment at GP Clinic | Study Period<br>(1 week ±4 days to 6 weeks) |   |
|---|--|---|---|
|   |  | VISIT 2 (phone call):<br>GP                 | VISIT 3: Urologist <sup>a</sup><br>(up to 6 weeks after V1) |
| Informed consent  | X  |   |   |
| Inclusion and exclusion criteria  | X  |   |   |
| Demography  | X  |   |   |
| Medical history   | X  |   |   |
| Concomitant medications (all ongoing and within 30 days prior to Visit 1)       | X  |   |   |
| IPSS screening tool   | X  |   |   |
| BPE/BPO screening tool  | X  |   |   |
| <b>PROCEDURES AFTER SUBJECT IS ENROLLED<sup>1</sup>:</b>                        |  |   |   |
| Urine strip test <sup>2</sup>   | X  |   |   |
| Urinalysis (only if urine strip test is positive) <sup>2</sup>                  | X  |   |   |
| PSA blood test <sup>3</sup>   | X  |   |   |
| Results phone call to subject <sup>4</sup>                                      |  | X   |   |
| Digital rectal exam (DRE) <sup>5</sup>  | X  |   | X   |
| Brief physical examination  |  |   | X   |
| Enter prostate-related results in the CRF from non-protocol required procedures |  |   | X   |
| AE/SAE review (related to study procedures and/or participation)                | ←-----→  |   |   |
| Concomitant medication review   | ←-----→  |   |   |

1. Subject is enrolled after meeting eligibility requirements, which includes a positive BPE/BPO screening tool and/or positive IPSS screening tool.
2. Urinalysis sent to local laboratory only if urine strip test is positive.
3. PSA blood test sent to local lab. Local lab results and reference ranges are entered in the CRF.
4. For Visit 2, the GP calls the subject to report yes or no for probable BPH. If the subject has probable BPH, the GP schedules the subject for Visit 3 with the urologist. If the subject does not have probable BPH, then the subject has completed the study.
5. DRE is performed by the urologist. The GP may conduct a DRE at visit 1 however the DRE will be repeated by the urologist to confirm the diagnosis and to rule out an abnormality suggesting prostate cancer.
6. Information collected during visit 3 will be entered into the eCRF by the Principal Investigator.

Rationale for the change: Clarified conduction of DRE exam diagnosis and to maintain consistency with other sections of protocol and to clarify data entry at visit 3

### 6.3.1.1 Time period and Frequency for collecting AE and SAE information

#### PREVIOUS TEXT

- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.

#### REVISED TEXT

- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) ~~or related to a GSK product~~ will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.

Rationale for the change: Delete GSK product as there is no investigation of a product in this study.

### 6.3.1.3 Regulatory Reporting Requirements for SAEs

#### PREVIOUS TEXT

Prompt notification by the investigator to GSK or designee of SAEs related to study treatment (even for non- interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

#### REVISED TEXT

Prompt notification by the investigator to GSK or designee of SAEs related to study treatment ~~(even for non- interventional post-marketing studies)~~ or related to a GSK product is essential so that legal obligations and ethical responsibilities towards the safety of subjects ~~and the safety of a product under clinical investigation~~ are met.

Rationale for the change: Edited to for ease of reading and to delete “and the safety of a product under clinical investigation” as the study is not investigating a product.

## 8.2 Sample Size Consideration

## PREVIOUS TEXT

Sufficient general practice centres (approximately 50 subjects per centre) in the top 5 European markets will be recruited to administer the BPE/BPO screening tool to 1,500 men using protocol defined criteria presenting to clinic. It is expected that 33% of the 1,500 presenting (or approximately 500) will have a positive result on the BPE/BPO and/or IPSS screening tools and a probable BPH assessment by GP and thus will be assessed by a urologist.

## REVISED TEXT

Sufficient general practice centres (approximately 50 subjects per centre) in the ~~top 5 European~~ various markets will be recruited to administer the BPE/BPO screening tool to 1,500 men using protocol defined criteria presenting to clinic. It is expected that 33% of the 1,500 presenting (or approximately 500) will have a positive result on the BPE/BPO and/or IPSS screening tools and a probable BPH assessment by GP and thus will be assessed by a urologist.

Rationale for change: The wordings have been edited to widen the scope for centre selection.