Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan for ARI114265: A randomized, double-blind, parallel group study to compare the efficacy and safety of combination treatment with dutasteride (0.5mg) and tamsulosin (0.2mg) with tamsulosin (0.2mg) monotherapy, administered once daily for 2 years, on the improvement of symptoms and health outcomes in men with moderate to severe benign prostatic hyperplasia
Compound Number	:	GI198745+GI138525
Effective Date	:	09-DEC-2016

Description :

The purpose of this RAP is to describe the planned summaries and statistical analyses to be included in the Clinical Study Report (CSR) for Protocol ARI114265. This document contains the RAP Amendment 01.

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Approved by:

Original	PPD *(e-mail approval dated 15-Dec-2015)* Director Statistics & Programming, GSK	15-DEC-2015
Amendment 01	PPD *(email approval dated 09-Dec-2016)* Director Statistics & Programming, GSK	09-DEC-2016

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1. REPORTING & ANALYSIS PLAN SYNOPSIS

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<tr><td>Protocol</td><td>This RAP is based on the protocol amendment 04 (Republished) (Dated: 08/JUL/2014) of study ARI114265 [GSK Document No. : RM2010/00134/05]. This document contains the RAP amendment 01.

The aim of the study is to investigate whether combination therapy with dutasteride and tamsulosin is more effective than tamsulosin monotherapy for the improvement of symptoms and health outcomes in a population at increased risk of BPH clinical progression including older men (≥50yrs), with moderate-severe symptoms of BPH, enlarged prostates (≥30cc) and PSA≥1.5ng/mL.</td></tr>
<tr><td>Primary Objective</td><td>The primary objective is to assess the efficacy of combination treatment with dutasteride 0.5mg and tamsulosin 0.2mg once daily in providing superior symptomatic improvement in subjects with BPH compared with once daily tamsulosin 0.2mg monotherapy after 2 years of treatment.</td></tr>
<tr><td>Primary Endpoint</td><td>The primary endpoint is change from baseline IPSS at Year 2 (Month 24 Visit); earlier timepoints (Month 21 -> Month 3) are considered secondary endpoints.</td></tr>
<tr><td>Study Design</td><td>This is a multicenter, randomized, double-blind, parallel group study. Eligible subjects will receive placebo tamsulosin and placebo dutasteride for four weeks in a single-blind, placebo, run-in period. Each subject will then be randomized to one of the following two treatment groups (1:1 ratio) for the double-blind phase (104 weeks) of the study:
--Dutasteride 0.5mg once daily + tamsulosin 0.2mg once daily or
--Dutasteride placebo once daily + tamsulosin 0.2mg once daily

Subjects will self-administer the study medication once daily for up to 104 weeks (2 years). Subjects will return to the clinic at 13 week intervals post-randomization during the 2 year treatment period (i.e. at 13, 26, 39, 52, 65, 78, 91, and 104 weeks).</td></tr>
<tr><td>Planned Analyses</td><td>Within this RAP, the following additional references may be made for brevity:
<table>
<tr><th>--Full Treatment Description--</th><th>--Short Treatment Descriptions--</th></tr>
<tr><td>Dutasteride 0.5mg once daily + tamsulosin 0.2mg once daily or</td><td>-Combination
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-Placebo + Tam 0.2mg
-Tam</td></tr>
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The study population, efficacy, safety, and health outcomes summaries and analyses will be based on the Intent-to-Treat (ITT) population; few exceptions will be</td></tr>
</table>

Overview	Key Elements of the RAP
	noted within the RAP. Summaries and analyses are defined within this RAP. The following are high level summary and analyses types. • Study population summaries will be presented overall and by treatment group and will include accountability, disposition, demographic characteristics, baseline characteristics, protocol deviations, and concomitant medications. • The primary efficacy analyses and treatment group comparisons will be in terms of IPSS change from baseline. • Secondary efficacy analyses and treatment group comparisons will be in terms of prostate volume, Qmax, IPSS improvement levels (≥2 points, ≥3 points, ≥25%), Qmax improvement levels (≥3 ml/sec, ≥30%), and time to AUR or BPH-related surgery. • Safety summaries will be presented by treatment group and will be in terms of study drug exposure, adverse events, clinical laboratory evaluations, serum PSA, post void residual volume, qualitative breast examination, digital rectal examination, vital signs, and suicidality assessment using C-SSRS. • Health Outcomes analyses and treatment group comparisons will be in terms of BPH-Related Health Status (IPSS Question 8), BPH Impact Index, and Problem Assessment Scale of the Sexual Function Inventory (PAS SFI).
Analysis Populations	• The ITT Population is comprised of all randomized subjects regardless of whether or not treatment was administered. • The Per-Protocol (PP) Population is comprised of all ITT subjects who comply closely with the protocol. Specifically this includes ITT subjects who do not have a deviation which requires exclusion from the PP population. The PP population will not be analyzed if this population comprises more than 80% of the ITT population.
Hypothesis	The primary endpoint is change from baseline IPSS at Year 2. Let the following represent the mean change from baseline IPSS for each treatment group: $H_{dut+tam}$: Combination (dutasteride 0.5mg and tamsulosin 0.2mg) treatment group H_{tam}: Tamsulosin (tamsulosin 0.2mg treatment group) Then the primary null and alternative hypotheses to be tested at Year 2 are as follows: Null Hypothesis: $H_{dut+tam} = H_{tam}$ Alternative Hypothesis: $H_{dut+tam} \neq H_{tam}$ Two-sided tests of the null hypothesis will be conducted at the 0.05 level of significance to show superiority of the combination treatment group compared to tamsulosin 0.2mg at 2 years of treatment.
Primary Analyses	The primary efficacy parameter after two years of study treatment is change from baseline IPSS. Change in IPSS from baseline will be compared at each scheduled post-baseline visit for combination treatment versus tamsulosin 0.2mg using a general linear model with effects for treatment, cluster, and baseline IPSS.
Secondary	Secondary efficacy analyses will be in terms of prostate volume, Qmax, IPSS

Overview	Key Elements of the RAP
Analyses	improvement levels, Qmax improvement levels, and time to AUR or BPH-related surgery using appropriate statistical methodology defined within this RAP.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There were no changes or deviations to the originally planned statistical analysis specified in the ARI114265 protocol amendment 04 (Republished) (Dated 08/JUL/2014).

This document contains the RAP amendment 01 which is based on the protocol amendment 04 noted above. RAP amendment 01 revisions primarily include programming and reporting clarifications, limited expansion of efficacy subgroup summaries, and limited expansion of supporting analyses for secondary endpoints. This amendment 01 includes no major changes to the planned analyses. The summary of RAP amendment 01 changes is contained in Appendix 17.

2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To assess the efficacy of combination treatment with dutasteride 0.5mg and tamsulosin 0.2mg once daily in providing superior symptomatic improvement in subjects with BPH compared with once daily tamsulosin 0.2mg monotherapy after 2 years of treatment	• Change in IPSS from baseline at Year 2.
Secondary Objectives	**Secondary Endpoints**
• To assess efficacy and safety of combination treatment with dutasteride 0.5mg and tamsulosin 0.2mg including the clinical outcomes of AUR or BPH-related prostatic surgery compared with tamsulosin 0.2mg monotherapy after 2 years of treatment.	**Efficacy** • Percent change in prostate volume from baseline • Proportion of subjects with IPSS improvement of ≥2 points and ≥3 points from baseline and, separately, ≥25% improvement from baseline • Change in Qmax from baseline • Proportion of subjects with Qmax improvement of ≥3mL/sec and, separately, ≥30% improvement from baseline • Time to event/ proportion of subjects with AUR or BPH related prostatic surgery • Time to event/proportion of subjects with AUR • Time to event/proportion of subjects undergoing BPH related prostatic surgery **Health Outcome Measures** • Change in BPH-Related Health Status (Q8 of IPSS) from Baseline • Change in BPH Impact Index (BII) from Baseline

Objectives	Endpoints
	• Change in Problem Assessment Scale of the Sexual Function Inventory (PAS-SFI), from Baseline • Resource Use related to AUR and BPH-related surgical events. **Safety** • Adverse Events • Change in total serum PSA from baseline • Vital signs • Post-void residual volume • Clinical laboratory measurements (including haematology, chemistry) • Physical examination: digital rectal examination (DRE) and qualitative breast examination • Suicidality (C-SSRS)
Exploratory Objectives	**Exploratory Endpoints**
• Pharmacogenetics (PGx) Research Note: PGx planned summaries and analyses will be documented outside this RAP.	• Relationships between genetic variants in DNA from patient blood and any unexplained or unexpected response to treatment (as monitored by safety, tolerability, and efficacy parameters) that may have an underlying genetic mechanism.
• Population Pharmacokinetics (PPK) Research Note: PPK planned summaries and analyses will be documented outside this RAP	• Characterization of PPK of dutasteride when given in combination with tamsulosin to Chinese men with BPH.

2.3. Study Design

Overview of Study Design and Key Features	
Design Features	• Multicenter within 4 countries: China, Japan, Korea, and Taiwan. • Randomized, double-blind, parallel group study to assess the efficacy of combination treatment with dutasteride 0.5mg and tamsulosin 0.2mg once daily in providing superior symptomatic improvement in subjects with BPH compared with once daily tamsulosin 0.2mg monotherapy after 2 years of treatment.
Dosing / Treatment Assignment	• Placebo tamsulosin and placebo dutasteride for four weeks in a single-blind, placebo, run-in period. • Thereafter randomized to one of the following two treatment groups (1:1 ratio) for the double-blind phase (104 weeks) of the study: --Dutasteride 0.5mg once daily + tamsulosin 0.2mg once daily or --Dutasteride placebo once daily + tamsulosin 0.2mg once daily.
Interim Analysis	No interim analyses are planned for this study.

2.4. Statistical Hypotheses

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

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

H_{tam}: Tamsulosin 0.2mg treatment group

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

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

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

3. PLANNED ANALYSES

3.1. Interim Analyses

No interim analyses are planned for this study.

3.2. Final Analysis

The planned primary analyses will be performed after completion of the following sequential steps:

1. All subjects have completed the 104-week study treatment period study as defined in the protocol.
2. All required database cleaning activities have been completed and primary database release and primary database freeze have been declared by Data Management. Reference 'primary database' description below.
3. All criteria for unblinding the randomization codes have been met.
4. Randomization codes have been distributed according to RandAll NG procedures.

The primary database freeze, using standard Data Management practices, will occur after the last subject completes the 104-week randomized treatment phase. Statistical analysis and reporting in support of international regulatory submissions will be in terms of this primary database freeze and will be referred to as the 'Final Analysis' or primary 'Statistical Analysis Complete' (SAC). Reference Section 9, Country-Specific Summaries and Analyses, for a description of a secondary country-based statistical analysis complete package.

3.3. Targeted Follow-Up Questionnaire (TFUQ) Report

As documented in protocol and elsewhere in this RAP, this study includes a Targeted Follow-Up Questionnaire (TFUQ) for subjects with sexual function related adverse events leading to study withdrawal. Using the TFUQ, subjects will be followed for up to 6 months after the last dose of study drug. It is anticipated that the final TFUQ data component will be included in the above referenced primary database freeze.

However, if there are ongoing TFUQs at the time of primary database freeze, and anticipated follow-up and receipt of these data would create a delay in analyzing and reporting the study results then the primary freeze may occur with exclusion of outstanding TFUQ data. Thereafter, a secondary database freeze will occur in terms of newly finalized and recorded TFUQ data (since primary freeze). The decision to perform a secondary freeze will be made soon after last subject last visit milestone by Project Team with input from Data Management, International Regulatory Affairs, Clinical Statistics, Clinical Development, and Clinical Operations. This secondary freeze will be in terms of datasets containing the actual TFUQ and as well as any TFUQ-related datasets. Only TFUQ-related tabular summaries and listings (related to newly frozen datasets) will be updated with the secondary freeze. TFUQ-related summaries and listings for this secondary freeze will be referred to as 'TFUQ Report'.

4. ANALYSIS POPULATIONS

Analysis populations are defined in the following table.

Population	Definition / Criteria	Analyses Evaluated
Intent-To-Treat (ITT)	• Comprised of all randomized subjects regardless of whether or not treatment was administered • This population will be based on the treatment to which the subject was randomized. • Any subject who receives a treatment randomization number will be considered to have been randomized.	• All.
Per-Protocol (PP)	• Comprised of all ITT subjects who comply closely with the protocol. Specifically this includes ITT subjects who do not have a deviation which requires exclusion from the PP population. • Protocol deviations that would exclude subjects from the PP population are defined in Section 4.1.3 (Deviations which Require Exclusion from the Per-Protocol Population) and Appendix 1 (Exclusions from the Per-Protocol Population). • The PP population will not be analyzed if this population comprises more than 80% of the ITT population.	• Primary efficacy endpoint only if this population comprises 80% or less of the ITT Population. Details on specific summaries and analyses are outlined in Section 7, Primary Statistical Analyses.

NOTES :

- 'All Enrolled Subjects' is referenced in at least one tabular summary. Enrolled subjects include those who entered placebo run-in phase and/or who were randomized.

4.1. Protocol Deviations

4.1.1. Inclusion / Exclusion Criteria Deviations

All inclusion / exclusion criteria deviations which are recorded on the inclusion / exclusion screens of the eCRF will be summarized and listed. The tabular summary will be in terms of number and percent of Intent-to-Treat population subjects violating any criterion and violating each criterion. Summaries will be output by each of the two randomized treatment groups and overall.

4.1.2. Important Protocol Deviations

All protocol deviations identified during the course of the study will be tracked and reviewed by the study team in accordance with SOP-130050 and the ARI114265 Protocol Deviations Management Plan (PDMP). As outlined in the PDMP and Data Management procedures, the ARI114265 Study Team will identify protocol deviations which are considered to be 'Important' and flag on the team's protocol deviations spreadsheet. This spreadsheet will be subsequently loaded to the Data Management file system and formatted for HARP Analysis & Reporting.

Important Deviations will be summarized and listed. The tabular summary will be in terms of number and percent of subjects with any Important Deviation and with each Important Deviation. Summaries will be output by the eCRF category and subcategories for each of the two randomized treatment groups and overall. The eCRF categories and subcategories are standardized for this study; examples are provided in the tabular summary shells.

4.1.3. Deviations which Require Exclusion from the Per-Protocol Population

In accordance with SOP-130050 and the ARI114265 PDMP, deviations which require exclusion from the Per-Protocol population should be identified; the 19 deviations are listed in the below table. The historical term used to describe these deviations in ARI114265 protocol is 'major'. In this RAP and for future reporting the phrase 'deviations which require exclusion from the Per-Protocol population' will replace 'major'.

Number	Deviations which Require Exclusion from the Per-Protocol Population
01	Missed placebo run-in phase
02	Incorrect study drug (wrong treatment) consumed
03	Randomized but did not consume double-blind study drug
04	Cumulative study drug compliance <75%
05	Cumulative study drug compliance >125%
	Violation of Inclusion Criteria (protocol #)
06	Confirmed BPH clinical diagnosis (Inclusion 2)
07	IPSS ≥12 at Screening (Inclusion 3)
08	Prostate volume ≥30cc by TRUS at Screening (Inclusion 4)
09	PSA ≥1.5ng/ml and ≤10ng/mL at Screening (Inclusion 5)
10	Qmax >5 mL/sec and ≤15mL/sec with Voided Volume ≥125mL/sec at Screening (Inclusion 6)
	Violation of Exclusion Criteria (protocol #)
11	Any conditions other than BPH, which may in the judgement of the investigator, result in urinary symptoms or changes in flow rate (Exclusion 6)
12	Use of 5ARI within 6 months of Screening or historical TRUS and throughout the study (Exclusion 10a)
13	Use of anabolic steroids within 6 months of Screening and throughout the study (Exclusion

Number	Deviations which Require Exclusion from the Per-Protocol Population
	10b)
14	Use of phytotherapy for BPH within 2 weeks of Screening and throughout the study (Exclusion 10c)
15	Use of alpha-adrenoreceptor blockers within 2 weeks of Screening and throughout the study, except study meds (Exclusion 10d)
16	Use of alpha-adrenoreceptor agonists or anticholinegics or cholinergics within 48 hours prior to all uroflowmetry and IPSS assessments (Exclusion 10e)
17	Use of selective beta 3-adrenoreceptor agonist (mirabegron) within 2 weeks prior to all uroflowmetry and IPSS assessments (Exclusion 10f)
18	Prohibited medications and non-drug therapies of Protocol Section 6.2 and not otherwise classified above.
	Other
19	Any condition which should exclude a subject from the Per-Protocol population which is not included above; identified by Study Team.

Please refer to Appendix 1: Exclusions from the Per-Protocol Population for details on sources and processing these deviations.

Deviations which require exclusion from the Per-Protocol population will be summarized and listed. The Per-Protocol deviations tabular summary will be in terms of number and percent of subjects with any deviation and for each deviation. Summaries will be output by each of the two randomized treatment groups and overall.

4.1.4. Deviations which Require Exclusion from the Per-Protocol Population but not Tracked or Identified as Important by Study Team

For brevity, in this section ‘deviations which require exclusion from the per-protocol population’, defined in Section 4.1.3, will be referred to as ‘Per-Protocol Deviations’. In accordance with SOP-130050 and as clarified in GUI-315049, Per-Protocol Deviations are a subset of Important Protocol Deviations. As described in Appendix 1, some Per-Protocol Deviations may be identified programmatically and/or some may be identified post database freeze and unblinding. Therefore, it is not feasible to manually enter all Per-Protocol Deviations to the Study Team spreadsheet (referenced in Section 4.1.2) and thus not all Per-Protocol Deviations will be tracked or identified as Important by Study Team.

Per-Protocol Deviations which were not tracked or identified as Important by Study Team will be reported in 1) Listing of Important Deviations and flagged as such, and 2) Summary of Important Protocol Deviations.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

Table 1 provides a list of appendices primarily related to considerations for data analyses and data handling conventions. A full set of appendices is provided in Section 11.

Table 1 Overview of Appendices

Section	Component
11.1	Appendix 1: Exclusions from the Per-Protocol Population
11.3	Appendix 3: Assessment Windows
11.4	Appendix 4: Multicenter Studies
11.5	Appendix 5: Data Display Standards & Handling Conventions
11.6	Appendix 6: Derived and Transformed Data
11.7	Appendix 7: Premature Withdrawals & Handling of Missing Data
11.8	Appendix 8: Adverse Event Time Periods and Special Adverse Event Definitions
11.9	Appendix 9: Threshold Factors for Clinical Laboratory Tests and Vital Signs

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

The study population analyses will be based on the ITT population, unless otherwise specified in text or data display shells.

Table 2 provides an overview of the planned study population summaries and listings. A list of planned data displays is in Appendix 15: List of Data Displays.

Reference Section 4 (Analysis Populations) and Appendix 6 (Derived and Transformed Data) for supporting definitions on all below subsections.

Formal statistical treatment comparisons will not be performed in terms of the study population data.

Table 2 Overview of Planned Study Population Analyses

Display Type	Data Displays Generated		
	Table		Listing
Subject Accountability			
Numbers of Subjects, including: Enrolled, Placebo Run-In, Randomized (ITT Population), Per-Protocol Population	Y		Y
Subject Disposition			
Withdrawals During Placebo Run-In	Y		Y
Randomized by Country and Center	Y		Y
Withdrawals During Double-Blind including totals, reasons, and by time of discontinuation	Y		Y
Inclusion / Exclusion Criteria Deviations	Y		Y
Important Protocol Deviations	Y		Y
Deviations which Require Exclusion from the Per-Protocol Population	Y		Y
Demographic and Baseline Characteristics			
Demographic Characteristics	Y		Y
Ethnicity, Race, and Racial Combination Details	Y		Y
Selected Safety Measures at Baseline, Overall and by Country	Y		[1]
Selected Efficacy and Health Outcome Measures at Baseline, Overall and by Country	Y		[1]
Medical Conditions and Concomitant Medications			
Medical Conditions by Body System	Y		Y
Specific Medical Conditions	Y		Y
BPH History	Y		Y
Alpha-Blocker, 5-Alpha-Reductase Inhibitor, Phytotherapy Use [2]	Y		Y
Sexual Function	Y		Y
Family History: Premature Coronary Artery Disease, Breast Cancer, Prostate Cancer	Y		Y
Concomitant Medications	Y		Y

Display Type	Data Displays Generated		
	Table		Listing
Investigational Product Discontinuation, Exposure, Treatment Compliance			
Investigational Product Discontinuation	Y		Y
Study Drug Exposure	Y		Y
Study Drug Compliance	Y		Y
Treatment Blind Broken			Y

NOTES :

- Y = Yes display generated.
- There are no planned Study Population figures.

[1] Reference specific measurement listing in safety, efficacy, and health outcomes
[2] Summaries generated for each Alpha-Blocker, 5-Alpha-Reductase Inhibitor, Phytotherapy Use as well as a) Alpha-Blocker or 5-Alpha-Reductase Inhibitor Use and b) Alpha-Blocker or 5-Alpha-Reductase Inhibitor or Phytotherapy Use).

6.2. Subject Accountability

Summaries for the following will be produced in terms of total number overall:

- enrolled subjects
- subjects who entered placebo run-in phase
- subjects who entered placebo run-in but withdrew prior to randomization.

Enrolled subjects includes those who entered placebo run-in phase and/or who were randomized.

Summaries for the following will be produced by treatment and in terms of total number overall:

- number of subjects who were randomized to double-blind but missed placebo run-in
- number of subjects who were randomized to double-blind but do not have a double-blind treatment start date
- number of subjects who have a double-blind treatment start date but were not randomized
- number of subjects who were randomized to double-blind and did not take at least one dose of study medication
- number of randomized subjects (ITT population) and defined as subjects with a nonmissing treatment number
- number of subjects in the Per-Protocol population.

Summaries of the ITT population will be produced by country and center and output by randomized treatment and overall.

A listing of randomized subjects (ITT population) will be produced and will include the scheduled randomized treatment and the actual randomized treatment. A flag will be included on the listing to indicate if the scheduled treatment differs from the actual

randomized treatment; as well, any such cases will be included as per-protocol deviations.

6.3. Subject Disposition

A subject may withdraw from the study at any time at the investigator's discretion or at the request of the subject.

The reason for study withdrawal is recorded in the eCRF for subjects who entered placebo run-in but withdrew prior to randomization. A tabular summary will be produced for number and percentage of subjects who entered placebo run-in and withdrew prior to randomization, overall and by reason. For this summary, the percentages are calculated using total subjects who entered placebo run-in as the denominator.

The reason for study withdrawal is recorded in the eCRF for randomized subjects who prematurely withdrew from the study in advance of the Month 24 visit. A tabular summary will be produced for number and percentage of subjects prematurely withdrawing from the study, overall and by reason, and will be output by treatment group and total. For this summary, the percentages are calculated using the ITT population as the denominator.

A listing will be produced for the ITT population with key accountability data including placebo run-in start and stop dates, randomization date, treatment start and stop dates, subject withdrawal (yes or no), completion or withdrawal date, and all visit dates.

ITT population subject discontinuation will be summarized by visit intervals as overall totals and by discontinuation reason; these summaries will be output by treatment group and total. Visit interval determination used for these summaries is defined in Appendix 3 (Assessment Windows).

6.4. Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized overall and by treatment group for the ITT population; summaries will be repeated by country:

- sex
- age in years
- age categories: <65, ≥ 65, <75, ≥ 75 years
- ethnicity: Hispanic, Not Hispanic
- race / ethnicity: Asian, Hispanic / Latino, White, Not-Hispanic
- height
- weight
- body mass index
- history of tobacco use including number of cigarettes smoked per day
- alcohol use including number of units per week
- baseline safety including ECG, PSA, systolic blood pressure, diastolic blood pressure, heart rate, and C-SSRS
- baseline efficacy including IPSS, prostate volume, and Qmax

- baseline health outcome measures including BII and QOL Q8
- baseline C-SSRS

Race and racial combinations, will be summarized overall and by treatment group for the ITT population. Reference Appendix 6 for race and ethnicity details and combinations.

6.5. Medical Conditions and Concomitant Medications

The following medical conditions and medication history are GSK standardized data collections and/or are of interest in terms of the protocol population, study treatments, and indication. These characteristics will be summarized overall and by treatment group for the ITT population.

- medical conditions by body system (includes GSK standardized collection)
- specific medical conditions (more specific or in addition to the above body systems)
- BPH history including time since first LUTS and time since BPH diagnosis
- alpha-blocker use
- 5-alpha-reductase inhibitor use
- alpha-blocker and 5-alpha-reductase inhibitor use
- phytotherapy for BPH use
- sexual function including activity status at screening along with impotence and lack of libido status of prior 3 months
- family history of premature coronary artery disease
- family history of breast cancer
- family history of prostate cancer

Note: ARI114265 eCRF is designed to collect affirmative 'Yes' responses to the following: Alpha-blocker use, 5-alpha-reductase inhibitor use, and phytotherapy use. 'No' responses are not collected. For purposes of the related summaries, then number of subjects with a 'No' response will be assumed as the Intent-to-Treat Population treatment arm minus the 'Yes' responses. Both 'Yes' and 'No' usage along with (%) of population will be presented on relevant tables.

Concomitant medication data are collected on eCRF log forms and will be coded using the GSK-Drug Anatomical Therapeutic Chemical (ATC) dictionary. Concomitant medications will be defined as any medication documented as such in the database, irrespective of start or stop dates or ongoing status.

A summary of concomitant medications will be provided for the ITT population. The number and percentage of subjects reporting the use of each concomitant medication will be summarized by treatment group and in total, ATC Level 1 and ingredient. A listing of the collected concomitant mediations, by treatment and subject, will be provided. A listing of the relationship between the ATC Level 1, ingredient and verbatim text for concomitant medications will be provided.

6.6. Investigational Product Discontinuation, Exposure, and Compliance

Reasons for investigational product discontinuation are recorded in the eCRF and may differ from a subject's study discontinuation reason. A tabular summary will be produced for number and percentage of subjects who prematurely discontinued investigational product. Summaries will be produced overall and by reason, and will be output by treatment group and total. For this summary, the percentages are calculated using the ITT population as the denominator.

A listing of subjects for whom the treatment blind was broken during the study, along with the reason, will be produced.

Study drug exposure (in days) is number of days between (double-blind) treatment start date and (double-blind) treatment stop date, both days inclusive. Study drug exposure is further explained in Appendix 6. Study drug exposure in days will be summarized by treatment group and overall. The number and proportion of subjects exposed to study drug will also be summarized by 180-day intervals for each treatment group and overall.

Overall study drug compliance is defined as 100 * Number of Pills Consumed / Number of Pills Prescribed. Compliance for a specific study drug component (e.g. Tamsulosin) is defined in the same way. Both of these definitions are explained further in Appendix 6. Overall study drug compliance will be summarized by treatment group and across the treatment groups. The number and proportion of subjects with overall compliance <75%, 75-125%, and >125%, will be summarized for each treatment group and across the treatment groups. Study drug compliance by component will also be summarized by treatment group and across the treatment groups.

7. PRIMARY STATISTICAL ANALYSES

7.1. Primary Efficacy Analyses

7.1.1. Overview of Planned Primary Efficacy Analyses

The primary efficacy parameter after the 2nd year of the study is change from baseline IPSS (International Prostate Symptom Score). The IPSS questionnaire consists of seven questions with each question score ranging from 0 to 5. It is administered at screening, baseline, and at each of the scheduled post-baseline treatment phase visits.

IPSS (also called IPSS total score) is the sum of the seven questions. IPSS summaries and analyses will be in terms of the total (score); exceptions will be noted such as for supporting summaries of individual questions. For calculation of the IPSS total, missing individual responses will be imputed when at least four of the seven questions are answered (nonmissing). For the imputation, the average of the nonmissing responses will be calculated and rounded to the nearest integer. This average will be imputed for the original missing response(s). If at least 20% of the subjects have at least one imputed IPSS then the statistical analyses will be repeated based on non-imputed scores.

The efficacy analyses will be based on the Intent-to-Treat (ITT) population. Table 3 provides an overview of the planned IPSS summaries and primary efficacy analyses. A list of planned data displays is in Appendix 15: List of Data Displays.

Table 3 Overview of Planned Primary Efficacy Analyses

Endpoint	Absolute			Change from Baseline			% Change from Baseline		
	L	F	T	L	F	T	L	F	T
IPSS (International Prostate Symptom Score) Change from Baseline									
Primary Analysis (Month 24 Visit)	Y[1]		Y	Y[1]	Y	Y[2]			
Supporting and Sensitivity Analyses of Primary Endpoint									
Mixed-Model Repeated-Measures (MMRM) Analysis (At Visit)						Y			
IPSS Change from Baseline by Subgroup[3]						Y			
Individual IPSS Questions	Y[1]		Y			Y			
IPSS Percentage Change from Baseline							Y[1]		Y
IPSS Non-imputed Score Analysis[4]			Y		Y	Y			
IPSS Per-Protocol Population Analysis[5]			Y		Y	Y			

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated. All outputs are based on ITT population except [4].
- Tables and figures have separate outputs for LOCF and At Visit, except for baseline summaries.

1. Individual questions 1 – 7 responses, total score, total score change from baseline, and percentage change from baseline are combined in a single listing and presented for every visit.
2. Primary efficacy analyses are presented within this table; details are in the following section.
3. Subgroups are defined in Section 7.1.3 and Appendix 10: Examination of Covariates and Subgroups.
4. Analysis is performed only if RAP Section 7.1 imputation conditions are met.
5. Analysis is performed only if RAP Section 4 per-protocol conditions are met.

7.1.2. Planned Primary Efficacy Statistical Analyses

Endpoint: The primary efficacy parameter is the change from baseline IPSS at Year 2 (Month 24) using the last observation carried forward approach (LOCF) based on the Intent-to-Treat (ITT) population.

Table 3 provides an overview of the planned IPSS summaries and primary efficacy analyses. A list of planned data displays is in Appendix 15: List of Data Displays. Baseline and change from baseline are defined in Appendix 6. Last observation carried forward (LOCF) and At Visit approaches are defined in Appendix 7.

Note: IPSS timepoints earlier than Month 24, specifically Month 21 – Month 3, in this order, are classified as secondary endpoints. Summaries and analyses of these timepoints will be conducted in same manner and on same outputs as the primary analyses. Reference Table 4.

Model Specification and Results Presentation: Change from baseline IPSS at each scheduled post-baseline assessment will be compared in terms of combination treatment versus tamsulosin treatment using t-tests from a general linear model (GLM) with effects for treatment, cluster, and baseline IPSS. Two-sided tests at 0.05 level of significance will be conducted.

The adjusted mean estimates (mean and standard error), the adjusted mean difference, and the 95% confidence interval in terms of the adjusted mean difference will be presented. The adjusted mean difference will be in terms of combination treatment minus tamsulosin treatment. The model results will be presented on same tabular summary as the arithmetic mean, standard deviation, median, minimum and maximum. The results will be presented by treatment for each scheduled post-baseline assessment.

IPSS adjusted mean change from baseline will be plotted by treatment for each post-baseline scheduled visit in terms of each LOCF and At Visit approach.

Multiple Comparisons and Multiplicity: Reference Appendix 11, Multiple Comparisons and Multiplicity.

Model Checking and Diagnostics: Reference Appendix 12, Model Checking and Diagnostics for Statistical Analyses.

7.1.3. Supporting and Sensitivity Analyses of Primary Endpoint

The following describes supporting and sensitivity analyses of the primary endpoint.

Mixed-Model Repeated-Measures (MMRM) Analysis: As a supportive analysis, IPSS will be analyzed using a mixed-model repeated-measures (MMRM) analysis including ITT population data from the scheduled post-baseline assessments. Details are provided in Appendix 13, Mixed-Model Repeated-Measures Analysis.

IPSS Change from Baseline by Subgroup: For each subgroup, IPSS change from baseline summaries will be output by treatment group at Month 12 and at Month 24 for the ITT population using both LOCF and At Visit approaches. No statistical testing will be performed. Subgroups are defined in Appendix 10, Examination of Covariates and Subgroups.

Individual IPSS Questions 1 – 7: Each of the 7 IPSS individual question responses will be summarized at Baseline, Month 12, and Month 24 by treatment group. Month 12 and Month 24 change from baseline will be summarized by treatment group for each of the 7 questions. The summaries will be based on the ITT population and presented using both LOCF and At Visit approaches. No statistical testing will be performed.

IPSS Percentage Change from Baseline: Percentage change from baseline is defined in Appendix 6. IPSS percentage change from baseline will be summarized by treatment group at each scheduled post-baseline assessment. The summaries will be based on the ITT population and presented using both LOCF and At Visit approaches. No statistical testing will be performed.

IPSS Non-Imputed Score Analysis: IPSS missing response imputation procedure is described above. If at least 20% of the ITT subjects have at least one imputed IPSS then the tables, figures, and analyses described in Section 7.1.2 (Planned Primary Efficacy Statistical Analyses) will be repeated using non-imputed scores.

IPSS Per-Protocol Population Analysis: Per-Protocol (PP) population is defined in Section 4. If the PP population comprises 80% or less of the ITT population, then the tables, figures, and analyses described in Section 7.1.2 (Planned Primary Efficacy Statistical Analyses) will be repeated using the PP population.

8. SECONDARY STATISTICAL ANALYSES

8.1. Secondary Efficacy Analyses

8.1.1. Overview of Planned Secondary Efficacy Analyses

Table 4 Overview of Planned Secondary Efficacy Analyses

Endpoint	Absolute			Change from Baseline			% Change from Baseline		
	L	F	T	L	F	T	L	F	T
IPSS									
IPSS Months 3 – 21 (see Section 7.1.2)	Y		Y	Y	Y	Y			Y
Improvement Levels						Y[1]			Y[2]
Prostate Volume									
Absolute, Change, % Change [3]	Y		Y	Y		Y	Y	Y	Y
By Subgroup									Y
Improvement Levels									Y[4]
Maximum Urine Flow (Qmax)									
Absolute, Change, % Change [5]	Y		Y	Y	Y	Y	Y		Y
By Subgroup						Y			
Improvement Levels						Y[6]			Y[7]
AUR or BPH-Related Surgical Intervention[8]									
Time to event	Y	Y	Y						
Event incidence			Y						
Other Efficacy Measures [9]									
Urinary tract infection / urosepsis	Y		Y						
Urinary incontinence	Y		Y						
Renal insufficiency	Y		Y						

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Tables and figures have separate outputs for LOCF and At Visit, except for baseline summaries and AUR or BPH-related surgical intervention.

1. IPSS change from baseline five improvement categories are ≥1 point through ≥5 points. 'No change' and 'worsening' are also presented. Treatment comparisons are in terms of ≥2 points and separately ≥3 points.
2. IPSS percentage change from baseline seven improvement categories are >0%, ≥10%, ≥20%, ≥25%, ≥30%, ≥40%, and ≥50%. Treatment comparisons are in terms of ≥25%.
3. Prostate volume printed and summarized for absolute, change from baseline, percentage change from baseline; dimensions will be printed. Prostate volume analyses are based on percentage change from baseline.
4. Prostate volume percentage change from baseline seven improvement categories are >0%, ≥10%, ≥20%, ≥25%, ≥30%, ≥40%, and ≥50%. Treatment comparisons are in terms of ≥25%.
5. Qmax printed and summarized for absolute, change from baseline, percentage change from baseline; total voided volume will be printed. Qmax analyses are based on change from baseline.
6. Qmax change from baseline six improvement categories are >0 ml/sec and ≥1 ml/sec through ≥ 5 ml/sec. 'No change' and 'worsening' are also presented. Treatment comparisons are in terms of ≥3 ml/sec.
7. Qmax percentage change from baseline six improvement categories are >0%, ≥10%, ≥20%, ≥30%, ≥40%, and ≥50%. Treatment comparisons are in terms of ≥30%.
8. Summaries are repeated individually for AUR and BPH-Related Surgical Intervention.
9. Data of other efficacy measures are summarized. No treatment comparisons are performed.

8.1.2. IPSS Improvement Levels

Symptom improvement is assessed using IPSS continuous data changes as the primary efficacy endpoint and using categorical changes as a secondary efficacy endpoint. Improvement is a post-baseline score which is lower than the baseline score. Worsening is a post-baseline score which is higher than the baseline score. The number and percentage of subjects with IPSS percentage change from baseline categories of 1) improvement, 2) no change, and 3) worsening will be summarized by treatment group using both the LOCF and At Visit approaches at each scheduled post-baseline assessment.

IPSS change from baseline will be presented using five improvement levels: ≥1 point through ≥5 points. IPSS percentage change from baseline will be presented using seven improvement levels: >0%, ≥10%, ≥20%, ≥25%, ≥30%, ≥40%, and ≥50%. Treatment comparisons for combination versus tamsulosin will be performed for each ≥ 2 points, ≥3 points, and ≥25% using a Mantel-Haenszel test controlling for cluster at alpha=0.05.

8.1.3. Prostate Volume

Prostate dimensions are measured at the second screening visit (1b) and at each Month 12 and Month 24 (or end of treatment) visits. For analysis and reporting,

- Prostate Volume =
  pi/6 (Anteroposterior Width x Cephalocaudal Width x Transverse Width).

Prostate volume percentage change from baseline is a secondary efficacy endpoint.

Table 4 provides an overview of the planned prostate volume summaries and analyses. A list of planned data displays is in Appendix 15: List of Data Displays. Baseline, change from baseline, and percentage change from baseline are defined in Appendix 6. Last observation carried forward (LOCF) and At Visit approaches are defined in Appendix 7. Summaries and analyses will be in terms of the ITT population; LOCF approach will be considered primary. Prostate volume summary statistics will be presented for baseline, Month 12 visit, and the Month 24 visit; change from baseline and percentage change from baseline summary statistics will be presented for the Month 12 and Month 24 visits.

Combination treatment and tamsulosin treatment will be compared in terms of prostate volume percentage change from baseline at the Month 12 and Month 24 visits using t-tests from the following general linear model; two-sided tests at 0.05 level of significance will be conducted:

- log (post baseline prostate volume / baseline prostate volume) =
  log (baseline prostate volume) + treatment + cluster

The adjusted mean estimates (mean and standard error), the adjusted mean difference, and the 95% confidence interval in terms of percentage change from baseline will be reported. The adjusted mean differences will be in terms of combination treatment minus tamsulosin treatment. The model results will be presented on same tabular summary as the arithmetic mean, standard deviation, median, minimum and maximum. The results will be presented by treatment for each scheduled post-baseline assessment.

Prostate volume adjusted mean percentage change from baseline will be plotted by treatment for each post-baseline scheduled visit in terms of each LOCF and At Visit approach.

The number and percentage of subjects with prostate volume percentage change from baseline categories of 1) improvement, 2) no change, and 3) worsening will be summarized by treatment group using both the LOCF and At Visit approaches at each scheduled post-baseline assessment. Improvement is a post-baseline prostate volume which is lower than the baseline prostate volume. Worsening is a post-baseline prostate volume which is higher than the baseline prostate volume.

Prostate volume percentage change from baseline will be presented using seven improvement levels: >0%, ≥10%, ≥20%, ≥25%, ≥30%, ≥40%, and ≥50%. Treatment comparisons for combination versus tamsulosin will be performed for ≥25% prostate volume improvement using a Mantel-Haenszel test controlling for cluster at alpha=0.05.

Supportive subgroup summaries of prostate volume percentage change from baseline will be presented in manner similar to that described for primary efficacy in Appendix 10, Examination of Covariates. Reference Appendix 15 for a list of planned prostate volume subgroup tables.

Model checking associated with prostate volume percentage change from baseline will be conducted in manner similar to that described for primary efficacy in Appendix 12. Reference Appendix 15 for a list of prostate volume model checking outputs.

Reference Appendix 11 for multiplicity considerations.

8.1.4. Maximum Urine Flow (Qmax)

Qmax and associated total voided volume are measured at screening (Visit 1a with possible repeat at Visit 1b), baseline, and at each Month 6, Month 12, Month 18, and Month 24 (or end of treatment) visits. Qmax change from baseline is a secondary efficacy endpoint. Qmax measurements with voided volumes <125 ml will not be included in the analysis.

Table 4 provides an overview of the planned Qmax summaries and analyses. A list of planned data displays is in Appendix 15: List of Data Displays. Baseline, change from baseline, and percentage change from baseline are defined in Appendix 6. Last observation carried forward (LOCF) and At Visit approaches are defined in Appendix 7. Summaries and analyses will be in terms of the ITT population; LOCF approach will be considered primary. Qmax summary statistics will be presented for each scheduled visit; change from baseline and percentage change from baseline will be presented for each scheduled post-baseline visit.

Change from baseline Qmax at each scheduled post-baseline assessment will be compared in terms of combination treatment versus tamsulosin treatment using t-tests from a general linear model (GLM) with effects for treatment, cluster, and baseline Qmax. Two-sided tests at 0.05 level of significance will be conducted.

The adjusted mean estimates (mean and standard error), the adjusted mean difference, and the 95% confidence interval in terms of the adjusted mean difference will be presented. The adjusted mean difference will be in terms of combination treatment minus tamsulosin treatment. The model results will be presented on same tabular summary as the arithmetic mean, standard deviation, median, minimum and maximum. The results will be presented by treatment for each scheduled post-baseline assessment.

Qmax adjusted mean change from baseline will be plotted by treatment for each post-baseline scheduled visit in terms of each LOCF and At Visit approach.

Qmax improvement is also assessed using categorical changes. Improvement is a post-baseline Qmax which is higher than the baseline Qmax. Worsening is a post-baseline Qmax which is lower than the baseline Qmax. The number and percentage of subjects with Qmax percentage change from baseline categories of 1) improvement, 2) no change, and 3) worsening will be summarized by treatment group using both the LOCF and At Visit approaches at each scheduled post-baseline assessment.

Qmax change from baseline will be presented using six improvement levels: >0 ml/sec and ≥1 ml/sec through ≥5ml/sec. Qmax percentage change from baseline will be presented using six improvement levels: >0%, ≥10%, ≥20%, ≥30%, ≥40%, and ≥50%. Treatment comparisons for combination versus tamsulosin will be performed for each ≥3ml/sec and ≥30% using a Mantel-Haenszel test controlling for cluster at alpha=0.05.

Supportive subgroup summaries of Qmax change from baseline will be presented in manner similar to that described for primary efficacy in Appendix 10, Examination of Covariates. Reference Appendix 15 for a list of planned Qmax subgroup tables.

Model checking associated with Qmax change from baseline will be conducted in manner similar to that described for primary efficacy in Appendix 12. Reference Appendix 15 for a list of Qmax model checking outputs. As a supportive analysis, Qmax will be analyzed using a mixed-model repeated-measures (MMRM) analysis in a manner similar to that described for primary efficacy in Appendix 13.

Reference Appendix 11 for multiplicity considerations.

8.1.5. AUR or BPH-Related Surgical Intervention

All AUR and BPH-related surgery events during participation in the study are recorded. Subjects who discontinue from the study are followed for AUR and BPH-related surgery until the 24 month anniversary of randomization. This follow-up is in terms of biannual telephone contacts beginning at the first six month scheduled interval after discontinuation. Analyses will be in terms of events recorded at clinic visits and also collected in the biannual telephone contacts. Table 4 provides an overview of the planned summaries and analyses. A list of planned data displays is in Appendix 15: List of Data Displays.

Time to first AUR or BPH-related surgery will be defined as the number of days from treatment start date to date of the first event (earliest occurring of either AUR or BPH-related surgery) for each subject. Time to first AUR or BPH-related surgery is classified as a secondary efficacy endpoint and will be analyzed in terms of the Intent-to-Treat population.

Censoring will occur at the earliest of the following dates as applicable: the date of prostatectomy, the date of last contact for AUR and surgical intervention, and the date of death. For censoring, 'prostatectomy' will be determined from the eCRF prostatic surgical intervention log using the following codes associated with 'prostatectomy': open, retropubic with or without nerve-sparing, suprapubic, transvesical, perineal, salvage, laparoscopic, laparoscopic assisted. Note this excludes 'partial prostatectomy'.

The 'date of last contact for AUR and surgical intervention assessment' will be assigned as the latest of:
--Date of last treatment-phase visit
and
--Date of last successful biannual follow-up telephone contact.

Partial dates will be handled as described in Appendix 7, Premature Withdrawals & Handling of Missing Data.

The number of subjects having the first AUR or BPH-related surgery event on or after treatment start will be tabulated by treatment, by the two annual time periods (Month 12 and Month 24), as well as by three month intervals (quarterly) along with the number of subjects at risk during each of these time periods.

Note: Cut-off dates are defined in Appendix 6; definition is repeated here:
Month k Cut-off Date (for k= 3, 6, 9, 12, 15, 18, 21, 24): The maximum of [Month k clinic visit date, Month k lab visit date, Baseline Date + (k * 91/3)].

The primary analysis of this endpoint will compare combination treatment versus tamsulosin treatment in terms of time to first AUR or BPH-related surgery for the ITT population using a log rank test stratified by cluster at the 0.05 level of significance. The relative risk (hazard ratio) for the treatment effect and associated two-sided 95% confidence intervals will be estimated using a Cox proportional hazards model with treatment as the only covariate and stratified by cluster. Estimates and corresponding confidence intervals for the relative risk (hazard ratio) and risk reduction (1-hazard ratio) of combination treatment versus tamsulosin treatment will be presented along with the log rank p-value. Assessment of the Cox modeling procedure will include examination of diagnostic plots to assess the assumption of proportional hazards and the review of results obtained by fitting separate models by cluster to assess the homogeneity of treatment effect across clusters.

Time to first AUR or BPH-related surgery, expressed as months, will be summarized by treatment group for the ITT population using product-limit estimates computed by the Kaplan-Meier method and displayed graphically as Kaplan-Meier curves.

The number of subjects with at least one AUR or BPH-related surgery will be summarized by treatment group across the 2 year period. The crude rate of AUR or BPH-related surgery incidence will be calculated using the Intent-to-Treat population of each treatment as the denominator; the associated 95% confidence interval will be output. This crude rate will be compared for combination treatment versus tamsulosin treatment using the Mantel-Haenszel test stratified by cluster at the 0.05 level of significance.

AUR or BPH-related surgery event details per subject will be summarized by treatment and will include: event component (first occurring of either AUR or BPH-related surgery) and time period of first occurring event (during treatment or after treatment stop). BPH-relatedness (yes/no) and AUR precipitating factors will be summarized by treatment for subjects in which AUR is the primary efficacy event's initial component. Types of surgery/intervention will be summarized by treatment for subjects in which BPH-related surgery is the primary efficacy event's initial component.

Time from last dose to first AUR or BPH-related surgery event will be summarized for those subjects experiencing the first event after treatment stop.

Hospitalization details for the initial AUR will be summarized by treatment group for patient admission status (inpatient or outpatient). For inpatients, the ward type and hospitalization days will be summarized by treatment.

The frequency and percentage of subjects with multiple AUR or BPH-related surgery events will be summarized by treatment. The frequencies of subjects with 2 events, 3 events, or ≥4 events will be summarized. Among subjects with both events, the pattern of occurrence (AUR/Surgery or Surgery/AUR) will be summarized.

The above described summaries and analyses of AUR or BPH-related surgery will be repeated, when applicable, for the individual components 1) AUR and 2) BPH-related surgery.

All AUR and surgical intervention data will be listed by treatment and subject. Time to first AUR or BPH-related event will be listed for each subject along with the dates used in the computation of these values.

8.1.6. Other Efficacy Measures

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

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

Each of the three 'other efficacy measures' will be summarized by treatment group for number of subjects with at least one post-randomization event across the 2-year period. The crude rate of each measure will be calculated using the Intent-to-Treat population of

each treatment as the denominator; the associated 95% confidence interval will be output. No formal treatment comparisons will be performed.

Data collected in terms of these other efficacy measures will be listed by treatment and subject.

8.2. Safety Analyses

Safety summaries and analyses are reported in terms of the following data classifications: adverse events, clinical laboratory assessments (haematology and clinical chemistry), total serum prostate specific antigen (PSA), qualitative breast examination, digital rectal examination, vital signs, suicidality, and post void residual volume.

All safety analyses will be performed using the ITT population unless otherwise specified in text or data display shells. Applicable safety analysis and reporting definitions and presentations within "Program Safety Analysis Plan (PSAP, 2016) for GI198745 (dutasteride) and GSK2285985 (fixed dose combination of dutasteride [GI198745] and tamsulosin [GI138525]" are utilized within this RAP, with any deviations noted.

8.2.1. Overview of Adverse Event Tabular Summaries

Table 5 provides an overview of the planned adverse event tabular summaries. A list of planned data displays is in Appendix 15: List of Data Displays.

Reference Section 4 (Analysis Populations) and Appendix 6 (Derived and Transformed Data) for supporting definitions on all below subsections.

Table 5 Overview of Planned Adverse Event Tabular Summaries

Adverse Event Types, High Level								
		Any	Drug-Related	Non-Serious	Serious	Leading to W/D from Study	Perm. D/C of Study Drug	Fatal
By Type		---------- 3.1 (6 above categories, excluding Non-serious) ----------						
Overall		3.2 3.3 [1] 3.4 [2] 3.13 [3]	3.18 3.19 [1] 3.20 [2]	3.5	3.25 3.26 [1] 3.27 [2]	3.35	3.38	3.33
By 6-Month Onset Period		3.6 3.14 [3]	3.21		3.28			
By Age (<65, ≥65)		3.7	3.22		3.29			
By Age (<75, ≥75)		3.8	3.23		3.30			
By Country		3.9	3.24		3.31			
By Descending Frequency		3.10		3.12	3.11			
By Maximum Intensity		3.15						
Most Common		3.16		3.17				
Adverse Event Types, Two Levels								
	Drug-Related and Serious	Drug-Related and Fatal	Drug-Related and Leading to W/D from Study	Serious and Leading to W/D from Study	Drug-Related and Leading to Perm D/C of Study Drug	Serious and Leading to Perm D/C of Study Drug		
Overall	3.32	3.34	3.36	3.37	3.39	3.40		
Sexual and Breast Adverse Events of Special Interest								
		Altered (Decreased) Libido	Impotence	Ejaculation Disorders	Breast Disorders (includes Enlargement and Tenderness)			
MedDRA		----------3.41----------						
Overall (and by baseline characteristics)		3.42	3.43	3.44	3.45, 3.46 [4], 3.47 [5]			
By Type		----------3.48----------						
Not Resolved & Leading to Study Withdrawal	Overall	----------3.49----------						
	By Type	3.50	3.51	3.52	3.53			
Prostate Cancer Adverse Event of Special Interest								
Prostate Cancer Overall		3.54						
Cardiovascular Adverse Events of Special Interest								
	Acute Coronary Syndrome	Ischemic Cerebro-vascular Events	Cardiac Failure	Ischemic Coronary [6]	Cardiac Arrhyth-mia	Peripheral Vascular Disease	Cardio-vascular Events	
MedDRA	----------3.55----------							
Overall	3.56	3.57	3.58	3.59	3.60	3.61	3.62	
Infrequent Tier 1 Adverse Events of Special Interest								
MedDRA	3.63							

Notes: Summaries are in terms of 'Starting Post-Randomization' (defined in Appendix 8) unless otherwise noted as [1] – [3]:

1. Starting On-Treatment; defined in Appendix 8.
2. Starting Post-Treatment; defined in Appendix 8.

3. Starting On-Treatment and in terms of 'Study Drug Exposure Basis" in which [Rate] is the number of subjects per 100 person-years of study drug exposure; adverse events for subjects with missing study drug exposure are excluded.
4. Breast Disorders: subcategory Breast Enlargement
5. Breast Disorders: subcategory Breast Tenderness
6. Ischemic Coronary Artery Disorders / Atherosclerosis

8.2.2. Adverse Events

Adverse events (AEs) will be coded using the MedDRA (Medical Dictionary for Regulatory Activities) coding dictionary. As specified in the protocol, disease related events will not be reported as AEs or serious adverse events (SAEs) unless the investigator assesses the event as more severe than expected for the subject's condition. A mapping of the MedDRA primary system organ class and preferred term to which each verbatim term has been coded will be provided in a listing.

Adverse events (AEs) are to be recorded on the electronic case report form (eCRF) from the start of the placebo run-in phase study treatment until the end of the two year study period. Serious AEs (SAEs) are to be recorded over the same time period as non-serious AEs. However, any SAEs assessed **as related** to study participation or related to a GSK concomitant medication, will be recorded from the time a subject consents to participate in the study up to the end of the two year study period. After discontinuation of study treatment, the investigator will monitor all AEs/SAEs that are ongoing until resolution or stabilization of the event or until the subject is lost to follow-up. Investigators are not required to actively seek information on adverse events occurring after the follow-up contact, but may report any adverse event that they believe may be related to investigational product regardless of when the event occurs. Adverse events summaries will include non-serious as well as serious AEs.

Subjects with sexual function related adverse events leading to study withdrawal, will be followed up for up to 6 months after the last dose of study drug using the sexual function Targeted Follow-Up Questionnaire (TFUQ).

If an AE occurs which, in the investigator's judgment, is possibly related to suicidality, a Possible Suicidality-Related Adverse Event (PSRAE) form should be completed by investigators or their designated staff.

Each AE will be categorized into the following periods according to its onset date: pretreatment, post-randomization, on-treatment, post-treatment. These periods are not mutually exclusive and an AE could be categorized into more than one period. The definitions of these categories are provided in Appendix 8: Adverse Event Time Periods and Special Adverse Event Definitions.

Pre-treatment AEs will not be summarized; they will be included in the AE listing specified later in this section.

The number of post-randomization adverse events, the number and the percentage of subjects reporting any post-randomization AE will be summarized by treatment group for the following:

- All AEs
- Drug-related AEs
- Serious AEs
- AEs leading to study drug discontinuation
- AEs leading to withdrawal from study
- Fatal AEs

Comparisons of treatment groups for each of these sets of AEs will be performed using Fisher's Exact Test.

Total number of adverse events reported in the study as well as the number and percentage of subjects reporting at least one AE will be provided for each treatment group. Total number of AEs as well as the number and percentage of subjects reporting each AE will be reported by treatment group, primary system organ class and preferred term. On-treatment and post-treatment AEs will be summarized separately, as well as together as post-randomization AEs. Non-serious post-randomization AEs will be summarized by treatment group. A summary of post-randomization AEs will be provided by treatment group and six month time period of onset (Months 1-6, Months 7-12, Months 13-18, Months 19-24), by treatment group and age group (<65 years, ≥65 years), by treatment group and age group (<75 years, ≥75 years), and by treatment group and country.

A summary of post-randomization AEs will be provided by treatment group and preferred term by descending frequency of preferred term (regardless of system organ class). In addition, such summaries will be done for serious post-randomization AEs and also for non-serious post-randomization AEs.

For on-treatment AEs, the event rate per 100 person-years of study drug exposure will be summarized by treatment group, primary system organ class and preferred term overall and by time period (Months 1-6, Months 7-12, Months 13-18, Months 19-24).

A summary of post-randomization AEs will also be provided by treatment group and maximum intensity. If the same AE occurs on multiple occasions in the same subject, the AE with the highest intensity will be presented. Intensity will be categorized as mild, moderate, or severe; a category for missing/not applicable intensity will be included.

The most common AEs (Tier 2 events) are defined as those preferred terms occurring in at least 5% of the subjects within any treatment group (non-rounded). The total number of events as well as the number and percentage of subjects reporting at least one most common AE preferred term starting post-randomization will be provided for each treatment group. The number of events, the number and percentage of subjects reporting the most common AE preferred terms starting post-randomization will be provided by treatment group displayed by decreasing frequency of preferred terms (regardless of primary system organ class). For each of these most common AEs, the percentage of subjects in the treatment groups will be compared using Fisher's exact test. In addition, the percentage of subjects reporting each AE by treatment group along with the corresponding odds ratio and 95% confidence interval for each of the most common AEs

will be displayed in a figure sorted by odds ratio in descending order, by treatment group. The above summary will also be provided for the most common non-serious post-randomization AEs.

Total number of drug-related adverse events as well as the number and percentage of subjects reporting at least one drug-related AE will be provided for each treatment group. Total number of drug-related adverse events as well as the number and percentage of subjects reporting each drug-related AE will be reported by treatment group, primary system organ class and preferred term. On-treatment and post-treatment drug-related AEs will be summarized separately, as well as together as post-randomization drug-related AEs. A summary of post-randomization drug-related AEs will be provided by treatment group and time period (Months 1-6, Months 7-12, Months 13-18, Months 19-24), by treatment group and age group (<65 years, ≥65 years), by treatment group and age group (<75 years, ≥75 years) and by treatment group and country.

A listing of all AEs, a listing of AEs by onset period, and a listing of which subjects reported specific AEs will be presented. A listing of Possible Suicidality Related Adverse Event (PSRAE) data will be provided. A listing of the sexual function Targeted Follow-Up Questionnaire (TFUQ) data will be provided.

8.2.3. Deaths and Serious Adverse Events

Total number of serious adverse events as well as the number and percentage of subjects reporting at least one serious AE will be provided for each treatment group. Total number of serious adverse events as well as the number and percentage of subjects reporting each serious AE will be reported by treatment group, primary system organ class and preferred term. On-treatment and post-treatment serious AEs will be summarized separately, as well as together as post-randomization serious AEs. A summary of post-randomization serious AEs will be provided by treatment group and time period (Months 1-6, Months 7-12, Months 13-18, Months 19-24), by treatment group and age group (<65 years, ≥65 years), by treatment group and age group (<75 years, ≥75 years), and by treatment group and country. A summary of all post-randomization drug-related serious AEs, of all post-randomization fatal AEs, and of all post-randomization drug-related fatal AEs will be provided by treatment group. Time to death will be summarized by treatment group using Kaplan-Meier estimates and displayed as Kaplan-Meier plots.

Individual subject listings of all non-fatal serious AEs and a separate listing of all fatal serious AEs will be provided. The listing will indicate the timing of the serious AE with respect to treatment start date.

8.2.4. Adverse Events Leading to Discontinuation of Investigational Product and/or Withdrawal From the Study and Other Significant Adverse Events

8.2.4.1. Adverse Events Leading to Discontinuation of Investigational Product and/or Withdrawal from the Study

A summary of adverse events starting post-randomization and leading to withdrawal from the study will be provided by treatment group for the following categories:

- All AEs
- Drug-related AEs
- Serious AEs

Similar summaries will be provided for adverse events leading to permanent discontinuation of the study medication.

Subject listings of AEs leading to withdrawal from the study and AEs leading to permanent discontinuation of study drug will be provided. The listings will indicate the timing of the AE with respect to treatment start date.

8.2.4.2. Adverse Events of Special Interest

Tier 1 adverse events of special interest are pre-specified adverse event preferred terms for which there are predefined hypotheses about the existence of a potential treatment effect. These events include the following:

- Sexual and breast events
- Prostate cancer
- Cardiovascular events
- Infrequent events

Summaries for these events are specified in the following sections and will be based on post-randomization AEs unless otherwise indicated. A mapping of the MedDRA primary system organ class and preferred term to which each verbatim term in the special interest AE categories has been coded will be provided in a listing.

8.2.4.3. Sexual and Breast Tier 1 Adverse Events of Special Interest

Altered (decreased) libido, impotence, ejaculation disorders, and breast disorders, will be defined as sexual and breast adverse events of special interest. In addition, two subgroups of breast disorders (breast disorders: breast enlargement, and breast disorders: breast tenderness) are of special interest. MedDRA system organ class and preferred terms included in these special interest adverse events are defined in Appendix 8, Table A.

Total number of, as well as number and percentage of the subjects experiencing, sexual and breast adverse events of special interest will be provided by treatment group. In addition, for each of the events of special interest, the number and percentage of subjects by treatment will be provided for the following:

- having an event
- having multiple events
- having an event in 6-month windows, starting from treatment start date

The following categories are related to the occurrence of the first event of the special interest AE; number and percentage of subjects in these categories will be provided by treatment group:

- drug-related AE
- serious AE
- AE leading to withdrawal from the study
- AE leading to permanent discontinuation of study drug
- AE outcome
- AE resolution status (on-therapy vs. off-therapy – see Appendix 8 for definition)
- AE maximum intensity

The number and percentage of the subjects experiencing an adverse event of special interest will be provided by treatment group for the following. The by-baseline summaries will be output in the above described overall tabular summaries:

- By baseline age group: < 65 years, ≥65 years
- By sexual activity at baseline (Yes, No) based on "sexually active" question.

The number and percentage of subjects experiencing the following types of sexual and breast adverse events of special interest will be provided by treatment group:

- Any Type (Impotence, Decreased Libido, Ejaculation Disorders, or Breast
- Disorders)
- One AE Type
- Two AE Types
- Three AE Types
- All Four AE Types

The time to first onset in days will be summarized by treatment group as a continuous variable as well as by time period of onset. In addition, time to first adverse event of special interest will be summarized by treatment group using estimates calculated by the Kaplan-Meier method and displayed graphically as Kaplan-Meier curves. Time to resolution for the first event in days will be summarized by treatment group.

Duration of adverse events of special interest will be summarized by treatment group for uncensored values, censored values, and all values. It is recognized that summary statistics such as means and medians involving censored values will be biased (low).

The number of sexual and breast adverse events leading to study withdrawal, as well as the number and percentage of subjects reporting at least one such sexual and breast adverse event will be provided for all event types and also by event type for each treatment group.

Resolution status at end of study (resolved, not resolved) and time from treatment stop date to AE resolution will be summarized by treatment group for the sexual and breast adverse events leading to study withdrawal and not resolved at Month 24 / End of Treatment visit.

Listings of sexual and breast adverse events of special interest will be provided. A listing of sexual and breast adverse event status data will be provided.

A listing of the TFUQ data for sexual and breast adverse events will be provided.

8.2.4.4. Prostate Cancer Tier 1 Adverse Events of Special Interest

Prostate cancer will be defined as an adverse event of special interest. MedDRA preferred terms and codes included in this special interest adverse event are defined in Appendix 8, Table B. Prostate cancer events will be summarized separately following the same format done for sexual and breast special interest AEs described above. Time to first event for prostate cancer events will be summarized separately by treatment group using estimates calculated by the Kaplan-Meier method and displayed graphically as Kaplan-Meier curves.

Listings of prostate cancer adverse events of special interest will be provided.

8.2.4.5. Cardiovascular Tier 1 Adverse Events of Special Interest

Cardiovascular adverse events of special interest will be defined as those included in the following six categories: acute coronary syndrome, ischemic coronary artery disorders/atherosclerosis, ischemic cerebrovascular events, cardiac failure, cardiac arrhythmias, and peripheral vascular disease. MedDRA preferred terms and codes included in these special interest adverse events are defined in Appendix 8, Table C. Total number of cardiovascular events as well as the number and percentage of subjects experiencing cardiovascular events will be provided by treatment group. Each category of cardiovascular events, and all cardiovascular events as one additional category, will be summarized separately following the same format done for sexual and breast special interest AEs described above. Time to first cardiovascular adverse event of special interest will be summarized by treatment group using estimates calculated by the Kaplan-Meier method and displayed graphically as Kaplan-Meier curves.

Listings of cardiovascular adverse events of special interest will be provided.

Note: The protocol Section 7.4.2.2 (Cardiovascular Events) indicates additional data collection required for some cardiovascular events and procedures; these data will be output in data listings. Cardiovascular events in protocol Section 7.4.2.2 are not the full set of cardiovascular adverse events defined in this RAP section.

8.2.4.6. Infrequent Tier 1 Adverse Events of Special Interest

Infrequent Tier 1 adverse events of special interest will be defined as those included in the following categories:

- Breast cancer
- Potential for decreased male fertility due to effects on sperm/semen characteristics
- Interference with formation of external genitalia in a male fetus if a woman carrying a male fetus is exposed to dutasteride

- Hair changes
- Allergic reactions
- Depressed mood
- Testicular pain and swelling
- Intraoperative floppy iris syndrome
- Orthostasis
- Priapism
- Stevens-Johnson syndrome
- Atrial fibrillation, tachycardia, arrhythmias

MedDRA preferred terms and codes included in these special interest adverse events are defined in Appendix 8, Table D. Total number of infrequent Tier 1 events as well as the number and percentage of subjects with infrequent Tier 1 events will be provided by treatment group.

Listings of infrequent Tier 1 adverse events of special interest will be provided.

8.2.5. Pregnancies

A listing of subjects whose female partner become pregnant during the study will be provided if there are any such subjects.

8.2.6. Clinical Laboratory Assessments

Clinical chemistry and hematology parameters are evaluated from samples scheduled at the first screening visit (1a) and at each Month 12 and Month 24 (or end of treatment) visits. The following tests will be performed:

Clinical Chemistry (serum): Alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, total protein, sodium, potassium, albumin, glucose, creatinine, UREA/BUN (blood urea nitrogen)

Hematology: Hemoglobin, platelet count, white blood cell count (WBC), red blood cell count (RBC)

For purposes of statistical analyses the baseline value of a parameter for each subject will be defined as the latest laboratory test value on or before the start of the randomized treatment for that subject.

The final value of a parameter for each subject is defined as the latest post-baseline value available in the study for that subject. A summary of parameter values, including the baseline and final value, will be provided by treatment group and scheduled visit. A summary of change from baseline in parameter values, including the final value, will also be provided by treatment group and scheduled visit.

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

The number and percentage of subjects with an abnormal laboratory value at baseline among subjects with a baseline laboratory value and at least one post baseline laboratory value will be provided by treatment group and by parameter. The number and percentage of subjects will be summarized by treatment group for each laboratory test for the following shift categories:

- Normal at baseline to abnormal at any time post-baseline
- Normal at baseline to high at any time post-baseline
- Normal at baseline to low at any time post-baseline
- Normal or low at baseline to high at any time post-baseline
- Normal or high at baseline to low at any time post-baseline

Laboratory data transitions from baseline to final assessment will be summarized for each parameter according to the following categories:

- Decrease: High to Low, Normal to Low, High to Normal
- No Change: Low to Low, Normal to Normal, High to High
- Increase: Low to Normal, Normal to High, Low to High

The threshold laboratory values are defined in terms of a multiplicative factor of the testing laboratory's normal range. A laboratory value that is above the upper limit factor multiplied by the upper limit of the normal range is considered a high threshold value. A laboratory value that is below the lower limit factor multiplied by the lower limit of the normal range is considered a low threshold value. Refer to Appendix 9 for a listing of the laboratory threshold factors.

The number and percentage of subjects with a threshold laboratory value at baseline among subjects with a baseline laboratory value and at least one post baseline laboratory value will be provided by treatment group and by parameter. Subjects with threshold values any time post-baseline with a non-threshold baseline laboratory value and at least one post-baseline laboratory value will also be summarized by treatment group and by parameter.

Listings of hematology and clinical chemistry data will be provided, along with listings of hematology and clinical chemistry data exceeding threshold.

The protocol defines possible drug-induced liver injury with hyperbilirubinaemia, for laboratory assessments planned in this study, as:

ALT ≥ 3xULN and Bilirubin ≥ 2xULN.

A listing of subjects meeting this defined liver function abnormality along with the corresponding data will be provided. If no subjects meet the defined criteria, a listing (page) will be produced indicating that no subjects met the criteria.

A blood draw for HBsAg and Hepatitis C Antibody is scheduled for Visit 2 (baseline). These measurements will be included in a data listing.

8.2.7. Serum PSA

Serum PSA samples are scheduled at the screening visit, and at each Month 6, Month 12, and Month 24 (or end of treatment) visits. Total PSA (absolute values, change from baseline values, and percentage change from baseline values) will be summarized by visit and treatment group using both the LOCF and At Visit approaches. Change from baseline total PSA will be compared in terms of combination treatment versus tamsulosin treatment at each scheduled post-baseline assessment using a general linear model with effects for treatment and baseline total PSA.

Listings of PSA data will be produced. A listing of PSA data will be provided, along with a listing of PSA data exceeding the upper limit of normal.

8.2.8. Post Void Residual Volume

Total voided volume (in conjunction with Qmax) is measured at screening (Visit 1a with possible repeat at Visit 1b), baseline, and at each Month 6, Month 12, Month 18, and Month 24 (or end of treatment) visits.

A list of planned data displays is in Appendix 15: List of Data Displays. Baseline, change from baseline, and percentage change from baseline are defined in Appendix 6. Last observation carried forward (LOCF) and At Visit approaches are defined in Appendix 7. Summaries and analyses will be in terms of the ITT population; LOCF approach will be considered primary. Post void residual volume summary statistics will be presented for each scheduled visit; change from baseline and percentage change from baseline will be presented for each scheduled post-baseline visit.

Post void residual volume change from baseline distribution at each scheduled post-baseline assessment will be compared in terms of combination treatment versus tamsulosin treatment using a nonparametric van Elteren test controlling for cluster at the 0.05 level of significance.

A listing of post void residual volume data will be provided.

8.2.9. Gynecomastia Evaluations

A qualitative breast examination is scheduled to be performed at the screening visit, and at each Month 6, Month 12, Month 18, and Month 24 (or end of treatment) visits. The number and percentage of subjects with palpable breast tissue or nipple tenderness and/or clinically significant palpable breast tissue or nipple tenderness at baseline, at each scheduled post-baseline assessment and the final assessment (the latest post-baseline evaluation available) will be presented by treatment. The number and percentage of subjects changing from ‘no’ at baseline to ‘yes’ at any post-baseline assessment for

palpable breast tissue and for nipple tenderness will be compared in terms of combination treatment versus tamsulosin treatment using Fisher's exact test.

The number and percentage of subjects changing from 'no' at baseline in clinical significance to 'yes' at any post-baseline assessment in clinical significance for palpable breast tissue and for nipple tenderness will be presented by treatment group.

A listing of gynecomastia data will be provided.

8.2.10. Digital Rectal Examinations

A digital rectal examination (DRE) is scheduled to be performed at the screening visit, and at each Month 6, Month 12, Month 18, and Month 24 (or end of treatment) visits. The results of normal versus focal abnormality will be summarized by treatment group at baseline, at each scheduled post baseline assessment and for the final assessment (the latest post-baseline evaluation available). Among subjects with focal abnormalities, summaries will include yes/no indication of clinical significance and a yes/no indication of biopsy recommendation. The number and percentage of subjects changing from 'normal' at baseline to 'focal abnormality' at any post-baseline assessment will be compared in terms of combination treatment versus tamsulosin treatment using Fisher's exact test.

A listing of digital rectal examination data will be provided.

8.2.11. Vital Signs

Vital signs (blood pressure and heart rate) are scheduled to be assessed at screening, baseline, and at each of the scheduled post-baseline treatment phase visits. Vital signs will be summarized by treatment group for baseline, each scheduled post-baseline assessment through Month 24 as well as for the final assessment (the latest post-baseline value available in the study). Change from baseline vital signs will also be summarized for each post-baseline assessment as well as for the final assessment.

Refer to Appendix 9 for a listing of the vital sign threshold ranges. For threshold vital sign summaries, high threshold, low threshold as well as either threshold will be presented separately. The number and percentage of subjects with a threshold value at baseline among subjects with a baseline and a post baseline value will be presented by treatment group. The number and percentage of subjects with at least one post baseline value in the threshold range will be presented by treatment group. For each systolic blood pressure, diastolic blood pressure, and heart rate, the incidence of exceeding threshold will be compared in terms of combination treatment versus tamsulosin treatment using Fisher's exact test.

A listing of vital signs data and a listing of vital signs data exceeding threshold will be provided.

8.2.12. Prostate Cancer Biopsies

A listing of data for biopsies performed to confirm prostate cancer will be provided.

8.2.13. Suicidality Assessment

Assessment of suicidality will be done using the Columbia Suicide Severity Rating Scale (C-SSRS) and is scheduled to be assessed at each Screening, Month 6, Month 12, and Month 24 (or end of treatment) visits. Tabular summaries of suicidal ideation and suicidal behavior will be produced at each of the scheduled assessments. Along with the aforementioned tabular summary, as well, for all subjects with suicidal ideation or behavior at any assessment, a listing of C-SSRS data will be provided (as a table), along with listings of details of suicidal ideation and suicidal behavior.

In addition a listing of C-SSRS assessments for all subjects will be provided. As noted in the adverse event section of this document, the possible suicidality-related adverse events will be produced.

8.3. Health Outcomes Analyses

Health outcomes analyses will be in terms of: BPH Impact Index (BII), BPH-Related Health Status (BHS), and the Problem Assessment Scale of the Sexual Function Inventory (PAS SFI). Health outcomes analyses will be performed using the ITT population unless otherwise specified in text or data display shells.

A list of planned Health Outcomes data displays is in Appendix 15: List of Data Displays. Baseline and change from baseline are defined in Appendix 6. Last observation carried forward (LOCF) and At Visit approaches are defined in Appendix 7. Reference Appendix 11 for descriptions of handling multiplicity.

8.3.1. BPH Impact Index

The BPH Impact Index (BII) consists of four questions. It is administered at screening, baseline and at each of the scheduled post-baseline treatment phase visits. The BII total score is the sum of the four questions; the total score range is 0 to 13. BII summaries and analyses will be in terms of the total (score); exceptions will be noted such as for supporting summaries of individual questions.

For calculation of the BII total, missing individual responses will be imputed when at least two of the four questions are answered (nonmissing). For the imputation, the average of the nonmissing responses will be calculated and rounded to the nearest integer. This average will be imputed for the original missing response(s). If at least 20% of the subjects have at least one imputed BII then the statistical analyses will be repeated based on non-imputed scores.

Total BII, change from baseline BII, and percentage change from baseline BII will be summarized by treatment group using both the LOCF and At Visit approaches at each scheduled post-baseline assessment. Change from baseline BII at each scheduled post-baseline assessment will be compared in terms of combination treatment versus

tamsulosin treatment using t-tests from a general linear model (GLM) with effects for treatment, cluster, and baseline BII. Two-sided tests at 0.05 level of significance will be conducted.

The adjusted mean estimates (mean and standard error), the adjusted mean difference, and the 95% confidence interval in terms of the adjusted mean difference will be presented. The adjusted mean difference will be in terms of combination treatment minus tamsulosin treatment. The model results will be presented on same tabular summary as the arithmetic mean, standard deviation, median, minimum and maximum. The results will be presented by treatment for each scheduled post-baseline assessment.

BII adjusted mean change from baseline will be plotted by treatment for each post-baseline scheduled visit in terms of each LOCF and At Visit approach.

Each of the four BII individual question responses will be summarized at Baseline, Month 12, and Month 24 by treatment group. Month 12 and Month 24 changes from baseline will be summarized by treatment group for each of the four questions. The summaries will be based on the ITT population and presented using both LOCF and At Visit approaches. No statistical testing will be performed.

Listings of BII individual question and total scores will be presented.

As a supportive analysis, BII will be analyzed using a mixed-model repeated-measures (MMRM) analysis in a manner similar to that described for primary efficacy in Appendix 13.

8.3.2. BPH-Related Health Status

BPH-Related Health Status (BHS) is collected as Question 8 the IPSS questionnaire and ranges from 0 to 6. The IPSS questionnaire is administered, and thus BHS is collected, at screening, baseline and at each of the scheduled post-baseline treatment phase visits.

Total BHS, change from baseline BHS, and percentage change from baseline BHS will be summarized by treatment group using both the LOCF and At Visit approaches at each scheduled post-baseline assessment. Change from baseline BHS at each scheduled post-baseline assessment will be compared in terms of combination treatment versus tamsulosin treatment using t-tests from a general linear model (GLM) with effects for treatment, cluster, and baseline BHS. Two-sided tests at 0.05 level of significance will be conducted.

The adjusted mean estimates (mean and standard error), the adjusted mean difference, and the 95% confidence interval in terms of the adjusted mean difference will be presented. The adjusted mean difference will be in terms of combination treatment minus tamsulosin treatment. The model results will be presented on same tabular summary as the arithmetic mean, standard deviation, median, minimum and maximum. The results will be presented by treatment for each scheduled post-baseline assessment.

BHS adjusted mean change from baseline will be plotted by treatment for each post-baseline scheduled visit in terms of each LOCF and At Visit approach.

A listing of BHS data will be presented.

As a supportive analysis, BHS will be analyzed using a mixed-model repeated-measures (MMRM) analysis in a manner similar to that described for primary efficacy in Appendix 13.

8.3.3. Problem Assessment Scale of the Sexual Function Inventory (PAS SFI)

The Problem Assessment Scale of the Sexual Function Inventory (PAS SFI) consists of three questions each with a range of 0 (Big Problem) to 4 (No Problem). It is administered at screening, baseline and at each Month 12 and Month 24 (or end of treatment) visits. The total PAS SFI is the sum of the three questions; the total score range is 0 to 12. PAS SFI summaries and analyses will be in terms of the total (score); exceptions will be noted such as for supporting summaries of individual questions.

For a given subject and visit, calculation of the PAS SFI total will not be performed or imputed if two or all three individual responses are missing. For a given subject and visit, a single missing individual response will be imputed when two of the three questions are answered (nonmissing). For the imputation, the average of the nonmissing responses will be calculated and rounded to the nearest integer. This average will be imputed for the original missing response. If at least 20% of the subjects have at least one imputed PAS SFI then the statistical analyses will be repeated based on non-imputed scores.

Total PAS SFI and change from baseline PAS SFI will be summarized by treatment group using both the LOCF and At Visit approaches at each scheduled post-baseline assessment. Change from baseline PAS SFI at each scheduled post-baseline assessment will be compared in terms of combination treatment versus tamsulosin treatment using t-tests from a general linear model (GLM) with effects for treatment, cluster, and baseline PAS SFI. Two-sided tests at 0.05 level of significance will be conducted.

The adjusted mean estimates (mean and standard error), the adjusted mean difference, and the 95% confidence interval in terms of the adjusted mean difference will be presented. The adjusted mean difference will be in terms of combination treatment minus tamsulosin treatment. The model results will be presented on same tabular summary as the arithmetic mean, standard deviation, median, minimum and maximum. The results will be presented by treatment for each scheduled post-baseline assessment.

Each of the three PAS SFI individual question responses will be summarized at Baseline, Month 12, and Month 24 by treatment group. Month 12 and Month 24 changes from baseline will be summarized by treatment group for each of the three questions. The summaries will be based on the ITT population and presented using both LOCF and At Visit approaches. No statistical testing will be performed.

A listing of PAS SFI data will be presented.

9. COUNTRY-SPECIFIC SUMMARIES AND ANALYSES

Four countries randomized subjects into this trial and include: China, Japan, Korea, and Taiwan. It is anticipated that each of these countries will conduct a regulatory submission using planned summaries and analyses of this ARI114265 study. For primary regulatory filings, summaries and analyses will be in terms of the Intent-to-Treat population which is based on pooled country data. These regulatory filings may also require complete or various sub-levels of data summaries and analyses for (their) specific country.

Each country's regulatory requirements will be fully defined at a time approaching the regulatory filing which will be after RAP finalization. Therefore, to address the *potential* requirements for complete country-specific summaries and analyses, all planned tables and figures, including planned statistical analyses, will be repeated for each of the four countries. Cluster (defined earlier in RAP as equal to country) will be excluded from the model-based within-country analysis. Exceptions will include planned by-country tabular summaries and listings. There will be no across-country multiplicity adjustments. The within-country statistical analyses will be underpowered because of their smaller sample sizes.

The summaries and analyses for each of the four countries will be provided by Clinical Statistics and Programming as part of a secondary (country-based) statistical analysis complete (SAC) package. Then, considering country regulatory filing plans and requirements, GSK regulatory staff of the individual countries will indicate to medical writing staff the summaries, analyses, and formats to be used in final reporting. Non-reporting of some or all country-based summaries and analyses by the individual countries will not result in a RAP revision.

It is anticipated that analysis and reporting of each country will add up to 2 weeks to the initial (Intent-to-Treat Population) SAC. Therefore, the "Country-specific SAC" will be "Primary SAC" plus 8 weeks. The country analysis may be ordered so that the country with earliest regulatory requirements will undergo first analysis and reporting. Changes to the anticipated '8 weeks' as well as action definition of country reporting order will not result in a RAP revision.

10. REFERENCES

GlaxoSmithKline Document Number RM2010/00134/05 Study ID ARI114265. Protocol Amendment 4: A randomized, double-blind, parallel group study to compare the efficacy and safety of combination treatment with dutasteride (0.5mg) and tamsulosin (0.2mg) with tamsulosin (0.2mg) monotherapy, administered once daily for 2 years, on the improvement of symptoms and health outcomes in men with moderate to severe benign prostatic hyperplasia. Report Date 08-JUL-2014.

GlaxoSmithKline Document: Program Safety Analysis Plan (PSAP) for GI198745 (dutasteride) and GSK2285985 (fixed dose combination of dutasteride [GI198745] and tamsulosin [GI138525]); PSAP approval date 09Dec2016. *Note: This reflects PSAP version at point of RAP finalization. Any PSAP updates/revisions at point of Statistical Analysis Complete (SAC) may be incorporated without a revision to this RAP; in this event, PSAP updates impacting analysis and reporting will be described in CSR.*

Mallinckrodt C, Lane P, Schnell D, Peng Y, Mancuso J. Recommendations for the Primary Analysis of Continuous Endpoints in Longitudinal Clinical Trials. Drug Information Journal. 2008; 42: 303-319

11. APPENDICES

Section	Appendix
Section 11.1	Appendix 1: Exclusions from the Per-Protocol Population
Section 11.2	Appendix 2: Time and Events
Section 11.3	Appendix 3: Assessment Windows
Section 11.4	Appendix 4: Multicenter Studies
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11.1. Appendix 1: Exclusions from the Per-Protocol Population

In accordance with SOP-130050 and the ARI114265 PDMP, deviations which require exclusion from the Per-Protocol population must be identified, when possible, in advance of treatment unblinding. The deviation review and programming processes, as well as spreadsheet and database capabilities, require that deviation identification must be made from two sources:

1. Study Team Assessment of deviations tracked on study team's protocol deviations spreadsheet and then indicated as 'Exclude from Per-Protocol'
and
2. Programmatic Assessment which outputs deviations through Statistics & Programming electronic SAS code execution.

The below table lists the 19 deviations which would exclude a subject from the Per-Protocol population along with identification methods. It is expected that a final analysis dataset will be generated with the two sources pooled. Details on the pooled dataset programming and any adjudication process required to reconcile the two sources will be defined in advance of database freeze through a RAP amendment or a high level note to Study File. If there is inconsistency between the two sources, it is anticipated that the programmatic determination will be considered definitive; this will be outlined through a RAP amendment or a high level note to Study File.

Number	Per-Protocol Deviation	Study Team Assessment	Programmatic Assessment [eCRF Code Note a]
01	Missed placebo run-in phase	Any evidence which implies or documents that subject missed the placebo run-in phase.	1) Placebo run-in treatment start and stop dates are missing or 2) Placebo run-in tablets consumed = zero [A5]
02	Incorrect study drug (wrong treatment) consumed	Any evidence which confirms that the incorrect container contains other-than-scheduled study treatment.	Treatment consumed (from incorrect dispensed container) unequal to treatment planned in randomization schedule. Note: this can only be determined after study unblinding. [A5]
03	Randomized but did not consume double-blind study drug	Any evidence which confirms that the zero tablets were consumed in double-blind phase	Final nonmissing cumulative study drug compliance = zero [A5]
04	Cumulative study drug compliance <75%	Study team is unable to calculate RAP-defined study drug compliance. Therefore, deviation will be determined based on programmatic	Final nonmissing cumulative study drug compliance < 75% [A5]

Number	Per-Protocol Deviation	Study Team Assessment	Programmatic Assessment [eCRF Code Note a]
		assessment.	
05	Cumulative study drug compliance >125%	Study team is unable to calculate RAP-defined study drug compliance. Therefore, deviation will be determined based on programmatic assessment.	Final nonmissing cumulative study drug compliance > 125% [A5]
	Violation of Inclusion Criteria (protocol #)		
06	Confirmed BPH clinical diagnosis (Inclusion 2)	Any evidence which confirms inclusion criterion 2 deviation.	Eligibility database indicates violation of inclusion criterion 2 [A1]
07	IPSS ≥12 at Screening (Inclusion 3)	Any evidence which confirms inclusion criterion 3 deviation.	Eligibility database indicates violation of inclusion criterion 3 [A1]
08	Prostate volume ≥30cc by TRUS at Screening (Inclusion 4)	Any evidence which confirms inclusion criterion 4 deviation.	Eligibility database indicates violation of inclusion criterion 4 [A1]
09	PSA ≥1.5ng/ml and ≤10ng/mL at Screening (Inclusion 5)	Any evidence which confirms inclusion criterion 5 deviation.	Eligibility database indicates violation of inclusion criterion 5 [A1]
10	Qmax >5 mL/sec and ≤15mL/sec with Voided Volume ≥125mL/sec at Screening (Inclusion 6)	Any evidence which confirms inclusion criterion 6 deviation.	Eligibility database indicates violation of inclusion criterion 6 [A1]
	Violation of Exclusion Criteria (protocol #)		
11	Any conditions other than BPH, which may in the judgement of the investigator, result in urinary symptoms or changes in flow rate (Exclusion 6)	Any evidence which confirms exclusion criterion 6 deviation.	Eligibility database indicates violation of exclusion criterion 6 [A1]
12	Use of 5ARI within 6 months of Screening or historical TRUS and throughout the study (Exclusion 10a)	Any evidence which confirms exclusion criterion 10a deviation.	Reference Note b. [A1]
13	Use of anabolic steroids within 6 months of Screening and throughout the study (Exclusion 10b)	Any evidence which confirms exclusion criterion 10b deviation.	Reference Note b. [A1]
14	Use of phytotherapy for BPH within 2 weeks of Screening and throughout the study (Exclusion 10c)	Any evidence which confirms exclusion criterion 10c deviation.	Reference Note b. [A1]

Number	Per-Protocol Deviation	Study Team Assessment	Programmatic Assessment [eCRF Code Note a]
15	Use of alpha-adrenoreceptor blockers within 2 weeks of Screening and throughout the study, except study meds (Exclusion 10d)	Any evidence which confirms exclusion criterion 10d deviation.	Reference Note b. [A1]
16	Use of alpha-adrenoreceptor agonists or anticholinegics or cholinergics within 48 hours prior to all uroflowmetry and IPSS assessments (Exclusion 10e)	Any evidence which confirms exclusion criterion 10e deviation.	Reference Note b. [A1]
17	Use of selective beta 3-adrenoreceptor agonist (mirabegron) within 2 weeks prior to all uroflowmetry and IPSS assessments (Exclusion 10f)	Any evidence which confirms exclusion criterion 10f deviation.	Reference Note b. [A1]
18	Prohibited medications and non-drug therapies of Protocol Section 6.2 and not otherwise classified above.	Study team identification of prohibited medication or non-drug therapy which should require exclusion from per-protocol population and not otherwise classified above.	[A3]
	Other		
19	Any condition which should exclude a subject from the Per-Protocol population and is not include above.	Study team identification through review of multiple sources such as protocol deviation log text, study drug compliance outliers, concomitant medication logs, or site/monitor communications.	NA

Notes:

a. Reflects eCRF corresponding code to be applied programmatically; definitions in below table.

b. Exclusion 10 subsets (a – f) are not individually identified in the INFORM and Analysis & Reporting datasets. Therefore, deviation will be determined based on study team assessment.

Important Deviations Categories, Subcategories, and eCRF Codes (eCRF Codes define above indicated programmatic assignment)	
Category / Subcategory	**eCRF Codes**
Assessments and/or procedures	
Biological specimen sample procedures	6E
Equipment procedures	6G
Failure to comply with dosing procedure	6L
Failure to report SAE, pregnancy, or liver function abnormalities per-protocol	6B
Informed consent process	6A
Missed assessment or procedure	6I
Randomization procedures	6H
Study blind / unblind procedures	6C
Study treatment supply procedures	6D
Other	6OT
Eligibility criteria not met	A1
Prohibited medication or device	A3
Received wrong treatment or incorrect dose	A5
Visit, assessment or timepoint window	
Window for dose administration	4C
Window for efficacy assessments	4A
Window for safety assessments	4B
Other	4OT

11.2. Appendix 2: Time & Events

11.2.1. Protocol Defined Time & Events

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

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

Protocol Defined Time & Events, Notes

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

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

⇒ ongoing assessment

a. Including DRE and qualitative breast examination

b. Blood pressure and pulse to be taken after sitting quietly for 5 minutes

c. PSA sample must be taken before TRUS
d. Only Serious AEs (related to study participation) occurring between Screening (Visit 1a) and the start of placebo run-in medication need to be recorded
e. Single-blind medication to be dispensed at Visit 1b only
f. Double-blind medication dispensed from Visit 2 onwards.
g. Hepatitis B surface antigen and hepatitis C antibody (if hepatitis C antibody positive, a hepatitis C RNA test should be reflexively performed to confirm the result)
h. Only performed at Visit 8 (Month 18)
i. Performed for End of Study Treatment Assessments as well when a subject discontinues the study treatment.
j. Serum PK samples are only applicable to subjects of Chinese origin living in China.

11.3. Appendix 3: Assessment Windows

Boundaries for the scheduled assessments are defined in the protocol. The data will be summarized by nominal visit without regard to window days for all scheduled visits. The efficacy, safety, and health outcomes measures collected at nominal visits include IPSS, prostate volume, Qmax, PSA, post void residual volume, BII, BPH-related Health Status, and PAS-SFI. In order to utilize as much data as possible in these efficacy, safety, and health outcomes summaries and analyses, premature withdrawal visit data will be used as the scheduled visit data when both of the following criteria are met:

- The scheduled visit evaluation is not available, and
- The premature withdrawal visit date falls within 30 days (inclusive) for each of the scheduled post baseline visits (i.e., Months 3, 6, 9, 12, 15, 18, 21, and 24), or within 15 days (inclusive) of the scheduled Baseline visit (Month 0). The scheduled visit day for month k will be calculated as:
  Baseline Date + (k * 365/12) rounded to the nearest integer.

11.4. Appendix 4: Multicenter Studies

11.4.1. Methods for Handling Centers

The 4 countries which randomized subjects into this trial include: China, Japan, Korea, and Taiwan. Forty-six centers across these 4 countries randomized subjects into this trial.

Clusters will be used in the exploration of center effect and treatment-by-center interaction.

As stated in the protocol, it was anticipated that randomized subject accrual would be spread thinly across centers and summaries of data by center would be unlikely to be informative. It was expected that investigative centers would be pooled a priori into clusters based on geographic location. As stated in protocol, these clusters would be identified once randomization was complete and then used in statistical analyses in the exploration of center effects and treatment-by-center interaction.

Based on the actual randomization of sites within countries, it is reasonable and logical to assign each country as a single cluster. Therefore, the 4 clusters are the 4 countries: China, Japan, Korea, and Taiwan. The countries will be used in summaries of randomized subjects, subgroup summaries, and in statistical analyses of efficacy center effect and treatment-by-center interaction; these by-country summaries and analyses are described in relevant sections.

11.5. Appendix 5: Data Display Standards & Handling Conventions

11.5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG [1]		Data Displays for Reporting	
Code	Description	Description	Order [2]
A	Dutasteride 0.5mg once daily + tamsulosin 0.2mg once daily	Dut 0.5mg + Tam 0.2mg	2
B	Dutasteride placebo once daily + tamsulosin 0.2mg once daily	Placebo + Tam 0.2mg	1

NOTES:

1. RandAll NG (Next Generation) is a randomization creation and publishing tool for GSK studies.
2. Order represents treatments being presented in tables, listings, and figures.

Within this RAP, the following additional references may be made for brevity:

--Full Treatment Description--	--Short Treatment Descriptions--
Dutasteride 0.5mg once daily + tamsulosin 0.2mg once daily or	-Combination -Dut 0.5mg + Tam 0.2mg -Dut + Tam
Dutasteride placebo once daily + tamsulosin 0.2mg once daily	-Tamsulosin Monotherapy -Tam 0.2mg -Placebo + Tam 0.2mg -Tam

11.5.2. Reporting Process & Standards

The following reporting process and reporting standards details apply to all RAP defined endpoints.

Reporting Process	
Software	
• SAS software will be used for all analyses except when noted. It is anticipated that the SAS software version 9.3 will be in use at statistical analysis complete; use of a version other than 9.3 will be documented in IMMS Study File.	
Reporting Areas *The following server and areas are identified as of RAP finalization. Revisions to these areas, for example due to platform / server relocation and/or CDISC reporting standards, will be documented in IMMS Study File.*	
HARP Server	US1SALX00259
HARP Area	The high level area is defined as: /arenv/arprod/gi198745/ari114265/final.
QC Documentation Area	QC process and documentation for analysis and reporting will be maintained as a text file on HARP server US1SALX00259 within above noted area.
Analysis Datasets	
• Analysis datasets for international regulatory submissions will not be created according to CDISC standards. GSK exemption for ARI114265 CDISC-based dataset creation and reporting was granted in June 2016.	
Generation of RTF Files	
• RTF files will be generated for all tabular summaries with the reporting efforts described in the RAP unless clearly stated as not required by the assigned Scientific and Medical Writer(s).	

Reporting Standards
General
The current GSK Integrated Data Standards Library (IDSL) and GSK IDSL Statistical Principles will be applied for reporting, unless otherwise stated within RAP text or indicated in table, listing, figure shells: • 4.03 to 4.24: General Principles • 5.01 to 5.08: Principles Related to Data Listings • 6.01 to 6.11: Principles Related to Summary Tables • 7.01 to 7.13: Principles Related to Graphics From the above standards and principles as well as to be aligned with historical reporting for this compound and indication, the key reporting standards to be applied are: • All data will be reported according to the actual treatment the subject received unless otherwise stated. • Within listings, numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of decimal places. • Within tabular summaries, the minimum and maximum values are presented with the same

Reporting Standards
number of decimal places as the raw data collected on the eCRF. The mean and percentiles (e.g. median, Q1, and Q3) are presented using one additional decimal place. The standard deviation and standard error are presented using two additional decimal places. • Continuous variables (e.g., age) will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. • Categorical variables will be summarized using the number of subjects (n) and percentage (%) in each category. • P-values greater than 0.10 will be reported to two decimal accuracy. P-values less than or equal to 0.10 will be reported to three decimal accuracy. P-values less than 0.001 will be reported as '<0.001'. • Applicable safety analysis and reporting definitions and presentations within "Program Safety Analysis Plan (PSAP) for GI198745 (dutasteride) and GSK2285985 (fixed dose combination of dutasteride [GI198745] and tamsulosin [GI138525]" will be referenced; any deviations will be noted within this RAP.

11.6. Appendix 6: Derived and Transformed Data

(Placebo) Run-In Start and Stop Dates
• Placebo run-in start date = Start date of (placebo) study treatment recorded for the run-in period. If the recorded start dates for the two study drug containers differ, then select the earlier start date. • Placebo run-in stop date = End date of (placebo) study treatment recorded for the run-in period. If the recorded stop dates for the two study drug containers differ, then select the later stop date. Note: a subject with a nonmissing placebo run-in start date will be considered as included in the Placebo Run-in Phase.
Randomization Date
• Randomization date is the randomization telephone call in date which is recorded in the eCRF. This date is defined here for completeness and no derivations are made. Note: a subject with a nonmissing randomization number recorded in eCRF will be considered Randomized.
(Double-Blind) Treatment Start and Stop Dates
• Treatment start date = Start date of study treatment recorded for the (double-blind) treatment period. If the recorded start dates for the two study drug containers differ, then select the earlier start date. • Treatment stop date = Stop date of study treatment recorded for the (double-blind) treatment period. If the recorded stop dates for the two study drug containers differ, then select the later stop date.

Study Drug Exposure and Compliance
• As explained in the protocol: -Dutasteride study treatment is dispensed as capsules within bottles. -Tamsulosin study treatment is dispensed as tablets within blister packs. Within this RAP, the following general terms are used for exposure and compliance: ---"Pill" refers to a capsule or a tablet ---"Container" refers to a bottle or a blister pack. • Study drug exposure (in days) is number of days between (double-blind) treatment start date and (double-blind) treatment stop date, both days inclusive (i.e. Study drug exposure =Treatment Stop Date – Treatment Start Date +1). • Number of pills consumed during the study is defined for double-blind period as total number of pills dispensed (sum over all containers dispensed) minus total number of pills returned (sum over all containers dispensed) minus total number of pills lost or wasted (sum over all containers dispensed). If any of the containers is not returned or number of pills returned or wasted is missing for any container, number of pills consumed during the study is missing. • Overall study drug compliance is defined for double-blind period as 100 * Number of Pills Consumed / Number of Pills Prescribed. Number of Pills Prescribed = 2 * Study Drug Exposure, since the protocol prescribes that subjects consume 2 pills for each day a subject is on treatment (one pill of Placebo or Dutasteride, and one pill of Tamsulosin). Overall study drug compliance is missing if either the number of pills consumed during the study or the study drug exposure is missing. • Compliance by study drug component: Study drug compliance by component will be output for: --Placebo + Tam 0.2mg for each of the two components: Placebo and Tam 0.2mg --Dut 0.5mg + Tam 0.2mg for each of the two components: Dut 0.5mg and Tam 0.2mg Compliance is defined as 100 * Number of Pills Consumed / Number of Pills Prescribed, where the only pills considered are those for a specific(e.g. Tamsulosin). Number of Pills Prescribed = Study Drug Exposure, since the protocol prescribes that subjects consume 1 pill of any study drug component (e.g. Tamsulosin) for each day a subject is on treatment.
Baseline Date
• A subject's baseline date will be the latest non-missing value of either (double-blind) treatment start date or randomization date. Baseline date will be used in the derivation of study day values and Baseline Values. 'Baseline date' may differ from the Visit 2 (Baseline Visit) date recorded in eCRF.
Baseline Value
• For purposes of data analyses, the subject's baseline value of an assessment will be defined as the latest assessment on or before the Baseline Date.
Change and % Change from Baseline
• Change from Baseline = Post-baseline Value – Baseline • % Change from Baseline = 100 x [(Post-baseline Value – Baseline) / Baseline]

Study Day

Study Day is calculated as the number of days from Baseline Date:

- Reference Date = Missing → Study Day = Missing
- Reference Date < Baseline Date → Study Day = Reference Date – Baseline Date
- Reference Date ≥ Baseline Date → Study Day = Reference Date – (Baseline Date) + 1

Cut-off Dates

-Month k Cut-off Date (for k= 3, 6, 9, 12, 15, 18, 21, 24): The maximum of [Month k clinic visit date, Month k lab visit date, Baseline Date + (k * 91/3)].

Time Since LUTS First Noted (in years)

-Time Since LUTS First Noted = Baseline Date minus Date LUTS First Noted by Patient / 365

Time Since BPH Clinical Diagnosis (in years)

-Time Since BPH Diagnosis = Baseline Date minus Date of BPH Clinical Diagnosis / 365

Age

Only year of birth is collected in the eCRF. For purposes of calculating age for a given subject, date of birth will be defined as June 30th of the corresponding year of birth. Age is calculated in terms of Screening (Visit 1b) date and output as a truncated integer. Age categories include <65, ≥65, <75, and ≥75 years.

Body Mass Index (BMI) (kg/sq m)

BMI = Weight (kg) / $[\text{Height (m)}]^2$

Race / Ethnicity

Race / ethnicity will be determined based on a subject's reported ethnicity and geographic ancestry as defined in the following table.

	Race / Ethnicity			
	Asian	**White (But Not Hispanic)**	**Hispanic**	**Other**
Ethnicity	Not Hispanic or Latino	Not Hispanic or Latino	Hispanic or Latino	Not Hispanic or Latino
Geographic Ancestry	Any combination of (restricted to the categories below only): - Asian – East Asian Heritage - Asian – Japanese Heritage - Asian - South East Asian Heritage - Asian – Central / South Asian Heritage	Any combination of (restricted to the below categories only): - White – Arabic/ North African Heritage - White – White/ Caucasian/ European Heritage	Any combination	Any combination not considered 'Asian' or 'White (But Not Hispanic)'

IPSS (total score)

IPSS (total score) = Sum of IPSS individual questions 1 – 7. Reference Section 7.1.1 for imputation procedure.

Prostate Volume

Prostate Volume = pi/6 (Anteroposterior Width x Cephalocaudal Width x Transverse Width)

11.7. Appendix 7: Premature Withdrawals & Handling of Missing Data

11.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) is defined as completion of the 4-week placebo run-in and the 104-week study treatment period. • Withdrawn subjects will not be replaced in the study. • All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified. • Number and percent of ITT population completing the study and those withdrawing from the study, along with eCRF recorded reasons for premature withdrawals, will be summarized by treatment and overall.
Note	This section addresses Premature Withdrawals from the study. Premature discontinuation of investigational product, along with reasons, is a separate data collection and is reported separately.

11.7.2. Handling of Missing Data

11.7.2.1. Handling of Missing or Partial Dates

For efficacy time to event endpoints, such as 'Time to AUR or BPH-Related Surgery' the following approach will be used for unknown event dates unless otherwise indicated. If the month and year are known but the day of the month is unknown, then the day of the month will be imputed to be the 15th . If the year is known but the month and day are unknown then the date will be imputed to be July 2 in that year. In all the preceding cases, if it is not definitive that the onset date is on or after the treatment start date based on the non-missing (non-imputed) dates, then the date will be imputed to be the treatment start date. If the year is unknown then the onset date is considered to be prior to treatment start; hence, the event will be excluded from summaries of events on or after treatment start. For subjects without events, the censoring dates will be established using non-missing dates, and using dates with only days missing. Dates with missing months and years will not be used in establishing the censoring dates.

Partial adverse event dates will be handled as described in Appendix 8.

11.7.2.2. Handling of Missing Data for Statistical Analysis

Endpoints measured at specific visits and analyzed in terms of visit numbers include: IPSS, prostate volume, Qmax, PSA, post void residual volume, BPH Impact Index (BII), BPH-Related Health Status, and PAS-SFI. Analysis of the data collected in terms of visit numbers will be performed using two different approaches to account for missing data.

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

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

11.7.3. Questionnaire Total Score Imputation

Calculations of IPSS total and BII total, including imputation for missing responses, are described in the respective RAP sections.

11.8. Appendix 8: Adverse Event Time Periods and Special Adverse Event Definitions

Date-related derivations and transformations related to adverse events (AEs) are described below.

AE Onset Time since First Dose
= AE Onset Date – Treatment Start Date if treatment start date > AE onset date
= AE Onset Date – Treatment Start Date +1 if treatment start date <= AE start date
= missing otherwise

AE Duration (in days) = AE Resolution Date – AE Onset Date + 1

The timing of AEs will be categorized as follows:

- An AE is "Pre-Treatment" if the AE onset date is before the treatment start date.
- An AE is "On Treatment" if the AE onset date is on or after the treatment start date (but on or before the treatment stop date, if that is non-missing), or if the onset date is missing.
- An AE is "Post-Treatment" if the treatment stop date is non-missing, and the AE onset date is after the treatment stop date.
- An AE is "Post-Randomization" if the AE is either On Treatment or Post-Treatment.

Note: Cut-off dates are defined in Appendix 6; definition is repeated here, in terms of 6-month treatment periods, since this is used to determine AE onset period:
Month k Cut-off Date (for k= 6, 12, 18, 24): The maximum of [Month k clinic visit date, Month k lab visit date, Baseline Date + (k * 91/3)].

An on-treatment AE is uniquely identified as having onset within one of the following four time periods: Months 1-6, Months 7-12, Months 13-18, or Months 19-24.

- An AE is considered to have onset in the Months 1-6 time period if it is an on-treatment AE and the onset date is on or before the Month 6 cut-off date.
- An AE is considered to have onset in the Months 7-12 time period if it is an on-treatment AE and the onset date is after the Month 6 cut-off date and is on or before the Month 12 cut-off date.
- An AE is considered to have onset in the Months 13-18 time period if it is an on-treatment AE and the onset date is after the Month 12 cut-off date and is on or before the Month 18 cut-off date.
- An AE is considered to have onset in the Months 19-24 time period if it is an on-treatment AE and the onset date is after the Month 18 cut-off date.

If the AE onset date is partially missing, the timing is determined as follows:
1. If the non-missing parts of the date (either just year or year/month) are unambiguously before the start of treatment, the AE is considered Pre-Treatment.

2. If the non-missing parts of the date are unambiguously after the stop of treatment, the AE is considered Post-Treatment.
3. If #1 or #2 above cannot be assigned, then the AE is considered On-Treatment.

If an on-treatment AE onset date is partially missing, then, for the purpose of assigning the 6-month treatment period referenced above, the onset date will be imputed according to the algorithm described in the second paragraph below, and the imputed date will be used to assign the period.

An AE is considered drug-related if the relationship variable indicates so, or the variable value is missing. When an AE has an outcome of Resolved/Recovered with or without sequelae, it may be categorized for resolution status as follows: if resolution date is on or before treatment stop date, the AE is considered resolved on-therapy, or if either the resolution date or the treatment stop date is missing and the action taken is not 'investigational product withdrawn', the AE is considered resolved on-therapy. If a resolved AE is not resolved on-therapy, it is considered resolved off-therapy.

For the purpose of Kaplan-Meier estimates for Special Interest AEs, and for categorizing AEs by time intervals, the following algorithm will be used:

1) If an AE start date is partial, it will be imputed as follows:
    a. If all components of the date (day, month and year) are missing, then the date will not be imputed, but the AE will be categorized in the first 6-month time period.
    b. If both day and month are missing, then the day and month will be imputed as 01 January.
    c. If only day is missing, then the day will be imputed as 01.
    d. Any imputation described in items 1b and 1c above will be revised if it is in conflict with the treatment start date: if the month and year of treatment start date is same as those in the imputed date, the imputed date will be changed to the treatment start date.
2) A subject not having the particular AE will be censored at the latter of the following two dates: date of last clinic visit, latest AE start date.
3) If an AE end date is partial, it will be imputed as follows:
    a. If all components of the date (day, month and year) are missing, then the end date will be missing.
    b. If both day and month are missing, then the day and month will be imputed as 31 December.
    c. If only day is missing, then the day will be imputed as the last day of the corresponding month.

For computing AE duration, partial AE start and end dates will be imputed as previously described, and events with completely unknown (missing) end dates will be censored at the latter of the following two dates: date of last clinic visit, latest AE start date. AE duration is the total number of non-overlapping days for all events per subject, and will be considered censored if any contributing event is censored.

Time to death is defined as (date of death – treatment start date +1). For subjects who do not experience death, time to death is censored at the date of last clinic visit (if missing,

the subject will be censored at the treatment start date).

Special interest adverse events, including MedDRA preferred terms and codes, are presented below in Table A-Table D:

Table A: Sexual and Breast Adverse Events of Special Interest
Table B: Prostate Cancer Adverse Events of Special Interest
Table C: Cardiovascular Adverse Events of Special Interest
Table D: Infrequent Tier 1 Adverse Events of Special Interest

Table A. Sexual and Breast Adverse Events of Special Interest: MedDRA Preferred Terms and Codes		
Special Interest Event	**MedDRA Preferred Term**	**PT_Code**
Altered (Decreased) Libido	Sexual dysfunction	10040477
	Male sexual dysfunction	10057672
	Libido decreased	10024419
	Loss of libido	10024870
	Libido disorder	10061221
Impotence	Erectile dysfunction	10061461
	Organic erectile dysfunction	10052004
	Disturbance in sexual arousal	10058929
	Psychogenic erectile dysfunction	10052005
Ejaculation Disorders	Ejaculation delayed	10014325
	Ejaculation disorder	10014326
	Ejaculation failure	10014328
	Retrograde ejaculation	10038967
	Anorgasmia	10002652
	Orgasm abnormal	10031085
	Premature ejaculation	10036596
	Male orgasmic disorder	10025513
	Orgasmic sensation decreased	10052449
	Semen volume decreased	10039944
Breast Disorders	Breast hyperplasia	10006256
	Breast enlargement	10006242
	Gynaecomastia	10018800
	Nipple disorder	10029417
	Breast engorgement	10006240
	Breast swelling	10006312
	Breast pain	10006298
	Breast tenderness	10006313
	Nipple pain	10029421
	Nipple swelling	10058680
	Breast discomfort	10049872
Breast Disorders: Breast Enlargement	Breast hyperplasia	10006256
	Breast enlargement	10006242
	Gynaecomastia	10018800
	Nipple disorder	10029417
	Breast engorgement	10006240
	Breast swelling	10006312
Breast Disorders: Breast Tenderness	Breast pain	10006298
	Breast tenderness	10006313
	Nipple pain	10029421
	Nipple swelling	10058680
	Breast discomfort	10049872

Table B. Prostate Cancer Adverse Events of Special Interest: MedDRA Preferred Terms and Codes		
Special Interest Event	**MedDRA Preferred Term**	**PT_Code**
Prostate Cancer	Prostate cancer	10060862
	Prostate cancer stage 0	10036912
	Prostate cancer stage I	10036917
	Prostate cancer stage II	10036918
	Prostate cancer stage III	10036919
	Prostate cancer stage IV	10036920
	Prostate cancer recurrent	10036911
	Prostate cancer metastatic	10036909

Table C. Cardiovascular Adverse Events of Special Interest: MedDRA Preferred Terms and Codes		
Special Interest Event	**MedDRA Preferred Term**	**PT_Code**
Acute Coronary Syndrome	Acute myocardial infarction	10000891
	Myocardial infarction	10028596
	Silent myocardial infarction	10049768
	Sudden cardiac death	10049418
	Angina unstable	10002388
	Cardiac arrest	10007515
	Cardio-respiratory arrest	10007617
	Cardiac death	10049993
	Acute coronary syndrome	10051592
Ischemic Cerebrovascular Events	Cerebrovascular accident	10008190
	Transient ischemic attack	10044390
	Cerebral infarction	10008118
	Cerebrovascular disorder	10008196
	Cerebral artery embolism	10008088
	Cerebral artery occlusion	10008089
	Cerebral artery thrombosis	10008092
	Ischemic stroke	10061256
	Cerebral circulatory failure	10008097
	Cerebellar infarction	10008034
	Thalamic infarction	10064961
	Reversible ischemic neurologic deficit	10050496
	Thrombotic stroke	10043647
	Embolic stroke	10014498
	Vertebral artery occlusion	10048965
	Carotid arterial embolus	10007684
	Carotid artery occlusion	10048964
	Carotid artery stenosis	10007687
	Carotid artery thrombosis	10007688
	Thrombotic cerebral infarction	10067347
	Brain stem infarction	10006147
	Embolic cerebral infarction	10060839
	Lacunar infarction	10051078
	Brain stem stroke	10068644
	Stroke in evolution	10059613
	Ischaemic cerebral infarction	10060840

Table C. Cardiovascular Adverse Events of Special Interest: MedDRA Preferred Terms and Codes (continued)		
Special Interest Event	**MedDRA Preferred Term**	**PT_Code**
Cardiac Failure	Cardiac failure congestive	10007559
	Cardiac failure	10007554
	Left ventricular failure	10024119
	Cardiac failure acute	10007556
	Cardiogenic shock	10007625
	Left ventricular failure acute	10063081
	Right ventricular failure	10039163
	Right ventricular failure acute	10063082
	Ventricular failure	10060953
	Cardiopulmonary failure	10051093
	Congestive cardiomyopathy	10056370
Ischemic Coronary Artery Disorders/ Atherosclerosis	Coronary artery embolism	10011084
	Coronary artery occlusion	10011086
	Coronary artery stenosis	10011089
	Coronary artery thrombosis	10011091
	Myocardial ischemia	10028600
	Coronary artery disease	10011078
	Arteriosclerosis coronary artery	10003211
Cardiac Arrhythmias	Ventricular extrasystoles	10047289
	Torsade de Pointes	10044066
	Ventricular fibrillation	10047290
	Cardiac Fibrillation	10061592
	Pulseless electrical activity	10058151
	Ventricular asystole	10047284
	Long QT syndrome	10024803
	Ventricular tachycardia	10047302
	Ventricular Arrhythmia	10047281
	Ventricular flutter	10047294
Peripheral Vascular Disease	Deep Vein Thrombosis	10051055

Table D. Infrequent Tier 1 Adverse Events of Special Interest: MedDRA Preferred Terms and Codes		
Special Interest Event	**MedDRA Preferred Term**	**PT_Code**
Relevant for dutasteride:		
Allergic reactions	Anaphylactic reaction	10002198
	Anaphylactic shock	10002199
	Anaphylactic transfusion reaction	10067113
	Anaphylactoid reaction	10002216
	Anaphylactoid shock	10063119
	Circulatory collapse	10009192
	Kounis syndrome	10069167
	Shock	10040560
	Type I hypersensitivity	10045240
	Allergic oedema	10060934
	Angioedema	10002424
	Circumoral oedema	10052250
	Conjunctival oedema	10010726
	Corneal oedema	10011033
	Epiglottic oedema	10015029
	Eye oedema	10052139
	Eye swelling	10015967
	Eyelid oedema	10015993
	Face oedema	10016029
	Gingival oedema	10049305
	Gingival swelling	10018291
	Gleich's syndrome	10066837
	Hereditary angioedema	10019860
	Idiopathic angioedema	10073257
	Idiopathic urticaria	10021247
	Laryngeal oedema	10023845
	Laryngotracheal oedema	10023893
	Limbal swelling	10070492
	Lip oedema	10024558
	Lip swelling	10024570
	Mouth Swelling	10075203
	Oculorespiratory syndrome	10067317
	Oedema mouth	10030110
	Oropharyngeal swelling	10031118
	Palatal oedema	10056998
	Palatal swelling	10074403
	Periorbital oedema	10034545
	Pharyngeal oedema	10034829
	Scleral oedema	10057431
	Swelling face	10042682
	Swollen tongue	10042727
	Tongue oedema	10043967
	Tracheal oedema	10044296
	Urticaria	10046735
	Urticaria cholinergic	10046740
	Urticaria chronic	10052568
	Urticaria papular	10046750
	Acquired epidermolysis bullosa	10056508
	Blister	10005191
	Blister rupture	10073385

Table D. Infrequent Tier 1 Adverse Events of Special Interest: MedDRA Preferred Terms and Codes		
Special Interest Event	**MedDRA Preferred Term**	**PT_Code**
	Bullous impetigo	10006563
	Conjunctivitis	10010741
	Corneal exfoliation	10064489
	Drug eruption	10013687
	Epidermolysis	10053177
	Epidermolysis bullosa	10014989
	Genital ulceration	10018180
	HLA-B*1502 assay positive	10074771
	HLA-B*5801 assay positive	10074774
	Lip exfoliation	10064482
	Mouth ulceration	10028034
	Mucocutaneous ulceration	10028084
	Mucosa vesicle	10028103
	Mucosal erosion	10061297
	Mucosal exfoliation	10064486
	Mucosal necrosis	10067993
	Mucosal ulceration	10028124
	Nikolsky's sign	10029415
	Noninfective conjunctivitis	10074701
	Oral mucosal blistering	10030995
	Oral mucosal exfoliation	10064487
	Oral papule	10031010
	Oropharyngeal blistering	10067950
	Pemphigoid	10034277
	Pemphigus	10034280
	Penile exfoliation	10064485
	Skin erosion	10040840
	Skin exfoliation	10040844
	Staphylococcal scalded skin syndrome	10041929
	Stomatitis	10042128
	Tongue exfoliation	10064488
	Vaginal exfoliation	10064483
	Vaginal ulceration	10046943
	Vulval ulceration	10047768
	Vulvovaginal rash	10071588
	Vulvovaginal ulceration	10050181
	Application site pruritus	10003053
	Aquagenic pruritus	10003071
	Injection site pruritus	10022093
	Pruritus	10037087
	Pruritus genital	10037093
	Rash pruritic	10037884
	Senile pruritus	10039986
	Itching scar	10050818
	Eyelids pruritus	10051627
	Catheter site pruritus	10052270
	Pruritus generalised	10052576
	Infusion site pruritus	10053664
	Vulvovaginal pruritus	10056530
	Incision site pruritus	10059386
	Uraemic pruritus	10060875
	Pruritus allergic	10063438
	Instillation site pruritus	10063763

Table D. Infrequent Tier 1 Adverse Events of Special Interest: MedDRA Preferred Terms and Codes		
Special Interest Event	**MedDRA Preferred Term**	**PT_Code**
	Implant site pruritus	10063785
	Cholestatic pruritus	10064190
	Polymorphic eruption of pregnancy	10066100
	Vessel puncture site pruritus	10067254
	Vaccination site pruritus	10068881
	Brachioradial pruritus	10071443
	Notalgia paraesthetica	10072643
Breast Cancer	Apocrine breast carcinoma	10066206
	Invasive breast carcinoma	10075713
	Triple negative breast cancer	10075566
	Breast cancer	10006187
	Breast cancer female	10057654
	Breast cancer in situ	10006189
	Breast cancer male	10061020
	Breast cancer metastatic	10055113
	Breast cancer recurrent	10006198
	Breast cancer stage I	10006199
	Breast cancer stage II	10006200
	Breast cancer stage III	10006201
	Breast cancer stage IV	10006202
	Breast sarcoma	10068582
	Breast sarcoma metastatic	10068583
	Breast sarcoma recurrent	10068584
	Electron radiation therapy to breast	10014437
	Extended radical mastectomy	10015721
	Gamma radiation therapy to breast	10017677
	HER-2 positive breast cancer	10065430
	Inflammatory carcinoma of breast recurrent	10021977
	Inflammatory carcinoma of breast stage III	10021978
	Inflammatory carcinoma of breast stage IV	10021979
	Inflammatory carcinoma of the breast	10021980
	Intraductal papillary breast neoplasm	10073540
	Intraductal proliferative breast lesion	10073094
	Invasive ductal breast carcinoma	10073095
	Invasive lobular breast carcinoma	10073096
	Invasive papillary breast carcinoma	10073098
	Lobular breast carcinoma in situ	10073099
	Malignant nipple neoplasm	10062051
	Malignant nipple neoplasm female	10053129
	Malignant nipple neoplasm male	10053128
	Mastectomy	10026878
	Medullary carcinoma of breast	10027095
	Metaplastic breast carcinoma	10073100
	Modified radical mastectomy	10027799
	Mucinous breast carcinoma	10073101
	Neuroendocrine breast tumour	10073103
	Oestrogen receptor assay positive	10054054
	Oestrogen receptor positive breast cancer	10070577
	Paget's disease of nipple	10033364
	Photon radiation therapy to breast	10034949
	Postmastectomy lymphoedema syndrome	10036390

Table D. Infrequent Tier 1 Adverse Events of Special Interest: MedDRA Preferred Terms and Codes		
Special Interest Event	**MedDRA Preferred Term**	**PT_Code**
	Progesterone receptor assay positive	10054057
	Radical mastectomy	10037773
	Radiotherapy to breast	10062090
	Simple mastectomy	10040700
	Tubular breast carcinoma	10073104
	X-ray therapy to breast	10048199
	Antioestrogen therapy	10002816
	Breast reconstruction	10006305
	Breast neoplasm	10006279
	Nipple neoplasm	10056286
	Phyllodes tumour	10071776
	Biopsy breast abnormal	10004745
	Breast calcifications	10048782
	Breast dysplasia	10006237
	Breast prosthesis implantation	10006303
	Computerised tomogram breast abnormal	10074534
Depressed mood	Activation syndrome	10066817
	Adjustment disorder with depressed mood	10001297
	Columbia suicide severity rating scale abnormal	10075616
	Adjustment disorder with mixed anxiety and depressed mood	10001299
	Agitated depression	10001496
	Anhedonia	10002511
	Antidepressant therapy	10054976
	Childhood depression	10068631
	Decreased interest	10011971
	Depressed mood	10012374
	Depression	10012378
	Depression postoperative	10012390
	Depressive symptom	10054089
	Dysphoria	10013954
	Electroconvulsive therapy	10014404
	Feeling guilty	10049708
	Feeling of despair	10016344
	Feelings of worthlessness	10016374
	Major depression	10057840
	Menopausal depression	10067371
	Post stroke depression	10070606
	Postictal depression	10071324
	Perinatal depression	10078366
	Completed suicide	10010144
	Depression suicidal	10012397
	Intentional overdose	10022523
	Intentional self-injury	10022524
	Poisoning deliberate	10036000
	Self-injurious ideation	10051154
	Suicidal behaviour	10065604
	Suicidal ideation	10042458
	Suicide attempt	10042464

Table D. Infrequent Tier 1 Adverse Events of Special Interest: MedDRA Preferred Terms and Codes		
Special Interest Event	**MedDRA Preferred Term**	**PT_Code**
Hair changes	Alopecia	10001760
	Alopecia areata	10001761
	Alopecia scarring	10001764
	Alopecia syphilitic	10001765
	Alopecia totalis	10001766
	Alopecia universalis	10001767
	Hypotrichosis	10021126
	Progeria	10036794
	Madarosis	10051235
	Follicular mucinosis	10056506
	Application site alopecia	10059046
	Androgenetic alopecia	10068168
	Satoyoshi syndrome	10070579
	Radiation alopecia	10072045
	Diffuse alopecia	10073736
	Hypertrichosis	10020864
Interference with formation of external genitalia in a male fetus	Congenital vas deferens absence	10010670
	Cryptorchism	10011498
	Epispadias	10015088
	Hypospadias	10021093
	Reproductive tract hypoplasia, male	10057858
	Testicular dysplasia	10059271
	Congenital genital malformation male	10059492
	Penoscrotal fusion	10064951
	Sertoli-cell-only syndrome	10066833
	Buried penis syndrome	10067131
	Penoscrotal transposition	10067287
	Penile torsion	10070235
Potential for decreased male fertility	Infertility tests	10021931
	pH semen	10034784
	pH semen decreased	10034786
	pH semen increased	10034788
	pH semen normal	10034790
	Red blood cells semen	10038176
	Red blood cells semen negative	10038179
	Red blood cells semen positive	10038180
	Semen liquefaction	10039931
	Semen liquefaction normal	10039933
	Semen liquefaction prolonged	10039934
	Semen liquefaction shortened	10039935
	Semen viscosity	10039936
	Semen viscosity decreased	10039938
	Semen viscosity increased	10039940
	Semen viscosity normal	10039942
	Semen volume abnormal	10039943
	Semen volume decreased	10039944
	Semen volume increased	10039946
	Semen volume normal	10039948
	Sperm analysis	10041476
	Sperm analysis abnormal	10041477
	Sperm analysis normal	10041478
	Spermatozoa abnormal	10041498
	Spermatozoa morphology	10041501

Table D. Infrequent Tier 1 Adverse Events of Special Interest: MedDRA Preferred Terms and Codes		
Special Interest Event	**MedDRA Preferred Term**	**PT_Code**
	Spermatozoa morphology abnormal	10041502
	Spermatozoa morphology normal	10041503
	Spermatozoa progressive motility abnormal	10041504
	Spermatozoa progressive motility decreased	10041506
	Spermatozoa progressive motility normal	10041507
	White blood cells semen	10047956
	White blood cells semen negative	10047959
	White blood cells semen positive	10047960
	Fructose semen decreased	10052476
	Fructose semen increased	10052477
	Prostatic fluid leukocytes increased	10053866
	Infertility tests abnormal	10062020
	Infertility tests normal	10062021
	pH semen abnormal	10062074
	Semen liquefaction abnormal	10062159
	Semen viscosity abnormal	10062160
	Semen analysis normal	10062238
	Semen analysis	10068482
	Semen analysis abnormal	10068483
	Sperm concentration decreased	10070925
	Sperm concentration increased	10070926
	Sperm concentration abnormal	10070927
	Sperm concentration normal	10070928
	Sperm concentration	10070929
	Sperm concentration zero	10070930
	Total sperm count	10070931
	Total sperm count decreased	10070932
	Infertility	10021926
	Infertility male	10021929
Testicular pain and swelling	Anorchism	10002641
	Eunuchoidism	10015532
	Hypogonadism male	10021011
	Testicular atrophy	10043298
	Testicular disorder	10043306
	Testicular failure	10043315
	Testicular failure postoperative	10043317
	Testicular failure primary	10043318
	Testicular hyperfunction	10043334
	Testicular infarction	10043337
	Testicular pain	10043345
	Testicular retraction	10043348
	Testicular swelling	10043354
	Testicular torsion	10043356
	Testicular necrosis	10049572
	Spermatic cord mass	10049792
	Testicular appendage torsion	10050476
	Spermatic cord pain	10051221
	Testicular injury	10051872
	Testicular haemorrhage	10051877
	Epididymal calculus	10052321
	Epididymal enlargement	10052322
	Epididymal tenderness	10052323
	Testis discomfort	10052531

Table D. Infrequent Tier 1 Adverse Events of Special Interest: MedDRA Preferred Terms and Codes		
Special Interest Event	**MedDRA Preferred Term**	**PT_Code**
	Monorchidism	10055002
	Epididymal disorder	10055045
	Spermatic cord disorder	10056348
	Testicular mass	10058901
	Testotoxicosis	10063654
	Spermatic cord haemorrhage	10065742
	Spermatic cord obstruction	10065805
	Spermatic cord perforation	10065806
	Spermatic cord stenosis	10065807
	Testicular perforation	10065808
	Testicular hypertrophy	10066101
	Testicular oedema	10066769
	Sperm granuloma	10067802
	Testicular microlithiasis	10067829
	Congenital monorchidism	10069505
	Testicular autoimmunity	10071574
Relevant for tamsulosin:		
Atrial fibrillation, tachycardia, arrhythmias	Arrhythmia	10003119
	Heart alternation	10058155
	Heart rate irregular	10019304
	Pacemaker generated arrhythmia	10053486
	Pacemaker syndrome	10051994
	Paroxysmal arrhythmia	10050106
	Pulseless electrical activity	10058151
	Reperfusion arrhythmia	10058156
	Withdrawal arrhythmia	10047997
	Arrhythmia supraventricular	10003130
	Atrial fibrillation	10003658
	Atrial flutter	10003662
	Atrial parasystole	10071666
	Atrial tachycardia	10003668
	Junctional ectopic tachycardia	10074640
	Sinus tachycardia	10040752
	Supraventricular extrasystoles	10042602
	Supraventricular tachyarrhythmia	10065342
	Supraventricular tachycardia	10042604
	ECG P wave inverted	10057526
	Electrocardiogram P wave abnormal	10050384
	Retrograde p-waves	10071187
	Anomalous atrioventricular excitation	10002611
	Cardiac flutter	10052840
	Extrasystoles	10015856
	Tachyarrhythmia	10049447
	Accelerated idioventricular rhythm	10049003
	Cardiac fibrillation	10061592
	Parasystole	10033929
	Rhythm idioventricular	10039111
	Torsade de pointes	10044066
	Ventricular arrhythmia	10047281
	Ventricular extrasystoles	10047289
	Ventricular fibrillation	10047290
	Ventricular flutter	10047294
	Ventricular parasystole	10058184

Table D. Infrequent Tier 1 Adverse Events of Special Interest: MedDRA Preferred Terms and Codes		
Special Interest Event	**MedDRA Preferred Term**	**PT_Code**
	Ventricular pre-excitation	10049761
	Ventricular tachyarrhythmia	10065341
	Ventricular tachycardia	10047302
Floppy Iris Syndrome	Floppy iris syndrome	10066373
Orthostasis	Dizziness	10013573
	Dizziness postural	10013578
	Orthostatic hypotension	10031127
	Hypotension	10021097
	Syncope	10042772
	Presyncope	10036653
	Blood pressure orthostatic abnormal	10053354
	Blood pressure orthostatic decreased	10053356
Priapism	Priapism	10036661
Stevens-Johnson syndrome	Acute generalised exanthematous pustulosis	10048799
	Cutaneous vasculitis	10011686
	Dermatitis bullous	10012441
	Dermatitis exfoliative	10012455
	Dermatitis exfoliative generalised	10012456
	Drug reaction with eosinophilia and systemic symptoms	10073508
	Epidermal necrosis	10059284
	Erythema multiforme	10015218
	Exfoliative rash	10064579
	Oculomucocutaneous syndrome	10030081
	Skin necrosis	10040893
	Stevens-Johnson syndrome	10042033
	Toxic epidermal necrolysis	10044223
	Toxic skin eruption	10057970

11.9. Appendix 9: Threshold Factors for Clinical Laboratory Tests and Vital Signs

Hematology and Clinical Chemistry Laboratory Tests, Codes and Threshold Factors				
LABORATORY TEST	Database LBTESTCD	Unit	Multiplicative Factors[1]	
			Low (x LLN)	High (x ULN)
HEMATOLOGY				
-Hemoglobin	HB_BLC	G/L	0.75	-
-Platelet count	PLT_BLC	GI/L	0.75	1.5
-WBC count	WBC_BLC	GI/L	0.5	3.0
-RBC count	RBC_BLC	GI/L	0.5	-
CLINICAL CHEMISTRY				
-Albumin	ALB_PLC	G/L	0.9	1.2
-ALT	ALT_PLC	IU/L	-	3.0
-Alkaline Phosphatase	ALP_PLC	IU/L	-	1.5
- AST	AST_PLC	IU/L	-	3.0
-Creatinine	CRT_PLC	UMOL/L	0.5	3.0
-Glucose	GLUC_PLC	MMOL/L	0.7	1.75
-Potassium	K_PLC	MMOL/L	0.75	1.4
-Sodium	NA_PLC	MMOL/L	0.9	1.15
-Total Bilirubin	BILT_PLC	UMOL/L	-	2.5
-Total Protein	TP_PLC	G/L	0.8	1.15
-Urea/BUN	UREA_PLC	MMOL/L	0.5	2.0

1. A laboratory value that is above the upper limit factor multiplied by the upper limit of the normal range is considered a high threshold value. A laboratory value that is below the lower limit factor multiplied by the lower limit of the normal range is considered a low threshold value.

Threshold Ranges for Vital Signs			
		Threshold Ranges	
Vital Sign	Unit	Lower	Upper
Systolic Blood Pressure	mmHg	<80	>165
Diastolic Blood Pressure	mmHg	<40	>105
Heart Rate	bpm	<40	>100

11.10. Appendix 10: Examination of Covariates and Subgroups

Endpoint(s)	IPSS change from baseline
Analysis	Subgroup Summaries and General Linear Model

A list of subgroups of interest for the primary efficacy endpoint is below. If the categorization defining the subgroups results in overly sparse data or if some baseline subgroups are homogeneous in response, then particular subgroups may be combined or not reported.

For each subgroup, IPSS change from baseline summaries will be output by treatment group at Month 12 and at Month 24 for the ITT population using both LOCF and At Visit approaches. No statistical comparisons will be performed.

The effects of baseline subgroups and their interactions with treatment will be assessed. As a minimum, these subgroups will include those in the below table except for country and center. These effects will be individually explored in terms of: 1) addition of subgroup effect to the model* and 2) addition of subgroup effect and subgroup effect by treatment interaction to the model*.

*Refers to primary efficacy General Linear Model (GLM):
Change from Baseline IPSS = treatment + cluster + baseline IPSS.

In these analyses, continuous variables will be treated as continuous and not as dichotomous subgroups. These assessments will focus on Month 24 LOCF, and separately Month 24 At Visit, and will be output as listings. Other analyses based on other time points will not be output unless substantive finding dictate.

Subgroups Summarized for Primary Efficacy Endpoint

Subgroup	Categorization for Tabular Summary Display
Baseline Age 65	<65, ≥65 years
Baseline Age 75	<75, ≥75 years
Baseline IPSS	<20, ≥20
Baseline BPH-Related Health Status	<4, ≥4
Baseline Prostate Volume	<40, ≥40cc
Baseline Qmax	<10, ≥10ml/sec
Alpha Blocker History	Yes, No
5-Alpha-Reductase Inhibitor History	Yes, No
Phytotherapy History	Yes, No
Alpha Blocker or 5-Alpha-Reductase Inhibitor History	Yes, No
Alpha Blocker or 5-Alpha-Reductase Inhibitor or Phytotherapy History	Yes, No
Baseline PSA	<3, ≥3ng/ml
Country (cluster)	China, Japan, Korea, Taiwan
Center	Each center with at least one randomized subject.

11.11. Appendix 11: Multiple Comparisons and Multiplicity

Results of all planned statistical analyses and thus all planned p-values will be reported. P-values ≤0.05 will be considered formally statistically significant if the below described conditions are satisfied for multiple endpoints and multiple time points. Otherwise p-values ≤0.05 will be considered nominally significant.

The comparisons are in terms of two treatment arms, Combination and Tamsulosin, so no multiplicity adjustment for treatment is necessary.

Multiplicity adjustment for multiple endpoints is described in this paragraph. For the primary efficacy endpoint, IPSS change from baseline at Month 24, if the Month 24 two-sided p-value is ≤0.05 and the treatment difference supports Combination superiority versus Tamsulosin, then formal statistical significance is declared and testing of each secondary endpoint may occur. For secondary endpoints evaluated at multiple time points, then the testing will begin at Month 24. For purposes of statistical testing, there is no hierarchical order assigned to the set of secondary endpoints at Month 24.

Multiplicity adjustment for multiple time points is described in this paragraph. For any endpoint that is tested over different visits, a step-down procedure for interpreting the p-values will be adopted. The final time point (Month 24) will be tested first. If the Month 24 two-sided p-value is ≤0.05 and the treatment difference supports Combination superiority versus Tamsulosin, the time point immediately preceding it will be interpreted for formal statistical significance; otherwise formal interpretation of significance will stop, but interpretation of nominal significance will continue for preceding endpoints. The interpretation of formal statistical significance will continue this way in a stepwise manner through all time points.

As an example, the time point testing visit sequence for the primary efficacy endpoint is: Month 24, Month 21, Month 18, Month 15, Month 12, Month 9, Month 6, and (last) Month 3.

11.12. Appendix 12: Model Checking and Diagnostics for Statistical Analyses

Endpoint(s)	IPSS change from baseline
Analysis	General Linear Model

- Assessments of the general linear model residuals will be performed. These assessments will include reviews of residual by predicted value plots and normal probability plots on residuals. This will be in terms of the change from baseline IPSS at Month 24 using the LOCF and At Visit approaches. Similar assessments of other time periods will not be reported unless dictated by substantive findings.

- If these assumptions are not met, appropriate non-parametric analyses will be performed to test the robustness of the results of the parametric analyses. If non-parametric analyses are performed further detailed information will be provided in the Statistical Appendix for the Clinical Report.

- The interaction of cluster with treatment will be assessed by adding the (interaction) term to the above planned analysis model at Month 24.

- The interaction of baseline IPSS with treatment will be assessed by adding the (interaction) term to the above stated model at Month 24.

- The effects of baseline subgroups and their interactions with treatment will also be assessed. This is described in Appendix 10, Examination of Covariates and Subgroups

11.13. Appendix 13: Mixed-Model Repeated-Measures Analysis

Mixed-Model Repeated-Measures (MMRM) Analysis: As a supportive analysis, IPSS change from baseline will be analyzed using a mixed-model repeated-measures (MMRM) analysis including data from the scheduled post-baseline assessments [Mallinckrodt, 2008]. Analyses will include the fixed, categorical effects of treatment, cluster, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline IPSS and baseline IPSS-by-visit interaction. An unstructured covariance structure will be used to model the within-patient errors, shared across treatments. PROC MIXED in SAS [Littell, 1996] will be used to fit the model, using the restricted maximum likelihood estimation method and the Kenward-Roger option to estimate denominator degrees of freedom and standard errors.

Corresponding SAS output will be provided as a listing. The treatment comparison will be the contrast between treatments (Combination minus Tamsulosin) at the Month 24 visit using the two-sided p-value from the corresponding t-test at $\alpha=0.05$. In this supportive analysis, superiority of the Combination vs. Tamsulosin treatment will be declared if the two-sided p-value for the contrast is less than or equal to 0.05 and the observed treatment effect supports superiority. A two-sided 95% confidence interval for the estimated treatment difference in the change from baseline at each scheduled visit will be computed. Estimated mean change from baseline and standard errors will be computed by treatment group and visit. If the model-fitting algorithm fails to converge then alternative initial parameter values and/or covariance structures will be considered.

11.14. Appendix 14 – Abbreviations & Trade Marks

11.14.1. Abbreviations

Abbreviation	Description
5ARI	5 Alpha-Reductase Inhibitor
ADaM	Analysis Data Model
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUR	Acute Urinary Retention
A&R	Analysis and Reporting
BHS	BPH-related Health Status
BII	BPH Impact Index
BPH	Benign Prostatic Hyperplasia
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating
DOB	Date of Birth
DRE	Digital Rectal Examination
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
FDC	Fixed Dose Combination
ICH	International Conference on Harmonization
IMMS	International Modules Management System
IP	Investigational Product
ITT	Intent-To-Treat
GUI	Guidance
LOCF	Last Observation Carried Forward
LUTS	Lower urinary tract symptoms
MMRM	Mixed-Model Repeated- Measures
PAS SFI	Problem Assessment Scale Sexual Function Inventory
PDE-5	Phosphodiesterase-5
PDMP	Protocol Deviation Management Plan
PGx	Pharmacogenetic
PPK	Population Pharmacokinetics
PP	Per-Protocol
PPSM	Patient Perception of Study Medication
PSA	Prostate Specific Antigen
PSAP	Program Safety Analysis Plan
PSRAE	Possible Suicidality Related Adverse Event
QC	Quality Control
Qmax	Maximum (peak) urinary flow rate
RAMOS	Randomization & Medication Ordering System

Abbreviation	Description
RandAll NG	RandAll is a randomization creation and publishing tool for GSK studies. NG represents Next Generation version.
RAP	Reporting & Analysis Plan
RBC	Red Blood Cell
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings
TFUQ	Targeted Follow-Up Questionnaire
TRUS	Transrectal ultrasound
UTI	Urinary Tract Infection
WBC	White Blood Cell

11.14.2. Trademarks

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Proscar
SAS
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11.15. Appendix 15: List of Data Displays

11.15.1. Data Display Numbering

The following numbering will be applied for RAP generated displays.

Section	Tables	Figures
Study Population	1.1 to 1.32	NA
Efficacy	2.1 to 2.165	2.1 to 2.9
Safety	3.1 to 3.98	3.1 to 3.18
Health Outcomes	4.1 to 4.58	4.1 to 4.4
Section	**Listings**	
ICH Listings (Study Population)	1.1 to 1.14	
ICH Listings (Efficacy)	2.1 to 2.8	
ICH Listings (Safety)	3.1 to 3.21	
ICH Listings (Health Outcomes)	-	
Other Listings includes Non-ICH listings	5.1 to 5.64	

11.15.2. Study Population Tables

Study Population Tables (Population=ITT except when noted)	
No.	**Title**
Subject Accountability	
1.1	Summary of Subject Accountability *Note: Population = All Enrolled Subjects*
Subject Disposition	
1.2	Summary of Subject Withdrawals During Placebo Run-in Phase *Note: Population = Subjects Who Entered Placebo Run-In*
1.3	Summary of Randomized Subjects by Country and Center
1.4	Summary of Subject Disposition
1.5	Summary of Subject Discontinuation by Visit
1.6	Summary of Primary Reason for Study Withdrawal, by Period of Discontinuation
1.7	Summary of Inclusion/Exclusion Criteria Deviations
1.8	Summary of Important Protocol Deviations
1.9	Summary of Deviations which Require Exclusion from the Per-Protocol Population
Demographic and Baseline Characteristics	
1.10	Summary of Baseline and Demographic Characteristics
1.11	Summary of Baseline and Demographic Characteristics by Country
1.12	Summary of Race and Racial Combinations
1.13	Summary of Race and Racial Combination Details
1.14	Summary of Selected Safety Measures at Baseline
1.15	Summary of Selected Safety Measures at Baseline by Country
1.16	Summary of Selected Efficacy and Health Outcome Measures at Baseline
1.17	Summary of Selected Efficacy and Health Outcome Measures at Baseline by Country
Medical Conditions and Concomitant Medications	
1.18	Summary of Medical Conditions at Screening, by Body System

Study Population Tables (Population=ITT except when noted)	
No.	**Title**
1.19	Summary of Specific Medical Conditions at Screening
1.20	Summary of BPH History
1.21	Summary of Alpha-Blocker Use
1.22	Summary of 5-Alpha-Reductase Inhibitor Use
	Note: Below strikethroughs and data display number revisions are associated with RAP Amendment 01. This approach permanently documents data display number revisions for traceability and reference.
~~1.23~~ 1.24	Summary of Alpha-Blocker, 5-Alpha-Reductase Inhibitor, and Phytotherapy for BPH Use
~~1.24~~ 1.23	Summary of Phytotherapy for BPH Use
1.25	Summary of Sexual Function at Screening
1.26	Summary of Family History of Premature Coronary Artery Disease
1.27	Summary of Family History of Breast Cancer
1.28	Summary of Family History of Prostate Cancer
1.29	Summary of Concomitant Medications
1.30	Summary of Investigational Product Discontinuation
1.31	Summary of Study Drug Exposure
1.32	Summary of Compliance to Study Drug

11.15.3. Efficacy Tables

Efficacy Tables (Population=ITT)	
No.	**Title**
IPSS Overview and Primary Analysis	
2.1	Summary of IPSS Imputations
2.2	Summary of IPSS at Screening and Baseline *includes Visit 1a, Visit 2, Baseline, Baseline for Subjects with IPSS at each Month n (3, 6, …24)*
2.3	Summary of IPSS at Each Post-Baseline Visit (LOCF)
2.4	Summary of IPSS at Each Post-Baseline Visit (At Visit)
2.5	Summary of IPSS Change from Baseline (LOCF)
2.6	Summary of IPSS Change from Baseline (At Visit)
IPSS MMRM	
2.7	Summary of MMRM Analysis for IPSS Change from Baseline
IPSS Change from Baseline Subgroup Summaries *presented for each Month 12 and Month 24*	
2.8	Summary of IPSS Change from Baseline, by Age (<65, ≥65 years) (LOCF)
2.9	Summary of IPSS Change from Baseline, by Age (<65, ≥65 years) (At Visit)
2.10	Summary of IPSS Change from Baseline, by Age (<75, ≥75 years) (LOCF)
2.11	Summary of IPSS Change from Baseline, by Age (<75, ≥75 years) (At Visit)
2.12	Summary of IPSS Change from Baseline, by Baseline IPSS (<20, ≥20) (LOCF)
2.13	Summary of IPSS Change from Baseline, by Baseline IPSS (<20, ≥20) (At Visit)
2.14	Summary of IPSS Change from Baseline, by Baseline BPH-Related Health Status (<4, ≥4) (LOCF)
2.15	Summary of IPSS Change from Baseline, by Baseline BPH-Related Health Status (<4, ≥4) (At Visit)
2.16	Summary of IPSS Change from Baseline, by Baseline Prostate Volume (<40, ≥40cc) (LOCF)
2.17	Summary of IPSS Change from Baseline, by Baseline Prostate Volume (<40, ≥40cc) (At Visit)
2.18	Summary of IPSS Change from Baseline, by Baseline Qmax (<10, ≥10ml/sec) (LOCF)
2.19	Summary of IPSS Change from Baseline, by Baseline Qmax (<10, ≥10ml/sec) (At Visit)

Efficacy Tables (Population=ITT)	
No.	**Title**
2.20	Summary of IPSS Change from Baseline, by Alpha-Blocker History (yes, no) (LOCF)
2.21	Summary of IPSS Change from Baseline, by Alpha-Blocker History (yes, no) (At Visit)
2.22	Summary of IPSS Change from Baseline, by 5-Alpha-Reductase Inhibitor History (yes, no) (LOCF)
2.23	Summary of IPSS Change from Baseline, by 5-Alpha-Reductase Inhibitor History (yes, no) (At Visit)
2.24	Summary of IPSS Change from Baseline, by Phytotherapy History (yes, no) (LOCF)
2.25	Summary of IPSS Change from Baseline, by Phytotherapy History (yes, no) (At Visit)
	Note: Below strikethroughs and data display number revisions are associated with RAP Amendment 01. This approach permanently documents data display number revisions for traceability and reference.
2.26	Summary of IPSS Change from Baseline, by Alpha-Blocker History or 5-Alpha-Reductase Inhibitor History (yes, no) (LOCF)
2.27	Summary of IPSS Change from Baseline, by Alpha-Blocker History or 5-Alpha-Reductase Inhibitor History (yes, no) (At Visit)
2.28	Summary of IPSS Change from Baseline, by Alpha-Blocker History or 5-Alpha-Reductase Inhibitor or Phytotherapy History (yes, no) (LOCF)
2.29	Summary of IPSS Change from Baseline, by Alpha-Blocker History or 5-Alpha-Reductase Inhibitor or Phytotherapy History (yes, no) (At Visit)
~~2.26~~ 2.30	Summary of IPSS Change from Baseline, by Baseline PSA (<3, ≥3ng/ml) (LOCF)
~~2.27~~ 2.31	Summary of IPSS Change from Baseline, by Baseline PSA (<3, ≥3ng/ml) (At Visit)
~~2.28~~ 2.32	Summary of IPSS Change from Baseline, by Country (LOCF)
~~2.29~~ 2.33	Summary of IPSS Change from Baseline, by Country (At Visit)
	Note: IPSS change from baseline summaries by center are output in Non-ICH Listings rather than in Tables.
Individual IPSS Questions 1 - 7	
~~2.30~~ 2.34	Summary of IPSS at Screening and Baseline: Question 1 *includes Visit 1a, Visit 2, Baseline, Baseline for Subjects with IPSS at each Months 12 and 24*
~~2.31~~ 2.35	Summary of IPSS at Months 12 and 24: Question 1 (LOCF) *each of the below individual question summaries is in terms of Months 12 and 24 only*.
~~2.32~~ 2.36	Summary of IPSS at Months 12 and 24: Question 1 (At Visit)
~~2.33~~ 2.37	Summary of IPSS Change from Baseline at Months 12 and 24: Question 1 (LOCF)
~~2.34~~ 2.38	Summary of IPSS Change from Baseline at Months 12 and 24: Question 1 (At Visit)

Efficacy Tables (Population=ITT)	
No.	**Title**
~~2.35~~ 2.39	Summary of IPSS at Screening and Baseline: Question 2
~~2.36~~ 2.40	Summary of IPSS at Months 12 and 24: Question 2 (LOCF)
~~2.37~~ 2.41	Summary of IPSS at Months 12 and 24: Question 2 (At Visit)
~~2.38~~ 2.42	Summary of IPSS Change from Baseline at Months 12 and 24: Question 2 (LOCF)
~~2.39~~ 2.43	Summary of IPSS Change from Baseline at Months 12 and 24: Question 2 (At Visit)
~~2.40~~ 2.44	Summary of IPSS at Screening and Baseline: Question 3
~~2.41~~ 2.45	Summary of IPSS at Months 12 and 24: Question 3 (LOCF)
~~2.42~~ 2.46	Summary of IPSS at Months 12 and 24: Question 3 (At Visit)
~~2.43~~ 2.47	Summary of IPSS Change from Baseline at Months 12 and 24: Question 3 (LOCF)
~~2.44~~ 2.48	Summary of IPSS Change from Baseline at Months 12 and 24: Question 3 (At Visit)
~~2.45~~ 2.49	Summary of IPSS at Screening and Baseline: Question 4
~~2.46~~ 2.50	Summary of IPSS at Months 12 and 24: Question 4 (LOCF)
~~2.47~~ 2.51	Summary of IPSS at Months 12 and 24: Question 4 (At Visit)
~~2.48~~ 2.52	Summary of IPSS Change from Baseline at Months 12 and 24: Question 4 (LOCF)
~~2.49~~ 2.53	Summary of IPSS Change from Baseline at Months 12 and 24: Question 4 (At Visit)
~~2.50~~ 2.54	Summary of IPSS at Screening and Baseline: Question 5
~~2.51~~ 2.55	Summary of IPSS at Months 12 and 24: Question 5 (LOCF)
~~2.52~~ 2.56	Summary of IPSS at Months 12 and 24: Question 5 (At Visit)
~~2.53~~ 2.57	Summary of IPSS Change from Baseline at Months 12 and 24: Question 5 (LOCF)
~~2.54~~ 2.58	Summary of IPSS Change from Baseline at Months 12 and 24: Question 5 (At Visit)
~~2.55~~ 2.59	Summary of IPSS at Screening and Baseline: Question 6
~~2.56~~ 2.60	Summary of IPSS at Months 12 and 24: Question 6 (LOCF)
~~2.57~~ 2.61	Summary of IPSS at Months 12 and 24: Question 6 (At Visit)

Efficacy Tables (Population=ITT)	
No.	**Title**
~~2.58~~ 2.62	Summary of IPSS Change from Baseline at Months 12 and 24: Question 6 (LOCF)
~~2.59~~ 2.63	Summary of IPSS Change from Baseline at Months 12 and 24: Question 6 (At Visit)
~~2.60~~ 2.64	Summary of IPSS at Screening and Baseline: Question 7
~~2.61~~ 2.65	Summary of IPSS at Months 12 and 24: Question 7 (LOCF)
~~2.62~~ 2.66	Summary of IPSS at Months 12 and 24: Question 7 (At Visit)
~~2.63~~ 2.67	Summary of IPSS Change from Baseline at Months 12 and 24: Question 7 (LOCF)
~~2.64~~ 2.68	Summary of IPSS Change from Baseline at Months 12 and 24: Question 7 (At Visit)
IPSS Percentage Change from Baseline	
~~2.65~~ 2.69	Summary of IPSS Percentage Change from Baseline (LOCF)
~~2.66~~ 2.70	Summary of IPSS Percentage Change from Baseline (At Visit)
IPSS Non-Imputed Score Analysis	
Performed only if RAP Section 7.1 imputation conditions are met; thus, table numbers are not listed.	
IPSS Per-Protocol Population Analysis	
Performed only if RAP Section 4 per-protocol conditions are met; thus, table numbers are not listed.	
IPSS Change-from-Baseline Improvement Levels	
~~2.67~~ 2.71	Summary of IPSS Change-from-Baseline Categories (LOCF)
~~2.68~~ 2.72	Summary of IPSS Change-from-Baseline Categories (At Visit)
IPSS Percentage Change-from-Baseline Improvement Levels	
~~2.69~~ 2.73	Summary of IPSS Percentage Change-from-Baseline Categories (LOCF)
~~2.70~~ 2.74	Summary of IPSS Percentage Change-from-Baseline Categories (At Visit)
Prostate Volume	
~~2.71~~ 2.75	Summary of Prostate Volume at Screening and Baseline
~~2.72~~ 2.76	Summary of Prostate Volume at Each Post-Baseline Visit (LOCF)
~~2.73~~ 2.77	Summary of Prostate Volume at Each Post-Baseline Visit (At Visit)
~~2.74~~ 2.78	Summary of Prostate Volume Change from Baseline (LOCF)

Efficacy Tables (Population=ITT)	
No.	**Title**
~~2.75~~ 2.79	Summary of Prostate Volume Change from Baseline (At Visit)
~~2.76~~ 2.80	Summary of Prostate Volume Percentage Change from Baseline (LOCF)
~~2.77~~ 2.81	Summary of Prostate Volume Percentage Change from Baseline (At Visit)
~~2.78~~ 2.82	Summary of Prostate Volume Percentage Change-from-Baseline Categories (LOCF)
~~2.79~~ 2.83	Summary of Prostate Volume Percentage Change-from-Baseline Categories (At Visit)
~~2.80~~ 2.84	Summary of Prostate Volume Percentage Change from Baseline, by Age (<65, ≥65 years) (LOCF)
~~2.81~~ 2.85	Summary of Prostate Volume Percentage Change from Baseline, by Age (<65, ≥65 years) (At Visit)
~~2.82~~ 2.86	Summary of Prostate Volume Percentage Change from Baseline, by Age (<75, ≥75 years) (LOCF)
~~2.83~~ 2.87	Summary of Prostate Volume Percentage Change from Baseline, by Age (<75, ≥75 years) (At Visit)
~~2.84~~ 2.88	Summary of Prostate Volume Percentage Change from Baseline, by Baseline IPSS (<20, ≥20) (LOCF)
~~2.85~~ 2.89	Summary of Prostate Volume Percentage Change from Baseline, by Baseline IPSS (<20, ≥20) (At Visit)
~~2.86~~ 2.90	Summary of Prostate Volume Percentage Change from Baseline, by Baseline BPH-Related Health Status (<4, ≥4) (LOCF)
~~2.87~~ 2.91	Summary of Prostate Volume Percentage Change from Baseline, by Baseline BPH-Related Health Status (<4, ≥4) (At Visit)
~~2.88~~ 2.92	Summary of Prostate Volume Percentage Change from Baseline, by Baseline Prostate Volume (<40, ≥40cc) (LOCF)
~~2.89~~ 2.93	Summary of Prostate Volume Percentage Change from Baseline, by Baseline Prostate Volume (<40, ≥40cc) (At Visit)
~~2.90~~ 2.94	Summary of Prostate Volume Percentage Change from Baseline, by Baseline Qmax (<10, ≥10ml/sec) (LOCF)
~~2.91~~ 2.95	Summary of Prostate Volume Percentage Change from Baseline, by Baseline Qmax (<10, ≥10ml/sec) (At Visit)
~~2.92~~ 2.96	Summary of Prostate Volume Percentage Change from Baseline, by Alpha-Blocker History (yes, no) (LOCF)
~~2.93~~ 2.97	Summary of Prostate Volume Percentage Change from Baseline, by Alpha-Blocker History (yes, no) (At Visit)
~~2.94~~ 2.98	Summary of Prostate Volume Percentage Change from Baseline, by 5-Alpha-Reductase Inhibitor History (yes, no) (LOCF)
~~2.95~~ 2.99	Summary of Prostate Volume Percentage Change from Baseline, by 5-Alpha-Reductase Inhibitor History (yes, no) (At Visit)
~~2.96~~ 2.100	Summary of Prostate Volume Percentage Change from Baseline, by Phytotherapy History (yes, no) (LOCF)
~~2.97~~ 2.101	Summary of Prostate Volume Percentage Change from Baseline, by Phytotherapy History (yes, no) (At Visit)

Efficacy Tables (Population=ITT)	
No.	**Title**
2.102	Summary of Prostate Volume Percentage Change from Baseline, by Alpha-Blocker History or 5-Alpha-Reductase Inhibitor History (yes, no) (LOCF)
2.103	Summary of Prostate Volume Percentage Change from Baseline, by Alpha-Blocker History or 5-Alpha-Reductase Inhibitor History (yes, no) (At Visit)
2.104	Summary of Prostate Volume Percentage Change from Baseline, by Alpha-Blocker History or 5-Alpha-Reductase Inhibitor or Phytotherapy History (yes, no) (LOCF)
2.105	Summary of Prostate Volume Percentage Change from Baseline, by Alpha-Blocker History or 5-Alpha-Reductase Inhibitor or Phytotherapy History (yes, no) (At Visit)
~~2.98~~ 2.106	Summary of Prostate Volume Percentage Change from Baseline, by Baseline PSA (<3, ≥3ng/ml) (LOCF)
~~2.99~~ 2.107	Summary of Prostate Volume Percentage Change from Baseline, by Baseline PSA (<3, ≥3ng/ml) (At Visit)
~~2.100~~ 2.108	Summary of Prostate Volume Percentage Change from Baseline, by Country (LOCF)
~~2.101~~ 2.109	Summary of Prostate Volume Percentage Change from Baseline, by Country (At Visit)
Note: Prostate volume percentage change from baseline summaries by center are output in Non-ICH Listings rather than in Tables.	
Qmax	
~~2.102~~ 2.110	Summary of Qmax at Screening and Baseline
~~2.103~~ 2.111	Summary of Qmax at Each Post-Baseline Visit (LOCF)
~~2.104~~ 2.112	Summary of Qmax at Each Post-Baseline Visit (At Visit)
~~2.105~~ 2.113	Summary of Qmax Change from Baseline (LOCF)
~~2.106~~ 2.114	Summary of Qmax Change from Baseline (At Visit)
2.115	Summary of MMRM Analysis for Qmax Change from Baseline
~~2.107~~ 2.116	Summary of Qmax Change from Baseline Categories (LOCF)
~~2.108~~ 2.117	Summary of Qmax Change from Baseline Categories (At Visit)
~~2.109~~ 2.118	Summary of Qmax Percentage Change from Baseline (LOCF)
~~2.110~~ 2.119	Summary of Qmax Percentage Change from Baseline (At Visit)
~~2.111~~ 2.120	Summary of Qmax Percentage Change-from-Baseline Categories (LOCF)
~~2.112~~ 2.121	Summary of Qmax Percentage Change-from-Baseline Categories (At Visit)

Efficacy Tables (Population=ITT)	
No.	**Title**
~~2.113~~ 2.122	Summary of Qmax Change from Baseline, by Age (<65, ≥65 years) (LOCF)
~~2.114~~ 2.123	Summary of Qmax Change from Baseline, by Age (<65, ≥65 years) (At Visit)
~~2.115~~ 2.124	Summary of Qmax Change from Baseline, by Age (<75, ≥75 years) (LOCF)
~~2.116~~ 2.125	Summary of Qmax Change from Baseline, by Age (<75, ≥75 years) (At Visit)
~~2.117~~ 2.126	Summary of Qmax Change from Baseline, by Baseline IPSS (<20, ≥20) (LOCF)
~~2.118~~ 2.127	Summary of Qmax Change from Baseline, by Baseline IPSS (<20, ≥20) (At Visit)
~~2.119~~ 2.128	Summary of Qmax Change from Baseline, by Baseline BPH-Related Health Status (<4, ≥4) (LOCF)
~~2.120~~ 2.129	Summary of Qmax Change from Baseline, by Baseline BPH-Related Health Status (<4, ≥4) (At Visit)
~~2.121~~ 2.130	Summary of Qmax Change from Baseline, by Baseline Prostate Volume (<40, ≥40cc) (LOCF)
~~2.122~~ 2.131	Summary of Qmax Change from Baseline, by Baseline Prostate Volume (<40, ≥40cc) (At Visit)
~~2.123~~ 2.132	Summary of Qmax Change from Baseline, by Baseline Qmax (<10, ≥10ml/sec) (LOCF)
~~2.124~~ 2.133	Summary of Qmax Change from Baseline, by Baseline Qmax (<10, ≥10ml/sec) (At Visit)
~~2.125~~ 2.134	Summary of Qmax Change from Baseline, by Alpha-Blocker History (yes, no) (LOCF)
~~2.126~~ 2.135	Summary of Qmax Change from Baseline, by Alpha-Blocker History (yes, no) (At Visit)
~~2.127~~ 2.136	Summary of Qmax Change from Baseline, by 5-Alpha-Reductase Inhibitor History (yes, no) (LOCF)
~~2.128~~ 2.137	Summary of Qmax Change from Baseline, by 5-Alpha-Reductase Inhibitor History (yes, no) (At Visit)
~~2.129~~ 2.138	Summary of Qmax Change from Baseline, by Phytotherapy History (yes, no) (LOCF)
~~2.130~~ 2.139	Summary of Qmax Change from Baseline, by Phytotherapy History (yes, no) (At Visit)
2.140	Summary of Qmax Change from Baseline, by Alpha-Blocker History or 5-Alpha-Reductase Inhibitor History (yes, no) (LOCF)
2.141	Summary of Qmax Change from Baseline, by Alpha-Blocker History or 5-Alpha-Reductase Inhibitor History (yes, no) (At Visit)
2.142	Summary of Qmax Change from Baseline, by Alpha-Blocker History or 5-Alpha-Reductase Inhibitor or Phytotherapy History (yes, no) (LOCF)
2.143	Summary of Qmax Change from Baseline, by Alpha-Blocker History or 5-Alpha-Reductase Inhibitor or Phytotherapy History (yes, no) (At Visit)
~~2.131~~ 2.144	Summary of Qmax Change from Baseline, by Baseline PSA (<3, ≥3ng/ml) (LOCF)

Efficacy Tables (Population=ITT)	
No.	**Title**
~~2.132~~ 2.145	Summary of Qmax Change from Baseline, by Baseline PSA (<3, ≥3ng/ml) (At Visit)
~~2.133~~ 2.146	Summary of Qmax Change from Baseline, by Country (LOCF)
~~2.134~~ 2.147	Summary of Qmax Change from Baseline, by Country (At Visit)
Note: Qmax change from baseline summaries by center are output in Non-ICH Listings rather than in Tables.	

AUR or BPH-Related Surgery	
~~2.135~~ 2.148	Summary of Time to AUR or BPH-Related Surgery
~~2.136~~ 2.149	Summary of Time to AUR or BPH-Related Surgery by Quarter
~~2.137~~ 2.150	Summary of AUR or BPH-Related Surgery
~~2.138~~ 2.151	Summary of Effect of Various Factors on Time to AUR or BPH-Related Surgery
~~2.139~~ 2.152	Summary of Hospitalization for AUR or BPH-Related Surgery
~~2.140~~ 2.153	Summary of Time from Treatment Stop to AUR or BPH-Related Surgery
~~2.141~~ 2.154	Summary of Time to First AUR
~~2.142~~ 2.155	Summary of Time to First AUR by Quarter
~~2.143~~ 2.156	Summary of AUR
~~2.144~~ 2.157	Summary of Hospitalization for AUR
~~2.145~~ 2.158	Summary of Time to BPH-Related Surgery
~~2.146~~ 2.159	Summary of Time to BPH-Related Surgery by Quarter
~~2.147~~ 2.160	Summary of BPH-Related Surgery
~~2.148~~ 2.161	Summary of Hospitalization for BPH-Related Surgery
~~2.149~~ 2.162	Summary of Prostatic Surgery
Other Efficacy Measures	
~~2.150~~ 2.163	Summary of Urinary Tract Infection / Urosepsis
~~2.151~~ 2.164	Summary of Urinary Incontinence
~~2.152~~ 2.165	Summary of Renal Insufficiency

11.15.4. Efficacy Figures

Efficacy Figures (Population=ITT)	
No.	**Title**
IPSS	
2.1	Plot of IPSS Adjusted Mean Change from Baseline (LOCF)
2.2	Plot of IPSS Adjusted Mean Change from Baseline (At Visit)
Prostate Volume	
2.3	Plot of Prostate Volume Adjusted Mean Percentage Change from Baseline (LOCF)
2.4	Plot of Prostate Volume Adjusted Mean Percentage Change from Baseline (At Visit)
Qmax	
2.5	Plot of Qmax Adjusted Mean Change from Baseline (LOCF)
2.6	Plot of Qmax Adjusted Mean Change from Baseline (At Visit)
AUR or BPH-Related Surgery	
2.7	Plot of Kaplan-Meier Estimates of Time to First AUR or BPH-Related Surgery
2.8	Plot of Kaplan-Meier Estimates of Time to First AUR
2.9	Plot of Kaplan-Meier Estimates of Time to First BPH-Related Surgery

11.15.5. Safety Tables

Safety	
3.1	Summary of Adverse Events Starting Post-Randomization by Type
3.2	Summary of Adverse Events Starting Post-Randomization
3.3	Summary of Adverse Events Starting On-Treatment
3.4	Summary of Adverse Events Starting Post-Treatment
3.5	Summary of Non-Serious Adverse Events Starting Post-Randomization
3.6	Summary of Adverse Events Starting Post-Randomization by Time Period of Onset
3.7	Summary of Adverse Events Starting Post-Randomization by Age Group (<65, ≥65)

Safety	
3.8	Summary of Adverse Events Starting Post-Randomization by Age Group (<75, ≥75)
3.9	Summary of Adverse Events Starting Post-Randomization by Country
3.10	Summary of Adverse Events Starting Post-Randomization by Descending Frequency
3.11	Summary of Serious Adverse Events Starting Post-Randomization by Descending Frequency
3.12	Summary of Non-Serious Adverse Events Starting Post-Randomization by Descending Frequency
3.13	Summary of Adverse Events Starting On-Treatment (Study Drug Exposure Basis)
3.14	Summary of Adverse Events Starting On-Treatment by Time Period (Study Drug Exposure Basis)
3.15	Summary of Adverse Events Starting Post-Randomization by Maximum Intensity
3.16	Summary of Most Common Adverse Events Starting Post-Randomization
3.17	Summary of Most Common Non-Serious Adverse Events Starting Post-Randomization
3.18	Summary of Drug-Related Adverse Events Starting Post-Randomization
3.19	Summary of Drug-Related Adverse Events Starting On-Treatment
3.20	Summary of Drug-Related Adverse Events Starting Post-Treatment
3.21	Summary of Drug-Related Adverse Events Starting Post-Randomization by Time Period of Onset
3.22	Summary of Drug-Related Adverse Events Starting Post-Randomization by Age Group (<65, ≥65)
3.23	Summary of Drug-Related Adverse Events Starting Post-Randomization by Age Group (<75, ≥75)
3.24	Summary of Drug-Related Adverse Events Starting Post-Randomization by Country
3.25	Summary of Serious Adverse Events Starting Post-Randomization
3.26	Summary of Serious Adverse Events Starting On-Treatment
3.27	Summary of Serious Adverse Events Starting Post-Treatment
3.28	Summary of Serious Adverse Events Starting Post-Randomization by Time Period of Onset
3.29	Summary of Serious Adverse Events Starting Post-Randomization by Age Group (<65, ≥65)
3.30	Summary of Serious Adverse Events Starting Post-Randomization by Age Group (<75, ≥75)
3.31	Summary of Serious Adverse Events Starting Post-Randomization by Country
3.32	Summary of Drug-Related Serious Adverse Events Starting Post-Randomization
3.33	Summary of Fatal Adverse Events Starting Post-Randomization
3.34	Summary of Drug-Related Fatal Adverse Events Starting Post-Randomization
3.35	Summary of Adverse Events Starting Post-Randomization Leading to Withdrawal from the Study
3.36	Summary of Drug-Related Adverse Events Starting Post-Randomization Leading to Withdrawal from the Study
3.37	Summary of Serious Adverse Events Starting Post-Randomization Leading to Withdrawal from the Study
3.38	Summary of Adverse Events Starting Post-Randomization Leading to Permanent Discontinuation of the Study Drug

Safety	
3.39	Summary of Drug-Related Adverse Events Starting Post-Randomization Leading to Permanent Discontinuation of the Study Drug
3.40	Summary of Serious Adverse Events Starting Post-Randomization Leading to Permanent Discontinuation of the Study Drug
3.41	Summary of Sexual and Breast Adverse Events of Special Interest Starting Post-Randomization
3.42	Summary of Special Interest Adverse Events Starting Post-Randomization: Altered (Decreased) Libido
3.43	Summary of Special Interest Adverse Events Starting Post-Randomization: Impotence
3.44	Summary of Special Interest Adverse Events Starting Post-Randomization: Ejaculation Disorders
3.45	Summary of Special Interest Adverse Events Starting Post-Randomization: Breast Disorders
3.46	Summary of Special Interest Adverse Events Starting Post-Randomization: Breast Disorders: Breast Enlargement
3.47	Summary of Special Interest Adverse Events Starting Post-Randomization: Breast Disorders: Breast Tenderness
	Note: Below strikethroughs and data display number revisions are associated with RAP Amendment 01. This approach permanently documents data display number revisions for traceability and reference.
~~3.48~~	~~Summary of Special Interest Adverse Events Starting Post-randomization By Baseline Characteristics: Altered (Decreased) Libido~~
~~3.49~~	~~Summary of Special Interest Adverse Events Starting Post-randomization By Baseline Characteristics: Impotence~~
~~3.50~~	~~Summary of Special Interest Adverse Events Starting Post-randomization By Baseline Characteristics: Ejaculation Disorders~~
~~3.51~~	~~Summary of Special Interest Adverse Events Starting Post-randomization By Baseline Characteristics : Breast Disorders~~
~~3.52~~	~~Summary of Special Interest Adverse Events Starting Post-randomization By Baseline Characteristics: Breast Disorders: Breast Enlargement~~
~~3.53~~	~~Summary of Special Interest Adverse Events Starting Post-randomization By Baseline Characteristics: Breast Disorders: Breast Tenderness~~
~~3.54~~ 3.48	Summary of Special Interest Sexual and Breast Adverse Events Starting Post-Randomization
~~3.55~~ 3.49	Summary of Sexual and Breast Adverse Events of Special Interest Leading to Study Withdrawal
~~3.56~~ 3.50	Summary of Sexual and Breast Adverse Events of Special Interest Leading to Study Withdrawal: Altered (Decreased) Libido
~~3.57~~ 3.51	Summary of Sexual and Breast Adverse Events of Special Interest Leading to Study Withdrawal: Impotence
~~3.58~~ 3.52	Summary of Sexual and Breast Adverse Events of Special Interest Leading to Study Withdrawal: Ejaculation Disorders
~~3.59~~ 3.53	Summary of Sexual and Breast Adverse Events of Special Interest Leading to Study Withdrawal: Breast Disorders
~~3.60~~ 3.54	Summary of Special Interest Adverse Events Starting Post-Randomization: Prostate Cancer
~~3.61~~ 3.55	Summary of Cardiovascular Adverse Events of Special Interest Starting Post-Randomization
~~3.62~~ 3.56	Summary of Special Interest Cardiovascular Adverse Events Starting Post-Randomization: Acute Coronary Syndrome
~~3.63~~ 3.57	Summary of Special Interest Cardiovascular Adverse Events Starting Post-Randomization: Ischemic Cerebrovascular Events
~~3.64~~ 3.58	Summary of Special Interest Cardiovascular Adverse Events Starting Post-Randomization: Cardiac Failure
~~3.65~~ 3.59	Summary of Special Interest Cardiovascular Adverse Events Starting Post-Randomization: Ischemic Coronary Artery Disorders/Atherosclerosis
~~3.66~~ 3.60	Summary of Special Interest Cardiovascular Adverse Events Starting Post-Randomization : Cardiac Arrhythmia
~~3.67~~ 3.61	Summary of Special Interest Cardiovascular Adverse Events Starting Post-Randomization: Peripheral Vascular Disease

Safety	
~~3.68~~ 3.62	Summary of Special Interest Cardiovascular Adverse Events Starting Post-Randomization: Cardiovascular Events
~~3.69~~ 3.63	Summary of Infrequent Tier 1 Adverse Events of Special Interest Starting Post-Randomization
~~3.70~~ 3.64	Summary of Laboratory Data
~~3.71~~ 3.65	Summary of Change from Baseline Laboratory Data
~~3.72~~ 3.66	Summary of Baseline Abnormal Laboratory Values
~~3.73~~ 3.67	Summary of Shift in Laboratory Values: Normal at Baseline to Abnormal at Any Time Post-Baseline
~~3.74~~ 3.68	Summary of Shift in Laboratory Values: Normal at Baseline to High at Any Time Post-Baseline
~~3.75~~ 3.69	Summary of Shift in Laboratory Values: Normal at Baseline to Low at Any Time Post-Baseline
~~3.76~~ 3.70	Summary of Shift in Laboratory Values: Normal or Low at Baseline to High at Any Time Post-Baseline
~~3.77~~ 3.71	Summary of Shift in Laboratory Values: Normal or High at Baseline to Low at Any Time Post-Baseline
~~3.78~~ 3.72	Summary of Laboratory Data Transitions: Change From Baseline to Final Assessment
~~3.79~~ 3.73	Summary of Baseline Threshold Laboratory Values
~~3.80~~ 3.74	Summary of Threshold Laboratory Values at Any Time Post-Baseline
~~3.81~~ 3.75	Summary of Baseline Total PSA Values (ng/ml)
~~3.82~~ 3.76	Summary of Total PSA (ng/ml) at Post-Baseline Visits (LOCF)
~~3.83~~ 3.77	Summary of Total PSA (ng/ml) at Post-Baseline Visits (At Visit)
~~3.84~~ 3.78	Summary of Total PSA Change From Baseline (ng/ml) (LOCF)
~~3.85~~ 3.79	Summary of Total PSA Change From Baseline (ng/ml) (At Visit)
~~3.86~~ 3.80	Summary of Total PSA Percentage Change From Baseline (LOCF)
~~3.87~~ 3.81	Summary of Total PSA Percentage Change From Baseline (At Visit)
~~3.88~~ 3.82	Summary of Post-Void Residual Volume at Screening and Baseline
~~3.89~~ 3.83	Summary of Post-Void Residual Volume at Each Post-Baseline Visit (LOCF)
~~3.90~~ 3.84	Summary of Post-Void Residual Volume at Each Post-Baseline Visit (At Visit)
~~3.91~~ 3.85	Summary of Post-Void Residual Volume Change from Baseline (LOCF)
~~3.92~~ 3.86	Summary of Post-Void Residual Volume Change from Baseline (At Visit)
~~3.93~~ 3.87	Summary of Post-Void Residual Volume Percentage Change from Baseline (LOCF)
~~3.94~~ 3.88	Summary of Post-Void Residual Volume Percentage Change from Baseline (At Visit)
~~3.95~~ 3.89	Summary of Gynecomastia Evaluation
~~3.96~~ 3.90	Summary of Change from Baseline Gynecomastia Evaluation
~~3.97~~ 3.91	Summary of Digital Rectal Examination

Safety	
~~3.98~~ 3.92	Summary of Change from Baseline Digital Rectal Examination
~~3.99~~ 3.93	Summary of Vital Signs
~~3.100~~ 3.94	Summary of Change from Baseline Vital Signs
~~3.101~~ 3.95	Summary of Vital Signs Exceeding Threshold at Baseline
~~3.102~~ 3.96	Summary of Vital Signs Exceeding Threshold at Any Post-Baseline Visit
~~3.103~~ 3.97	Summary of C-SSRS Data
~~3.104~~ 3.98	Listing of C-SSRS Data for Subjects With Suicidal Ideation and/or Behavior

11.15.6. Safety Figures

3.1	Plot of Study Drug Exposure
3.2	Plot of Power to Detect a Difference in Adverse Event Rate for Combination versus Tamsulosin
3.3	Most Common Adverse Events Starting Post-Randomization, Sorted by Odds Ratio
3.4	Plot of Kaplan-Meier Estimates of Time to First Altered (Decreased) Libido Adverse Event
3.5	Plot of Kaplan-Meier Estimates of Time to First Impotence Adverse Event
3.6	Plot of Kaplan-Meier Estimates of Time to First Ejaculation Disorder Adverse Event
3.7	Plot of Kaplan-Meier Estimates of Time to First Breast Disorder Adverse Event
3.8	Plot of Kaplan-Meier Estimates of Time to First Breast Disorder: Breast Enlargement Adverse Event
3.9	Plot of Kaplan-Meier Estimates of Time to First Breast Disorder: Breast Tenderness Adverse Event
3.10	Plot of Kaplan-Meier Estimates of Time to First Prostate Cancer Adverse Event
3.11	Plot of Kaplan-Meier Estimates of Time to First Acute Coronary Syndrome Adverse Event
3.12	Plot of Kaplan-Meier Estimates of Time to First Ischemic Cerebrovascular Adverse Event
3.13	Plot of Kaplan-Meier Estimates of Time to First Cardiac Failure Adverse Event
3.14	Plot of Kaplan-Meier Estimates of Time to First Ischemic CAD/Atherosclerosis Adverse Event
3.15	Plot of Kaplan-Meier Estimates of Time to First Cardiac Arrhythmia Adverse Event
3.16	Plot of Kaplan-Meier Estimates of Time to First Peripheral Vascular Disease Adverse Event
3.17	Plot of Kaplan-Meier Estimates of Time to First Cardiovascular Adverse Event
3.18	Plot of Kaplan-Meier Estimates of Time to Death

11.15.7. Health Outcome Tables

Health Outcomes Tables (Population=ITT)	
No.	**Title**
BII Overview and Primary Analysis	
4.1	Summary of BII Imputations
4.2	Summary of BII at Screening and Baseline *includes Visit 1a, Visit 2, Baseline, Baseline for Subjects with BII at each Month n (3, 6, …24)*
4.3	Summary of BII at Each Post-Baseline Visit (LOCF)
4.4	Summary of BII at Each Post-Baseline Visit (At Visit)
4.5	Summary of BII Change from Baseline (LOCF)
4.6	Summary of BII Change from Baseline (At Visit)
4.7	Summary of MMRM Analysis for BII Change from Baseline
Individual BII Questions 1 - 4	
~~4.7~~ 4.8	Summary of BII at Screening and Baseline: Question 1 *includes Visit 1a, Visit 2, Baseline, Baseline for Subjects with BII at each Months 12 and 24*
~~4.8~~ 4.9	Summary of BII at Months 12 and 24: Question 1 (LOCF) *each of the below individual question summaries is in terms of Months 12 and 24 only*.
~~4.9~~ 4.10	Summary of BII at Months 12 and 24: Question 1 (At Visit)
~~4.10~~ 4.11	Summary of BII Change from Baseline at Months 12 and 24: Question 1 (LOCF)
~~4.11~~ 4.12	Summary of BII Change from Baseline at Months 12 and 24: Question 1 (At Visit)
~~4.12~~ 4.13	Summary of BII at Screening and Baseline: Question 2
~~4.13~~ 4.14	Summary of BII at Months 12 and 24: Question 2 (LOCF)
~~4.14~~ 4.15	Summary of BII at Months 12 and 24: Question 2 (At Visit)
~~4.15~~ 4.16	Summary of BII at Months 12 and 24: Change from Baseline: Question 2 (LOCF)
~~4.16~~ 4.17	Summary of BII Change from Baseline at Months 12 and 24: Question 2 (At Visit)
~~4.17~~ 4.18	Summary of BII at Screening and Baseline: Question 3
~~4.18~~ 4.19	Summary of BII at Months 12 and 24: Question 3 (LOCF)
~~4.19~~ 4.20	Summary of BII at Months 12 and 24: Question 3 (At Visit)

Health Outcomes Tables (Population=ITT)	
No.	**Title**
~~4.20~~ 4.21	Summary of BII Change from Baseline at Months 12 and 24: Question 3 (LOCF)
~~4.21~~ 4.22	Summary of BII Change from Baseline at Months 12 and 24: Question 3 (At Visit)
~~4.22~~ 4.23	Summary of BII at Screening and Baseline: Question 4
~~4.23~~ 4.24	Summary of BII at Months 12 and 24: Question 4 (LOCF)
~~4.24~~ 4.25	Summary of BII at Months 12 and 24: Question 4 (At Visit)
~~4.25~~ 4.26	Summary of BII Change from Baseline at Months 12 and 24: Question 4 (LOCF)
~~4.26~~ 4.27	Summary of BII Change from Baseline at Months 12 and 24: Question 4 (At Visit)
BII Percentage Change from Baseline	
~~4.27~~ 4.28	Summary of BII Percentage Change from Baseline (LOCF)
~~4.28~~ 4.29	Summary of BII Percentage Change from Baseline (At Visit)
BII Non-Imputed Score Analysis	
Performed only if RAP Section11.7 imputation conditions are met; thus, table numbers are not listed.	
BPH-Related Health Status	
~~4.29~~ 4.30	Summary of BPH-Related Health Status at Screening and Baseline *includes Visit 1a, Visit 2, Baseline, Baseline for Subjects with BII at each Month n (3, 6, …24)*
~~4.30~~ 4.31	Summary of BPH-Related Health Status at Each Post-Baseline Visit (LOCF)
~~4.31~~ 4.32	Summary of BPH-Related Health Status at Each Post-Baseline Visit (At Visit)
~~4.32~~ 4.33	Summary of BPH-Related Health Status Change from Baseline (LOCF)
~~4.33~~ 4.34	Summary of BPH-Related Health Status Change from Baseline (At Visit)
4.35	Summary of MMRM Analysis for BPH-Related Health Status Change from Baseline
~~4.34~~ 4.36	Summary of BPH-Related Health Status Percentage Change from Baseline (LOCF)
~~4.35~~ 4.37	Summary of BPH-Related Health Status Percentage Change from Baseline (At Visit)

Health Outcomes Tables (Population=ITT)	
No.	**Title**
PAS SFI Overview and Primary Analysis	
~~4.36~~ 4.38	Summary of PAS SFI Imputations
~~4.37~~ 4.39	Summary of PAS SFI at Screening and Baseline *includes Visit 1b, Visit 2, Baseline, Baseline for Subjects with PAS SFI at each Month n (12 and 24)*
~~4.38~~ 4.40	Summary of PAS SFI at Each Post-Baseline Visit (LOCF)
~~4.39~~ 4.41	Summary of PAS SFI at Each Post-Baseline Visit (At Visit)
~~4.40~~ 4.42	Summary of PAS SFI Change from Baseline (LOCF)
~~4.41~~ 4.43	Summary of PAS SFI Change from Baseline (At Visit)
Individual PAS SFI Questions 1 - 3	
~~4.42~~ 4.44	Summary of PAS SFI at Screening and Baseline: Question 1 *includes Visit 1a, Visit 2, Baseline, Baseline for Subjects with PAS SFI at each Months 12 and 24*
~~4.43~~ 4.45	Summary of PAS SFI: Question 1 (LOCF) *each of the below individual question summaries is in terms of Months 12 and 24 only*.
~~4.44~~ 4.46	Summary of PAS SFI: Question 1 (At Visit)
~~4.45~~ 4.47	Summary of PAS SFI Change from Baseline: Question 1 (LOCF)
~~4.46~~ 4.48	Summary of PAS SFI Change from Baseline: Question 1 (At Visit)
~~4.47~~ 4.49	Summary of PAS SFI at Screening and Baseline: Question 2
~~4.48~~ 4.50	Summary of PAS SFI: Question 2 (LOCF)
~~4.49~~ 4.51	Summary of PAS SFI: Question 2 (At Visit)
~~4.50~~ 4.52	Summary of PAS SFI Change from Baseline: Question 2 (LOCF)
~~4.51~~ 4.53	Summary of PAS SFI Change from Baseline: Question 2 (At Visit)
~~4.52~~ 4.54	Summary of PAS SFI at Screening and Baseline: Question 3
~~4.53~~ 4.55	Summary of PAS SFI: Question 3 (LOCF)
~~4.54~~ 4.56	Summary of PAS SFI: Question 3 (At Visit)
~~4.55~~ 4.57	Summary of PAS SFI Change from Baseline: Question 3 (LOCF)
~~4.56~~ 4.58	Summary of PAS SFI Change from Baseline: Question 3 (At Visit)

11.15.8. Health Outcomes Figures

Health Outcomes Figures (Population=ITT)	
No.	**Title**
4.1	Plot of BII Adjusted Mean Change from Baseline (LOCF)
4.2	Plot of BII Adjusted Mean Change from Baseline (At Visit)
4.3	Plot of BPH-Related Health Status Adjusted Mean Change from Baseline (LOCF)
4.4	Plot of BPH-Related Health Status Adjusted Mean Change from Baseline (At Visit)

11.15.9. ICH and Non-ICH Listings

The following categorizes data listings as ICH (International Conference on Harmonization) used to support critical analyses or non-ICH. The two classifications are assigned with consideration for general regulatory requirements across countries at point of RAP finalization. Changes to these classifications may occur at point of reporting as a result of specific country requirements or requests and will not result in a RAP revision.

ICH	Non-ICH	Title
Study Population		
-	5.1	Listing of Subject Withdrawals During Placebo Run-in Phase
1.1		Listing of Randomized and Actual Treatments
1.2		Listing of Subject Accountability
1.3		Listing of Reasons for Study Withdrawal
1.4		Listing of Subjects with Inclusion/Exclusion Criteria Deviations
1.5		Listing of Important Protocol Deviations
1.6		Listing of Deviations which Require Exclusion from the Per-Protocol Population
1.7		Listing of Demographic Characteristics
1.8		Listing of Race Details
	5.2	Listing of Substance Use at Screening
	5.3	Listing of Medical Conditions at Screening
	5.4	Listing of Sexual Function at Screening
	5.5	Listing of Family History of Premature Coronary Artery Disease
	5.6	Listing of Electrocardiogram Results
	5.7	Listing of BPH History
	5.8	Listing of Alpha-Blocker, 5-Alpha-Reductase Inhibitor, and Phytotherapy Usage History
	5.9	Listing of Family History of Breast Cancer and Prostate Cancer
1.9		Listing of Concomitant Medications
1.10		Listing of Relationship Between ATC Level 1, Ingredient, and Verbatim Text
1.11		Listing of Investigational Product Discontinuation
1.12		Listing of Exposure to Study Drug
	5.10	Listing of Study Drug Dispensing
1.13		Listing of Study Drug Compliance

ICH	Non-ICH	Title
Study Population		
1.14		Listing of Subjects for Whom the Treatment Blind was Broken During the Study

ICH	Non-ICH	Title
Efficacy Listings		
IPSS		
2.1		Listing of IPSS
	5.11	Listing of IPSS MMRM Analysis: SAS Output
	5.12	GLM Analysis and Diagnostics for IPSS Change from Baseline at Month 24 (LOCF): SAS Output
	5.13	GLM Analysis and Diagnostics for IPSS Change from Baseline at Month 24 (At Visit): SAS Output
	5.14	Assessment of Subgroup Effects for IPSS Change from Baseline at Month 24 (LOCF)
	5.15	Assessment of Subgroup Effects for IPSS Change from Baseline at Month 24 (At Visit)
	5.16	Summary of IPSS Change from Baseline, by Center, at Months 12 and 24 (LOCF): SAS Output *Note, this LOCF table and below At Visit table are in Non-ICH listing rather than a table due to high number of centers, many with low enrollment. Output can be moved at point of CSR if necessary.*
	5.17	Summary of IPSS Change from Baseline, by Center, at Months 12 and 24 (At Visit)
Prostate Volume		
2.2		Listing of Prostate Volume
	5.18	GLM Analysis and Diagnostics for Prostate Volume Percentage Change from Baseline at Month 24 (LOCF): SAS Output
	5.19	GLM Analysis and Diagnostics for Prostate Volume Percentage Change from Baseline at Month 24 (At Visit): SAS Output
	5.20	Assessment of Subgroup Effects for Prostate Volume Percentage Change from Baseline at Month 24 (LOCF)
	5.21	Assessment of Subgroup Effects for Prostate Volume Percentage Change from Baseline at Month 24 (At Visit)
	5.22	Summary of Prostate Volume Percentage Change from Baseline, by Center, at Months 12 and 24 (LOCF)
	5.23	Summary of Prostate Volume Percentage Change from Baseline, by Center, at Months 12 and 24 (At Visit)

ICH	Non-ICH	Title
Efficacy Listings		
Qmax		
2.3		Listing of Subjects with Voided Volume less than 125ml
2.4		Listing of Qmax and Voided Volume
	5.24	GLM Analysis and Diagnostics for Qmax Change from Baseline at Month 24 (LOCF): SAS Output
	5.25	GLM Analysis and Diagnostics for Qmax Change from Baseline at Month 24 (At Visit): SAS Output
	5.26	Assessment of Subgroup Effects for Qmax Change from Baseline at Month 24 (LOCF)
	5.27	Assessment of Subgroup Effects for Qmax Change from Baseline at Month 24 (At Visit)
	5.28	Summary of Qmax Change from Baseline, by Center, at Months 12 and 24 (LOCF)
	5.29	Summary of Qmax Change from Baseline, by Center, at Months 12 and 24 (At Visit)
2.5		Listing of Biannual Follow-Up Telephone Contacts
2.6		Listing of Subjects with AUR
2.7		Listing of Subjects with Prostatic Surgery
2.8		Listing of Subjects with Non-Surgical Intervention for BPH
	5.30	Listing of Time to First AUR or BPH-Related Surgery Event
	5.31	Listing of Analysis of Time to First AUR or BPH-Related Surgery: SAS Output
	5.32	Listing of Time to First AUR
	5.33	Listing of Analysis of Time to First AUR: SAS Output
	5.34	Listing of Time to First BPH-Related Surgery Event
	5.35	Listing of Analysis of Time to First BPH-Related Surgery: SAS Output
	5.36	Listing of Subjects With Urinary Tract Infection / Urosepsis
	5.37	Listing of Subjects With Urinary Incontinence
	5.38	Listing of Subjects With Renal Insufficiency

ICH	Non-ICH	Title
Safety		
3.1		Listing of Relationship between System Organ Class and Verbatim Text
3.2		Listing of All Adverse Events
3.3		Listing of All Adverse Events by Onset Period
3.4		Listing of Subject Numbers for Specific Adverse Events
3.5		Listing of Fatal Adverse Events
3.6		Listing of Non-Fatal Serious Adverse Events
3.7		Listing of Adverse Events Leading to Permanent Discontinuation of Study Drug
3.8		Listing of Adverse Events Leading to Withdrawal from the Study
3.9		Listing of Possible Suicidality-Related Adverse Events
3.10		Listing of Possible Suicidality-Related Adverse Event Comments
		Note: Below strikethroughs and data display number revisions are associated with RAP Amendment 01. This approach permanently documents data display number revisions for traceability and reference.
~~3.11~~		~~Listing of Possible Suicidality-Related Adverse Event Data (Section 4)~~
~~3.12~~		~~Listing of Possible Suicidality-Related Adverse Event Data (Sections 5-8)~~
~~3.13~~ 3.11		Listing of Relationship between Special Interest Adverse Events and Verbatim Text
~~3.14~~ 3.12		Listing of Adverse Events of Special Interest
	5.39	Listing of Sexual and Breast Adverse Events of Special Interest Leading to Study Withdrawal
	5.40	Listing of Targeted Follow-Up Questionnaire Data
~~3.15~~ 3.13		Listing of Pregnancies in Female Partners of Male Study Participants
	5.41	Listing of Clinical Chemistry Data
	5.42	Listing of Hematology Data
~~3.16~~ 3.14		Listing of Clinical Chemistry Data Exceeding Threshold
~~3.17~~ 3.15		Listing of Hematology Data Exceeding Threshold

ICH	Non-ICH	Title
Safety		
	5.43	Listing of Baseline Hepatitis B Surface Antigen and Hepatitis C Antibody Data
	5.44	Listing of Serum PSA (ng/ml)
~~3.18~~ 3.16		Listing of Serum PSA Data Exceeding Upper Limit of Normal
~~3.19~~ 3.17		Listing of Subjects with ALT ≥ 3 times ULN and Bilirubin ≥ 2 times ULN
	5.45	Listing of Post-Void Residual Volume
	5.46	Listing of Gynecomastia Data
	5.47	Listing of Digital Rectal Examination Data
	5.48	Listing of Vital Signs Data
~~3.20~~ 3.18		Listing of Vital Signs Exceeding Threshold
~~3.21~~ 3.19		Listing of For-Cause Biopsy Results
	5.49	Listing of C-SSRS Data
~~3.22~~ 3.20		Listing of C-SSRS Suicidal Behavior Details for Subjects With Suicidal Behavior
~~3.23~~ 3.21		Listing of Details of Most Severe Suicidal Ideation at Each C-SSRS Assessment for Subjects With Suicidal Ideation
	5.50	Listing of Cardiovascular Events Recorded in the eCRF Log
	5.51	Listing of Cardiovascular Event Findings Recorded in the eCRF Log
	5.52	Listing of Cardiovascular Event Diagnostic Tests Recorded in the eCRF Log
	5.53	Listing of Health Resource Utilization Recorded in the eCRF Log
	5.54	Listing of Physical Evidence Recorded in the eCRF Log
	5.55	Listing of Surgery and Medical Procedures Related to Cardiovascular Events
	5.56	Listing of Risk Factors Recorded in the eCRF Log
	5.57	Listing of Labs Related to Cardiovascular Events Recorded in the eCRF Log
	5.58	Listing of Vital Signs Related to Cardiovascular Events Recorded in the eCRF Log

ICH	Non-ICH	Title
Safety		
	5.59	Listing of ECGs Related to Cardiovascular Events Recorded in the eCRF Log
	5.60	Listing of Status Variables Related to Cardiovascular Events Recorded in the eCRF Log
	5.61	Listing of Subjects Recorded on Surgery File Related to Cardiovascular Events, But with No Surgery Performed
Health Outcomes		
	~~5.50~~ 5.62	Listing of BPH Impact Index (BII)
	~~5.51~~ 5.63	Listing of BPH-Related Health Status
	~~5.52~~ 5.64	Listing of Problem Assessment Scale of the Sexual Function Inventory (PAS SFI)

11.16. Appendix 16: Mock Shells for Data Displays

Mock table shells are stored in IMMS, within same directory/cabinet as RAP, as separate documents.

11.17. Appendix 17: Amendment 01 Revisions

Item	RAP Revision General Description	RAP Section
01	Indicate RAP "Amendment Number 01" with administrative details including revision number, copyright year, effective date, description, author, and approver.	-Cover page -Document header -Document footer -Section 1: Key Elements of the RAP -Section 2.1: Changes to the Protocol Defined Statistical Analysis Plan
02	Clarify: -"IPSS primary analysis" is in terms of the Month 24 timepoint only. -Analyses of IPSS timepoints earlier than Month 24, specifically Month 21 – Month 3, in this order, are classified as secondary endpoints.	-Section 1: Synopsis -Table 3: Overview of Planned Primary Efficacy Analyses -Section 7.1.2: Planned Primary Efficacy Statistical Analyses -Table 4: Overview of Planned Secondary Efficacy Analyses
03	For each Alpha-Blocker, 5-Alpha-Reductase Inhibitor, and Phytotherapy for BPH prior use, document the eCRF collection of affirmative 'Yes' responses only. Indicate assumptions for 'No' responses and related tabular summary presentations.	-Section 6.5: Medical Conditions and Concomitant Medications
04	In addition to study population summaries of Alpha-Blocker, 5-Alpha-Reductase Inhibitor, and Phytotherapy for BPH prior use, expand summaries to include prior use of: [a] Alpha-Blocker OR 5-Alpha-Reductase Inhibitor Use [b] Alpha-Blocker OR 5-Alpha-Reductase Inhibitor OR Phytotherapy for BPH Use.	-Table 2: Overview of Planned Study Population Analyses -Section 11.15.2: Study Population Tables

Item	RAP Revision General Description	RAP Section
05	Within "Examination of Covariates and Subgroups", expand the list of subgroups to include: [a] Alpha-Blocker OR 5-Alpha-Reductase Inhibitor Use [b] Alpha-Blocker OR 5-Alpha-Reductase Inhibitor OR Phytotherapy for BPH Use. This is applicable for IPSS, prostate volume, and Qmax summaries.	-Appendix 10: Examination of Covariates -Section 11.15.3: Efficacy Tables
06	As a supporting analysis include a mixed-model repeated measures (MMRM) analysis to be conducted and output in a manner similar to the primary efficacy endpoint for: Qmax, BPH Impact Index, and BPH-Related Health Status.	-Section 8.1.4: Maximum, Urine Flow (Qmax) -Section 8.3.1: BPH Impact Index -Section 8.3.2: BPH-Related Health Status -Appendix 15: List of Data Displays
07	Improve format and conciseness of AE special interest tables by moving original "by baseline" age and sexual function summaries of Tables 3.48 – 3.53 into Tables 3.42-3.47. Therefore, Tables 3.48 – 3.53 are deleted and subsequent safety tables are renumbered accordingly.	-Table 5: Overview of Planned Adverse Event Tabular Summaries -Section 8.2.4.3: Sexual and Breast Tier 1 Adverse Events of Special Interest -11.15: Appendix 15: List of Data Displays
08	Update terms and MedDRA codes for AEs of Special Interest (due to MedDRA and Global Safety Team since original RAP). Revise the following within Table D, Infrequent Tier 1 Adverse Events of Special Interest: MedDRA Preferred Terms and Codes using MedDRA version 19.1 <u>Allergic reactions</u>: -delete "First use syndrome", code 10068159 -delete "Small bowel angioedema", code 10051401 <u>Breast cancer</u>: -delete "Contralateral breast cancer", code 10054784 <u>Depressed mood:</u>	-Appendix 8: Adverse Event Time Period and Special Adverse Event Definitions

Item	RAP Revision General Description	RAP Section
	-delete “Dysthymic disorder”, code 10013982 -replace “Postpartum depression” with “Perinatal depression”, code 10078366 -delete “Self injurious behavior”, code 10063495. Note this was replaced with, already included, “Intentional self-injury”.	
09	Revise title of Figure 2.1 – Figure 2.6 from “Figure of” to “Plot of”	-Section 11.15.4: Efficacy Figures
10	Expand IDSL list of principles from “4.23” to “4.24” to account for IDSL Jul2016 addition.	-Section 11.5.2: Reporting Process & Standards
11	Expand list of “Exclusions from the Per-Protocol Population” to account for relevant prohibited medications and non-drug therapies of Protocol Section 6.2 which are not otherwise classified in Appendix 1.	-Section 4.1.3: Deviations which Require Exclusion from the Per-Protocol Population -Appendix 1: Exclusions from the Per-Protocol Population
12	Improve format and conciseness of Possible Suicidality-Related Adverse Event Listings. This reduces the number of associated listings from four to two. Therefore, Listings 3.11 and 3.12 are deleted and subsequent listings are renumbered accordingly.	-11.15: Appendix 15: List of Data Displays
13	Apply proper and consistent first letter capitalization to data display titles; as an example revise “On-treatment” to “On-Treatment”.	-11.15: Appendix 15: List of Data Displays
14	Include reference to cardiovascular event data collection of protocol section 7.4.2.2. Insert additional associated data listings; renumber subsequent listings accordingly.	-Section 8.2.4.5: Cardiovascular Tier 1 Adverse Events of Special Interest -11.15: Appendix 15: List of Data Displays
15	Remove reference to CDISC-based dataset creation and reporting. Document that GSK exemption for ARI114265 CDISC-based dataset creation and reporting was	-Section 11.5.2: Reporting Process & Standards

Item	RAP Revision General Description	RAP Section
	granted June 2016.	
16	Clarify study drug compliance definition and calculations by treatment group and across the treatment groups.	-Section 6.6: Investigational Product Discontinuation, Exposure, and Compliance -Appendix 6: Derived and Transformed Data

Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan for ARI114265: A randomized, double-blind, parallel group study to compare the efficacy and safety of combination treatment with dutasteride (0.5mg) and tamsulosin (0.2mg) with tamsulosin (0.2mg) monotherapy, administered once daily for 2 years, on the improvement of symptoms and health outcomes in men with moderate to severe benign prostatic hyperplasia
Compound Number	:	GI198745+GI138525
Effective Date	:	15-DEC-2015

Description :

The purpose of this RAP is to describe the planned summaries and statistical analyses to be included in the Clinical Study Report (CSR) for Protocol ARI114265.

Author's Name and Functional Area:

PPD Associate Director, Biostatistics, PAREXEL International Employee of PAREXEL on behalf of GSK	15-DEC-2015

Approved by:

PPD *(e-mail approval dated 15-Dec-2015)* Director Statistics & Programming, GSK	15-DEC-2015

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<tr><td>Purpose</td><td>The purpose of this Reporting and Analysis Plan (RAP) is to describe the planned summaries and statistical analyses to be included in the Clinical Study Report (CSR) for Protocol ARI114265.</td></tr>
<tr><td>Protocol</td><td>This RAP is based on the protocol amendment 04 (Republished) (Dated: 08/JUL/2014) of study ARI114265 [GSK Document No. : RM2010/00134/05].

The aim of the study is to investigate whether combination therapy with dutasteride and tamsulosin is more effective than tamsulosin monotherapy for the improvement of symptoms and health outcomes in a population at increased risk of BPH clinical progression including older men (≥50yrs), with moderate-severe symptoms of BPH, enlarged prostates (≥30cc) and PSA≥1.5ng/mL.</td></tr>
<tr><td>Primary Objective</td><td>The primary objective is to assess the efficacy of combination treatment with dutasteride 0.5mg and tamsulosin 0.2mg once daily in providing superior symptomatic improvement in subjects with BPH compared with once daily tamsulosin 0.2mg monotherapy after 2 years of treatment.</td></tr>
<tr><td>Primary Endpoint</td><td>The primary endpoint is change from baseline IPSS at Year 2.</td></tr>
<tr><td>Study Design</td><td>This is a multicenter, randomized, double-blind, parallel group study. Eligible subjects will receive placebo tamsulosin and placebo dutasteride for four weeks in a single-blind, placebo, run-in period. Each subject will then be randomized to one of the following two treatment groups (1:1 ratio) for the double-blind phase (104 weeks) of the study:
--Dutasteride 0.5mg once daily + tamsulosin 0.2mg once daily or
--Dutasteride placebo once daily + tamsulosin 0.2mg once daily

Subjects will self-administer the study medication once daily for up to 104 weeks (2 years). Subjects will return to the clinic at 13 week intervals post-randomization during the 2 year treatment period (i.e. at 13, 26, 39, 52, 65, 78, 91, and 104 weeks).</td></tr>
<tr><td>Planned Analyses</td><td>Within this RAP, the following additional references may be made for brevity:
<table>
<tr><th>--Full Treatment Description--</th><th>--Short Treatment Descriptions--</th></tr>
<tr><td>Dutasteride 0.5mg once daily + tamsulosin 0.2mg once daily or</td><td>-Combination
-Dut 0.5mg + Tam 0.2mg
-Dut + Tam</td></tr>
<tr><td>Dutasteride placebo once daily + tamsulosin 0.2mg once daily</td><td>-Tamsulosin Monotherapy
-Tam 0.2mg
-Placebo + Tam 0.2mg
-Tam</td></tr>
</table>

The study population, efficacy, safety, and health outcomes summaries and analyses will be based on the Intent-to-Treat (ITT) population; few exceptions will be noted within the RAP. Summaries and analyses are defined within this RAP. The following are high level summary and analyses types.</td></tr>
</table>

Overview	Key Elements of the RAP
	• Study population summaries will be presented overall and by treatment group and will include accountability, disposition, demographic characteristics, baseline characteristics, protocol deviations, and concomitant medications. • The primary efficacy analyses and treatment group comparisons will be in terms of IPSS change from baseline. • Secondary efficacy analyses and treatment group comparisons will be in terms of prostate volume, Qmax, IPSS improvement levels (≥2 points, ≥3 points, ≥25%), Qmax improvement levels (≥3 ml/sec, ≥30%), and time to AUR or BPH-related surgery. • Safety summaries will be presented by treatment group and will be in terms of study drug exposure, adverse events, clinical laboratory evaluations, serum PSA, post void residual volume, qualitative breast examination, digital rectal examination, vital signs, and suicidality assessment using C-SSRS. • Health Outcomes analyses and treatment group comparisons will be in terms of BPH-Related Health Status (IPSS Question 8), BPH Impact Index, and Problem Assessment Scale of the Sexual Function Inventory (PAS SFI).
Analysis Populations	• The ITT Population is comprised of all randomized subjects regardless of whether or not treatment was administered. • The Per-Protocol (PP) Population is comprised of all ITT subjects who comply closely with the protocol. Specifically this includes ITT subjects who do not have a deviation which requires exclusion from the PP population. The PP population will not be analyzed if this population comprises more than 80% of the ITT population.
Hypothesis	The primary endpoint is change from baseline IPSS at Year 2. Let the following represent the mean change from baseline IPSS for each treatment group: $H_{dut+tam}$: Combination (dutasteride 0.5mg and tamsulosin 0.2mg) treatment group H_{tam}: Tamsulosin (tamsulosin 0.2mg treatment group) Then the primary null and alternative hypotheses to be tested at Year 2 are as follows: Null Hypothesis: $H_{dut+tam} = H_{tam}$ Alternative Hypothesis: $H_{dut+tam} \neq H_{tam}$ Two-sided tests of the null hypothesis will be conducted at the 0.05 level of significance to show superiority of the combination treatment group compared to tamsulosin 0.2mg at 2 years of treatment.
Primary Analyses	The primary efficacy parameter after two years of study treatment is change from baseline IPSS. Change in IPSS from baseline will be compared at each scheduled post-baseline visit for combination treatment versus tamsulosin 0.2mg using a general linear model with effects for treatment, cluster, and baseline IPSS.
Secondary Analyses	Secondary efficacy analyses will be in terms of prostate volume, Qmax, IPSS improvement levels, Qmax improvement levels, and time to AUR or BPH-related surgery using appropriate statistical methodology defined within this RAP.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There were no changes or deviations to the originally planned statistical analysis specified in the ARI114265 protocol amendment 04 (Republished) (Dated 08/JUL/2014).

2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To assess the efficacy of combination treatment with dutasteride 0.5mg and tamsulosin 0.2mg once daily in providing superior symptomatic improvement in subjects with BPH compared with once daily tamsulosin 0.2mg monotherapy after 2 years of treatment	• Change in IPSS from baseline at Year 2.
Secondary Objectives	**Secondary Endpoints**
• To assess efficacy and safety of combination treatment with dutasteride 0.5mg and tamsulosin 0.2mg including the clinical outcomes of AUR or BPH-related prostatic surgery compared with tamsulosin 0.2mg monotherapy after 2 years of treatment.	**Efficacy** • Percent change in prostate volume from baseline • Proportion of subjects with IPSS improvement of ≥2 points and ≥3 points from baseline and, separately, ≥25% improvement from baseline • Change in Qmax from baseline • Proportion of subjects with Qmax improvement of ≥3mL/sec and, separately, ≥30% improvement from baseline • Time to event/ proportion of subjects with AUR or BPH related prostatic surgery • Time to event/proportion of subjects with AUR • Time to event/proportion of subjects undergoing BPH related prostatic surgery **Health Outcome Measures** • Change in BPH-Related Health Status (Q8 of IPSS) from Baseline • Change in BPH Impact Index (BII) from Baseline • Change in Problem Assessment Scale of the Sexual Function Inventory (PAS-SFI), from Baseline • Resource Use related to AUR and BPH-related surgical events.

Objectives	Endpoints
	Safety • Adverse Events • Change in total serum PSA from baseline • Vital signs • Post-void residual volume • Clinical laboratory measurements (including haematology, chemistry) • Physical examination: digital rectal examination (DRE) and qualitative breast examination • Suicidality (C-SSRS)
Exploratory Objectives	**Exploratory Endpoints**
• Pharmacogenetics (PGx) Research Note: PGx planned summaries and analyses will be documented outside this RAP.	• Relationships between genetic variants in DNA from patient blood and any unexplained or unexpected response to treatment (as monitored by safety, tolerability, and efficacy parameters) that may have an underlying genetic mechanism.
• Population Pharmacokinetics (PPK) Research Note: PPK planned summaries and analyses will be documented outside this RAP	• Characterization of PPK of dutasteride when given in combination with tamsulosin to Chinese men with BPH.

2.3. Study Design

Overview of Study Design and Key Features	
Design Features	• Multicenter within 4 countries: China, Japan, Korea, and Taiwan. • Randomized, double-blind, parallel group study to assess the efficacy of combination treatment with dutasteride 0.5mg and tamsulosin 0.2mg once daily in providing superior symptomatic improvement in subjects with BPH compared with once daily tamsulosin 0.2mg monotherapy after 2 years of treatment.
Dosing / Treatment Assignment	• Placebo tamsulosin and placebo dutasteride for four weeks in a single-blind, placebo, run-in period. • Thereafter randomized to one of the following two treatment groups (1:1 ratio) for the double-blind phase (104 weeks) of the study: --Dutasteride 0.5mg once daily + tamsulosin 0.2mg once daily or --Dutasteride placebo once daily + tamsulosin 0.2mg once daily.
Interim Analysis	No interim analyses are planned for this study.

2.4. Statistical Hypotheses

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

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

H_{tam}: Tamsulosin 0.2mg treatment group

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

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

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

3. PLANNED ANALYSES

3.1. Interim Analyses

No interim analyses are planned for this study.

3.2. Final Analysis

The planned primary analyses will be performed after completion of the following sequential steps:

1. All subjects have completed the 104-week study treatment period study as defined in the protocol.
2. All required database cleaning activities have been completed and primary database release and primary database freeze have been declared by Data Management. Reference 'primary database' description below.
3. All criteria for unblinding the randomization codes have been met.
4. Randomization codes have been distributed according to RandAll NG procedures.

The primary database freeze, using standard Data Management practices, will occur after the last subject completes the 104-week randomized treatment phase. Statistical analysis and reporting in support of international regulatory submissions will be in terms of this primary database freeze and will be referred to as the 'Final Analysis' or primary 'Statistical Analysis Complete' (SAC). Reference Section 9, Country-Specific Summaries and Analyses, for a description of a secondary country-based statistical analysis complete package.

3.3. Targeted Follow-Up Questionnaire (TFUQ) Report

As documented in protocol and elsewhere in this RAP, this study includes a Targeted Follow-Up Questionnaire (TFUQ) for subjects with sexual function related adverse events leading to study withdrawal. Using the TFUQ, subjects will be followed for up to 6 months after the last dose of study drug. It is anticipated that the final TFUQ data component will be included in the above referenced primary database freeze.

However, if there are ongoing TFUQs at the time of primary database freeze, and anticipated follow-up and receipt of these data would create a delay in analyzing and reporting the study results then the primary freeze may occur with exclusion of outstanding TFUQ data. Thereafter, a secondary database freeze will occur in terms of newly finalized and recorded TFUQ data (since primary freeze). The decision to perform a secondary freeze will be made soon after last subject last visit milestone by Project Team with input from Data Management, International Regulatory Affairs, Clinical Statistics, Clinical Development, and Clinical Operations. This secondary freeze will be in terms of datasets containing the actual TFUQ and as well as any TFUQ-related datasets. Only TFUQ-related tabular summaries and listings (related to newly frozen datasets) will be updated with the secondary freeze. TFUQ-related summaries and listings for this secondary freeze will be referred to as 'TFUQ Report'.

4. ANALYSIS POPULATIONS

Analysis populations are defined in the following table.

Population	Definition / Criteria	Analyses Evaluated
Intent-To-Treat (ITT)	• Comprised of all randomized subjects regardless of whether or not treatment was administered • This population will be based on the treatment to which the subject was randomized. • Any subject who receives a treatment randomization number will be considered to have been randomized.	• All.
Per-Protocol (PP)	• Comprised of all ITT subjects who comply closely with the protocol. Specifically this includes ITT subjects who do not have a deviation which requires exclusion from the PP population. • Protocol deviations that would exclude subjects from the PP population are defined in Section 4.1.3 (Deviations which Require Exclusion from the Per-Protocol Population) and Appendix 1 (Exclusions from the Per-Protocol Population). • The PP population will not be analyzed if this population comprises more than 80% of the ITT population.	• Primary efficacy endpoint only if this population comprises 80% or less of the ITT Population. Details on specific summaries and analyses are outlined in Section 7, Primary Statistical Analyses.

NOTES :

- 'All Enrolled Subjects' is referenced in at least one tabular summary. Enrolled subjects include those who entered placebo run-in phase and/or who were randomized.

4.1. Protocol Deviations

4.1.1. Inclusion / Exclusion Criteria Deviations

All inclusion / exclusion criteria deviations which are recorded on the inclusion / exclusion screens of the eCRF will be summarized and listed. The tabular summary will be in terms of number and percent of Intent-to-Treat population subjects violating any criterion and violating each criterion. Summaries will be output by each of the two randomized treatment groups and overall.

4.1.2. Important Protocol Deviations

All protocol deviations identified during the course of the study will be tracked and reviewed by the study team in accordance with SOP-130050 and the ARI114265 Protocol Deviations Management Plan (PDMP). As outlined in the PDMP and Data Management procedures, the ARI114265 Study Team will identify protocol deviations which are considered to be 'Important' and flag on the team's protocol deviations spreadsheet. This spreadsheet will be subsequently loaded to the Data Management file system and formatted for HARP Analysis & Reporting.

Important Deviations will be summarized and listed. The tabular summary will be in terms of number and percent of subjects with any Important Deviation and with each Important Deviation. Summaries will be output by the eCRF category and subcategories for each of the two randomized treatment groups and overall. The eCRF categories and subcategories are standardized for this study; examples are provided in the tabular summary shells.

4.1.3. Deviations which Require Exclusion from the Per-Protocol Population

In accordance with SOP-130050 and the ARI114265 PDMP, deviations which require exclusion from the Per-Protocol population should be identified; the 18 deviations are listed in the below table. The historical term used to describe these deviations in ARI114265 protocol is 'major'. In this RAP and for future reporting the phrase 'deviations which require exclusion from the Per-Protocol population' will replace 'major'.

Number	Deviations which Require Exclusion from the Per-Protocol Population
01	Missed placebo run-in phase
02	Incorrect study drug (wrong treatment) consumed
03	Randomized but did not consume double-blind study drug
04	Cumulative study drug compliance <75%
05	Cumulative study drug compliance >125%
	Violation of Inclusion Criteria (protocol #)
06	Confirmed BPH clinical diagnosis (Inclusion 2)
07	IPSS ≥12 at Screening (Inclusion 3)
08	Prostate volume ≥30cc by TRUS at Screening (Inclusion 4)
09	PSA ≥1.5ng/ml and ≤10ng/mL at Screening (Inclusion 5)
10	Qmax >5 mL/sec and ≤15mL/sec with Voided Volume ≥125mL/sec at Screening (Inclusion 6)
	Violation of Exclusion Criteria (protocol #)
11	Any conditions other than BPH, which may in the judgement of the investigator, result in urinary symptoms or changes in flow rate (Exclusion 6)
12	Use of 5ARI within 6 months of Screening or historical TRUS and throughout the study (Exclusion 10a)
13	Use of anabolic steroids within 6 months of Screening and throughout the study (Exclusion 10b)

Number	Deviations which Require Exclusion from the Per-Protocol Population
14	Use of phytotherapy for BPH within 2 weeks of Screening and throughout the study (Exclusion 10c)
15	Use of alpha-adrenoreceptor blockers within 2 weeks of Screening and throughout the study, except study meds (Exclusion 10d)
16	Use of alpha-adrenoreceptor agonists or anticholinegics or cholinergics within 48 hours prior to all uroflowmetry and IPSS assessments (Exclusion 10e)
17	Use of selective beta 3-adrenoreceptor agonist (mirabegron) within 2 weeks prior to all uroflowmetry and IPSS assessments (Exclusion 10f)
	Other
18	Any condition which should exclude a subject from the Per-Protocol population which is not included above; identified by Study Team.

Please refer to Appendix 1: Exclusions from the Per-Protocol Population for details on sources and processing these deviations.

Deviations which require exclusion from the Per-Protocol population will be summarized and listed. The Per-Protocol deviations tabular summary will be in terms of number and percent of subjects with any deviation and for each deviation. Summaries will be output by each of the two randomized treatment groups and overall.

4.1.4. Deviations which Require Exclusion from the Per-Protocol Population but not Tracked or Identified as Important by Study Team

For brevity, in this section 'deviations which require exclusion from the per-protocol population', defined in Section 4.1.3, will be referred to as 'Per-Protocol Deviations'. In accordance with SOP-130050 and as clarified in GUI-315049, Per-Protocol Deviations are a subset of Important Protocol Deviations. As described in Appendix 1, some Per-Protocol Deviations may be identified programmatically and/or some may be identified post database freeze and unblinding. Therefore, it is not feasible to manually enter all Per-Protocol Deviations to the Study Team spreadsheet (referenced in Section 4.1.2) and thus not all Per-Protocol Deviations will be tracked or identified as Important by Study Team.

Per-Protocol Deviations which were not tracked or identified as Important by Study Team will be reported in 1) Listing of Important Deviations and flagged as such, and 2) Summary of Important Protocol Deviations.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

Table 1 provides a list of appendices primarily related to considerations for data analyses and data handling conventions. A full set of appendices is provided in Section 11.

Table 1 Overview of Appendices

Section	Component
11.1	Appendix 1: Exclusions from the Per-Protocol Population
11.3	Appendix 3: Assessment Windows
11.4	Appendix 4: Multicenter Studies
11.5	Appendix 5: Data Display Standards & Handling Conventions
11.6	Appendix 6: Derived and Transformed Data
11.7	Appendix 7: Premature Withdrawals & Handling of Missing Data
11.8	Appendix 8: Adverse Event Time Periods and Special Adverse Event Definitions
11.9	Appendix 9: Threshold Factors for Clinical Laboratory Tests and Vital Signs

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

The study population analyses will be based on the ITT population, unless otherwise specified in text or data display shells.

Table 2 provides an overview of the planned study population summaries and listings. A list of planned data displays is in Appendix 15: List of Data Displays.

Reference Section 4 (Analysis Populations) and Appendix 6 (Derived and Transformed Data) for supporting definitions on all below subsections.

Formal statistical treatment comparisons will not be performed in terms of the study population data.

Table 2 Overview of Planned Study Population Analyses

Display Type	Data Displays Generated		
	Table		Listing
Subject Accountability			
Numbers of Subjects, including: Enrolled, Placebo Run-In, Randomized (ITT Population), Per-Protocol Population	Y		Y
Subject Disposition			
Withdrawals During Placebo Run-In	Y		Y
Randomized by Country and Center	Y		Y
Withdrawals During Double-Blind including totals, reasons, and by time of discontinuation	Y		Y
Inclusion / Exclusion Criteria Deviations	Y		Y
Important Protocol Deviations	Y		Y
Deviations which Require Exclusion from the Per-Protocol Population	Y		Y
Demographic and Baseline Characteristics			
Demographic Characteristics	Y		Y
Ethnicity, Race, and Racial Combination Details	Y		Y
Selected Safety Measures at Baseline, Overall and by Country	Y		[1]
Selected Efficacy and Health Outcome Measures at Baseline, Overall and by Country	Y		[1]
Medical Conditions and Concomitant Medications			
Medical Conditions by Body System	Y		Y
Specific Medical Conditions	Y		Y
BPH History	Y		Y
Alpha-Blocker, 5-Alpha-Reductase Inhibitor, Phytotherapy Use	Y		Y
Sexual Function	Y		Y
Family History: Premature Coronary Artery Disease, Breast Cancer, Prostate Cancer	Y		Y
Concomitant Medications	Y		Y

Display Type	Data Displays Generated		
	Table		Listing
Investigational Product Discontinuation, Exposure, Treatment Compliance			
Investigational Product Discontinuation	Y		Y
Study Drug Exposure	Y		Y
Study Drug Compliance	Y		Y
Treatment Blind Broken			Y

NOTES :
- Y = Yes display generated.
- There are no planned Study Population figures.

[1] Reference specific measurement listing in safety, efficacy, and health outcomes.

6.2. Subject Accountability

Summaries for the following will be produced in terms of total number overall:

- enrolled subjects
- subjects who entered placebo run-in phase
- subjects who entered placebo run-in but withdrew prior to randomization.

Enrolled subjects includes those who entered placebo run-in phase and/or who were randomized.

Summaries for the following will be produced by treatment and in terms of total number overall:

- number of subjects who were randomized to double-blind but missed placebo run-in
- number of subjects who were randomized to double-blind but do not have a double-blind treatment start date
- number of subjects who have a double-blind treatment start date but were not randomized
- number of subjects who were randomized to double-blind and did not take at least one dose of study medication
- number of randomized subjects (ITT population) and defined as subjects with a nonmissing treatment number
- number of subjects in the Per-Protocol population.

Summaries of the ITT population will be produced by country and center and output by randomized treatment and overall.

A listing of randomized subjects (ITT population) will be produced and will include the scheduled randomized treatment and the actual randomized treatment. A flag will be included on the listing to indicate if the scheduled treatment differs from the actual randomized treatment; as well, any such cases will be included as per-protocol deviations.

6.3. Subject Disposition

A subject may withdraw from the study at any time at the investigator's discretion or at the request of the subject.

The reason for study withdrawal is recorded in the eCRF for subjects who entered placebo run-in but withdrew prior to randomization. A tabular summary will be produced for number and percentage of subjects who entered placebo run-in and withdrew prior to randomization, overall and by reason. For this summary, the percentages are calculated using total subjects who entered placebo run-in as the denominator.

The reason for study withdrawal is recorded in the eCRF for randomized subjects who prematurely withdrew from the study in advance of the Month 24 visit. A tabular summary will be produced for number and percentage of subjects prematurely withdrawing from the study, overall and by reason, and will be output by treatment group and total. For this summary, the percentages are calculated using the ITT population as the denominator.

A listing will be produced for the ITT population with key accountability data including placebo run-in start and stop dates, randomization date, treatment start and stop dates, subject withdrawal (yes or no), completion or withdrawal date, and all visit dates.

ITT population subject discontinuation will be summarized by visit intervals as overall totals and by discontinuation reason; these summaries will be output by treatment group and total. Visit interval determination used for these summaries is defined in Appendix 3 (Assessment Windows).

6.4. Demographic and Baseline Characteristics

The following demographic and baseline characteristics will be summarized overall and by treatment group for the ITT population; summaries will be repeated by country:

- sex
- age in years
- age categories: <65, ≥ 65, <75, ≥ 75 years
- ethnicity: Hispanic, Not Hispanic
- race / ethnicity: Asian, Hispanic / Latino, White, Not-Hispanic
- height
- weight
- body mass index
- history of tobacco use including number of cigarettes smoked per day
- alcohol use including number of units per week
- baseline safety including ECG, PSA, systolic blood pressure, diastolic blood pressure, heart rate, and C-SSRS
- baseline efficacy including IPSS, prostate volume, and Qmax
- baseline health outcome measures including BII and QOL Q8
- baseline C-SSRS

Race and racial combinations, will be summarized overall and by treatment group for the ITT population. Reference Appendix 6 for race and ethnicity details and combinations.

6.5. Medical Conditions and Concomitant Medications

The following medical conditions and medication history are GSK standardized data collections and/or are of interest in terms of the protocol population, study treatments, and indication. These characteristics will be summarized overall and by treatment group for the ITT population.

- medical conditions by body system (includes GSK standardized collection)
- specific medical conditions (more specific or in addition to the above body systems)
- BPH history including time since first LUTS and time since BPH diagnosis
- alpha-blocker use
- 5-alpha-reductase inhibitor use
- alpha-blocker and 5-alpha-reductase inhibitor use
- phytotherapy for BPH use
- sexual function including activity status at screening along with impotence and lack of libido status of prior 3 months
- family history of premature coronary artery disease
- family history of breast cancer
- family history of prostate cancer

Concomitant medication data are collected on eCRF log forms and will be coded using the GSK-Drug Anatomical Therapeutic Chemical (ATC) dictionary. Concomitant medications will be defined as any medication documented as such in the database, irrespective of start or stop dates or ongoing status.

A summary of concomitant medications will be provided for the ITT population. The number and percentage of subjects reporting the use of each concomitant medication will be summarized by treatment group and in total, ATC Level 1 and ingredient. A listing of the collected concomitant mediations, by treatment and subject, will be provided. A listing of the relationship between the ATC Level 1, ingredient and verbatim text for concomitant medications will be provided.

6.6. Investigational Product Discontinuation, Exposure, and Compliance

Reasons for investigational product discontinuation are recorded in the eCRF and may differ from a subject's study discontinuation reason. A tabular summary will be produced for number and percentage of subjects who prematurely discontinued investigational product. Summaries will be produced overall and by reason, and will be output by treatment group and total. For this summary, the percentages are calculated using the ITT population as the denominator.

A listing of subjects for whom the treatment blind was broken during the study, along with the reason, will be produced.

Study drug exposure (in days) is number of days between (double-blind) treatment start date and (double-blind) treatment stop date, both days inclusive Study drug exposure is further explained in Appendix 6. Study drug exposure in days will be summarized by treatment group and overall. The number and proportion of subjects exposed to study drug will also be summarized by 180-day intervals for each treatment group and overall.

Overall study drug compliance is defined as 100* (number of capsules consumed during the study) / (study drug exposure) / 2. Division by 2 is required since subjects were scheduled to consume 2 tablets per day. Overall study drug compliance as well as compliance by study drug component are further explained in Appendix 6. Overall study drug compliance will be summarized by treatment group and across the treatment groups. The number and proportion of subjects with overall compliance <75%, 75-125%, and >125%, will be summarized for each treatment group and across the treatment groups. Study drug compliance by component will be summarized by each treatment.

7. PRIMARY STATISTICAL ANALYSES

7.1. Primary Efficacy Analyses

7.1.1. Overview of Planned Primary Efficacy Analyses

The primary efficacy parameter after the 2nd year of the study is change from baseline IPSS (International Prostate Symptom Score). The IPSS questionnaire consists of seven questions with each question score ranging from 0 to 5. It is administered at screening, baseline, and at each of the scheduled post-baseline treatment phase visits.

IPSS (also called IPSS total score) is the sum of the seven questions. IPSS summaries and analyses will be in terms of the total (score); exceptions will be noted such as for supporting summaries of individual questions. For calculation of the IPSS total, missing individual responses will be imputed when at least four of the seven questions are answered (nonmissing). For the imputation, the average of the nonmissing responses will be calculated and rounded to the nearest integer. This average will be imputed for the original missing response(s). If at least 20% of the subjects have at least one imputed IPSS then the statistical analyses will be repeated based on non-imputed scores.

The efficacy analyses will be based on the Intent-to-Treat (ITT) population. Table 3 provides an overview of the planned IPSS summaries and primary efficacy analyses. A list of planned data displays is in Appendix 15: List of Data Displays.

Table 3 Overview of Planned Primary Efficacy Analyses

Endpoint	Absolute			Change from Baseline			% Change from Baseline		
	L	F	T	L	F	T	L	F	T
IPSS (International Prostate Symptom Score) Change from Baseline									
Primary Analysis	Y[1]		Y	Y[1]	Y	Y[2]			
Supporting and Sensitivity Analyses of Primary Endpoint									
Mixed-Model Repeated-Measures (MMRM) Analysis (At Visit)						Y			
IPSS Change from Baseline by Subgroup[3]						Y			
Individual IPSS Questions	Y[1]		Y			Y			
IPSS Percentage Change from Baseline							Y[1]		Y
IPSS Non-imputed Score Analysis[4]			Y		Y	Y			
IPSS Per-Protocol Population Analysis[5]			Y		Y	Y			

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated. All outputs are based on ITT population except [4].
- Tables and figures have separate outputs for LOCF and At Visit, except for baseline summaries.

1. Individual questions 1 – 7 responses, total score, total score change from baseline, and percentage change from baseline are combined in a single listing and presented for every visit.
2. Primary efficacy analyses are presented within this table; details are in the following section.
3. Subgroups are defined in Section 7.1.3 and Appendix 10: Examination of Covariates and Subgroups.
4. Analysis is performed only if RAP Section 7.1 imputation conditions are met.
5. Analysis is performed only if RAP Section 4 per-protocol conditions are met.

7.1.2. Planned Primary Efficacy Statistical Analyses

Endpoint: The primary efficacy parameter is the change from baseline IPSS at Year 2 (Month 24) using the last observation carried forward approach (LOCF) based on the Intent-to-Treat (ITT) population.

Table 3 provides an overview of the planned IPSS summaries and primary efficacy analyses. A list of planned data displays is in Appendix 15: List of Data Displays. Baseline and change from baseline are defined in Appendix 6. Last observation carried forward (LOCF) and At Visit approaches are defined in Appendix 7.

Model Specification and Results Presentation: Change from baseline IPSS at each scheduled post-baseline assessment will be compared in terms of combination treatment versus tamsulosin treatment using t-tests from a general linear model (GLM) with effects for treatment, cluster, and baseline IPSS. Two-sided tests at 0.05 level of significance will be conducted.

The adjusted mean estimates (mean and standard error), the adjusted mean difference, and the 95% confidence interval in terms of the adjusted mean difference will be presented. The adjusted mean difference will be in terms of combination treatment minus tamsulosin treatment. The model results will be presented on same tabular summary as

the arithmetic mean, standard deviation, median, minimum and maximum. The results will be presented by treatment for each scheduled post-baseline assessment.

IPSS adjusted mean change from baseline will be plotted by treatment for each post-baseline scheduled visit in terms of each LOCF and At Visit approach.

Multiple Comparisons and Multiplicity: Reference Appendix 11, Multiple Comparisons and Multiplicity.

Model Checking and Diagnostics: Reference Appendix 12, Model Checking and Diagnostics for Statistical Analyses.

7.1.3. Supporting and Sensitivity Analyses of Primary Endpoint

The following describes supporting and sensitivity analyses of the primary endpoint.

Mixed-Model Repeated-Measures (MMRM) Analysis: As a supportive analysis, IPSS will be analyzed using a mixed-model repeated-measures (MMRM) analysis including ITT population data from the scheduled post-baseline assessments. Details are provided in Appendix 13, Mixed-Model Repeated-Measures Analysis.

IPSS Change from Baseline by Subgroup: For each subgroup, IPSS change from baseline summaries will be output by treatment group at Month 12 and at Month 24 for the ITT population using both LOCF and At Visit approaches. No statistical testing will be performed. Subgroups are defined in Appendix 10, Examination of Covariates and Subgroups.

Individual IPSS Questions 1 – 7: Each of the 7 IPSS individual question responses will be summarized at Baseline, Month 12, and Month 24 by treatment group. Month 12 and Month 24 change from baseline will be summarized by treatment group for each of the 7 questions. The summaries will be based on the ITT population and presented using both LOCF and At Visit approaches. No statistical testing will be performed.

IPSS Percentage Change from Baseline: Percentage change from baseline is defined in Appendix 6. IPSS percentage change from baseline will be summarized by treatment group at each scheduled post-baseline assessment. The summaries will be based on the ITT population and presented using both LOCF and At Visit approaches. No statistical testing will be performed.

IPSS Non-Imputed Score Analysis: IPSS missing response imputation procedure is described above. If at least 20% of the ITT subjects have at least one imputed IPSS then the tables, figures, and analyses described in Section 7.1.2 (Planned Primary Efficacy Statistical Analyses) will be repeated using non-imputed scores.

IPSS Per-Protocol Population Analysis: Per-Protocol (PP) population is defined in Section 4. If the PP population comprises 80% or less of the ITT population, then the tables, figures, and analyses described in Section 7.1.2 (Planned Primary Efficacy Statistical Analyses) will be repeated using the PP population.

8. SECONDARY STATISTICAL ANALYSES

8.1. Secondary Efficacy Analyses

8.1.1. Overview of Planned Secondary Efficacy Analyses

Table 4 Overview of Planned Secondary Efficacy Analyses

Endpoint	Absolute			Change from Baseline			% Change from Baseline		
	L	F	T	L	F	T	L	F	T
IPSS									
Improvement Levels						Y[1]			Y[2]
Prostate Volume									
Absolute, Change, % Change [3]	Y		Y	Y		Y	Y	Y	Y
By Subgroup									Y
Improvement Levels									Y[4]
Maximum Urine Flow (Qmax)									
Absolute, Change, % Change [5]	Y		Y	Y	Y	Y	Y		Y
By Subgroup						Y			
Improvement Levels						Y[6]			Y[7]
AUR or BPH-Related Surgical Intervention[8]									
Time to event	Y	Y	Y						
Event incidence			Y						
Other Efficacy Measures [9]									
Urinary tract infection / urosepsis	Y		Y						
Urinary incontinence	Y		Y						
Renal insufficiency	Y		Y						

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Tables and figures have separate outputs for LOCF and At Visit, except for baseline summaries and AUR or BPH-related surgical intervention.

1. IPSS change from baseline five improvement categories are ≥1 point through ≥5 points. 'No change' and 'worsening' are also presented. Treatment comparisons are in terms of ≥2 points and separately ≥3 points.
2. IPSS percentage change from baseline seven improvement categories are >0%, ≥10%, ≥20%, ≥25%, ≥30%, ≥40%, and ≥50%. Treatment comparisons are in terms of ≥25%.
3. Prostate volume printed and summarized for absolute, change from baseline, percentage change from baseline; dimensions will be printed. Prostate volume analyses are based on percentage change from baseline.
4. Prostate volume percentage change from baseline seven improvement categories are >0%, ≥10%, ≥20%, ≥25%, ≥30%, ≥40%, and ≥50%. Treatment comparisons are in terms of ≥25%.
5. Qmax printed and summarized for absolute, change from baseline, percentage change from baseline; total voided volume will be printed. Qmax analyses are based on change from baseline.
6. Qmax change from baseline six improvement categories are >0 ml/sec and ≥1 ml/sec through ≥ 5 ml/sec. 'No change' and 'worsening' are also presented. Treatment comparisons are in terms of ≥3 ml/sec.
7. Qmax percentage change from baseline six improvement categories are >0%, ≥10%, ≥20%, ≥30%, ≥40%, and ≥50%. Treatment comparisons are in terms of ≥30%.
8. Summaries are repeated individually for AUR and BPH-Related Surgical Intervention.
9. Data of other efficacy measures are summarized. No treatment comparisons are performed.

8.1.2. IPSS Improvement Levels

Symptom improvement is assessed using IPSS continuous data changes as the primary efficacy endpoint and using categorical changes as a secondary efficacy endpoint. Improvement is a post-baseline score which is lower than the baseline score. Worsening is a post-baseline score which is higher than the baseline score. The number and percentage of subjects with IPSS percentage change from baseline categories of 1) improvement, 2) no change, and 3) worsening will be summarized by treatment group using both the LOCF and At Visit approaches at each scheduled post-baseline assessment.

IPSS change from baseline will be presented using five improvement levels: ≥1 point through ≥5 points. IPSS percentage change from baseline will be presented using seven improvement levels: >0%, ≥10%, ≥20%, ≥25%, ≥30%, ≥40%, and ≥50%. Treatment comparisons for combination versus tamsulosin will be performed for each ≥ 2 points, ≥3 points, and ≥25% using a Mantel-Haenszel test controlling for cluster at alpha=0.05.

8.1.3. Prostate Volume

Prostate dimensions are measured at the second screening visit (1b) and at each Month 12 and Month 24 (or end of treatment) visits. For analysis and reporting,

- Prostate Volume =
  pi/6 (Anteroposterior Width x Cephalocaudal Width x Transverse Width).

Prostate volume percentage change from baseline is a secondary efficacy endpoint.

Table 4 provides an overview of the planned prostate volume summaries and analyses. A list of planned data displays is in Appendix 15: List of Data Displays. Baseline, change from baseline, and percentage change from baseline are defined in Appendix 6. Last observation carried forward (LOCF) and At Visit approaches are defined in Appendix 7. Summaries and analyses will be in terms of the ITT population; LOCF approach will be considered primary. Prostate volume summary statistics will be presented for baseline, Month 12 visit, and the Month 24 visit; change from baseline and percentage change from baseline summary statistics will be presented for the Month 12 and Month 24 visits.

Combination treatment and tamsulosin treatment will be compared in terms of prostate volume percentage change from baseline at the Month 12 and Month 24 visits using t-tests from the following general linear model; two-sided tests at 0.05 level of significance will be conducted:

- log (post baseline prostate volume / baseline prostate volume) =
  log (baseline prostate volume) + treatment + cluster

The adjusted mean estimates (mean and standard error), the adjusted mean difference, and the 95% confidence interval in terms of percentage change from baseline will be reported. The adjusted mean differences will be in terms of combination treatment minus tamsulosin treatment. The model results will be presented on same tabular summary as the arithmetic mean, standard deviation, median, minimum and maximum. The results will be presented by treatment for each scheduled post-baseline assessment.

Prostate volume adjusted mean percentage change from baseline will be plotted by treatment for each post-baseline scheduled visit in terms of each LOCF and At Visit approach.

The number and percentage of subjects with prostate volume percentage change from baseline categories of 1) improvement, 2) no change, and 3) worsening will be summarized by treatment group using both the LOCF and At Visit approaches at each scheduled post-baseline assessment. Improvement is a post-baseline prostate volume which is lower than the baseline prostate volume. Worsening is a post-baseline prostate volume which is higher than the baseline prostate volume.

Prostate volume percentage change from baseline will be presented using seven improvement levels: >0%, ≥10%, ≥20%, ≥25%, ≥30%, ≥40%, and ≥50%. Treatment comparisons for combination versus tamsulosin will be performed for ≥25% prostate volume improvement using a Mantel-Haenszel test controlling for cluster at alpha=0.05.

Supportive subgroup summaries of prostate volume percentage change from baseline will be presented in manner similar to that described for primary efficacy in Appendix 10, Examination of Covariates. Reference Appendix 15 for a list of planned prostate volume subgroup tables.

Model checking associated with prostate volume percentage change from baseline will be conducted in manner similar to that described for primary efficacy in Appendix 12. Reference Appendix 15 for a list of prostate volume model checking outputs.

Reference Appendix 11 for multiplicity considerations.

8.1.4. Maximum Urine Flow (Qmax)

Qmax and associated total voided volume are measured at screening (Visit 1a with possible repeat at Visit 1b), baseline, and at each Month 6, Month 12, Month 18, and Month 24 (or end of treatment) visits. Qmax change from baseline is a secondary efficacy endpoint. Qmax measurements with voided volumes <125 ml will not be included in the analysis.

Table 4 provides an overview of the planned Qmax summaries and analyses. A list of planned data displays is in Appendix 15: List of Data Displays. Baseline, change from baseline, and percentage change from baseline are defined in Appendix 6. Last observation carried forward (LOCF) and At Visit approaches are defined in Appendix 7. Summaries and analyses will be in terms of the ITT population; LOCF approach will be considered primary. Qmax summary statistics will be presented for each scheduled visit; change from baseline and percentage change from baseline will be presented for each scheduled post-baseline visit.

Change from baseline Qmax at each scheduled post-baseline assessment will be compared in terms of combination treatment versus tamsulosin treatment using t-tests from a general linear model (GLM) with effects for treatment, cluster, and baseline Qmax. Two-sided tests at 0.05 level of significance will be conducted.

The adjusted mean estimates (mean and standard error), the adjusted mean difference, and the 95% confidence interval in terms of the adjusted mean difference will be presented. The adjusted mean difference will be in terms of combination treatment minus tamsulosin treatment. The model results will be presented on same tabular summary as the arithmetic mean, standard deviation, median, minimum and maximum. The results will be presented by treatment for each scheduled post-baseline assessment.

Qmax adjusted mean change from baseline will be plotted by treatment for each post-baseline scheduled visit in terms of each LOCF and At Visit approach.

Qmax improvement is also assessed using categorical changes. Improvement is a post-baseline Qmax which is higher than the baseline Qmax. Worsening is a post-baseline Qmax which is lower than the baseline Qmax. The number and percentage of subjects with Qmax percentage change from baseline categories of 1) improvement, 2) no change, and 3) worsening will be summarized by treatment group using both the LOCF and At Visit approaches at each scheduled post-baseline assessment.

Qmax change from baseline will be presented using six improvement levels: >0 ml/sec and ≥1 ml/sec through ≥5ml/sec. Qmax percentage change from baseline will be presented using six improvement levels: >0%, ≥10%, ≥20%, ≥30%, ≥40%, and ≥50%. Treatment comparisons for combination versus tamsulosin will be performed for each ≥3ml/sec and ≥30% using a Mantel-Haenszel test controlling for cluster at alpha=0.05.

Supportive subgroup summaries of Qmax change from baseline will be presented in manner similar to that described for primary efficacy in Appendix 10, Examination of Covariates. Reference Appendix 15 for a list of planned Qmax subgroup tables.

Model checking associated with Qmax change from baseline will be conducted in manner similar to that described for primary efficacy in Appendix 12. Reference Appendix 15 for a list of Qmax model checking outputs.

Reference Appendix 11 for multiplicity considerations.

8.1.5. AUR or BPH-Related Surgical Intervention

All AUR and BPH-related surgery events during participation in the study are recorded. Subjects who discontinue from the study are followed for AUR and BPH-related surgery until the 24 month anniversary of randomization. This follow-up is in terms of biannual telephone contacts beginning at the first six month scheduled interval after discontinuation. Analyses will be in terms of events recorded at clinic visits and also collected in the biannual telephone contacts. Table 4 provides an overview of the planned summaries and analyses. A list of planned data displays is in Appendix 15: List of Data Displays.

Time to first AUR or BPH-related surgery will be defined as the number of days from treatment start date to date of the first event (earliest occurring of either AUR or BPH-related surgery) for each subject. Time to first AUR or BPH-related surgery is classified

as a secondary efficacy endpoint and will be analyzed in terms of the Intent-to-Treat population.

Censoring will occur at the earliest of the following dates as applicable: the date of prostatectomy, the date of last contact for AUR and surgical intervention, and the date of death. For censoring, 'prostatectomy' will be determined from the eCRF prostatic surgical intervention log using the following codes associated with 'prostatectomy': open, retropubic with or without nerve-sparing, suprapubic, transvesical, perineal, salvage, laparoscopic, laparoscopic assisted. Note this excludes 'partial prostatectomy'.

The 'date of last contact for AUR and surgical intervention assessment' will be assigned as the latest of:
--Date of last treatment-phase visit
and
--Date of last successful biannual follow-up telephone contact.

Partial dates will be handled as described in Appendix 7, Premature Withdrawals & Handling of Missing Data.

The number of subjects having the first AUR or BPH-related surgery event on or after treatment start will be tabulated by treatment, by the two annual time periods (Month 12 and Month 24), as well as by three month intervals (quarterly) along with the number of subjects at risk during each of these time periods.

Note: Cut-off dates are defined in Appendix 6; definition is repeated here:
Month k Cut-off Date (for k= 3, 6, 9, 12, 15, 18, 21, 24): The maximum of [Month k clinic visit date, Month k lab visit date, Baseline Date + (k * 91/3)].

The primary analysis of this endpoint will compare combination treatment versus tamsulosin treatment in terms of time to first AUR or BPH-related surgery for the ITT population using a log rank test stratified by cluster at the 0.05 level of significance. The relative risk (hazard ratio) for the treatment effect and associated two-sided 95% confidence intervals will be estimated using a Cox proportional hazards model with treatment as the only covariate and stratified by cluster. Estimates and corresponding confidence intervals for the relative risk (hazard ratio) and risk reduction (1-hazard ratio) of combination treatment versus tamsulosin treatment will be presented along with the log rank p-value. Assessment of the Cox modeling procedure will include examination of diagnostic plots to assess the assumption of proportional hazards and the review of results obtained by fitting separate models by cluster to assess the homogeneity of treatment effect across clusters.

Time to first AUR or BPH-related surgery, expressed as months, will be summarized by treatment group for the ITT population using product-limit estimates computed by the Kaplan-Meier method and displayed graphically as Kaplan-Meier curves.

The number of subjects with at least one AUR or BPH-related surgery will be summarized by treatment group across the 2 year period. The crude rate of AUR or BPH-related surgery incidence will be calculated using the Intent-to-Treat population of each

treatment as the denominator; the associated 95% confidence interval will be output. This crude rate will be compared for combination treatment versus tamsulosin treatment using the Mantel-Haenszel test stratified by cluster at the 0.05 level of significance.

AUR or BPH-related surgery event details per subject will be summarized by treatment and will include: event component (first occurring of either AUR or BPH-related surgery) and time period of first occurring event (during treatment or after treatment stop). BPH-relatedness (yes/no) and AUR precipitating factors will be summarized by treatment for subjects in which AUR is the primary efficacy event's initial component. Types of surgery/intervention will be summarized by treatment for subjects in which BPH-related surgery is the primary efficacy event's initial component.

Time from last dose to first AUR or BPH-related surgery event will be summarized for those subjects experiencing the first event after treatment stop.

Hospitalization details for the initial AUR will be summarized by treatment group for patient admission status (inpatient or outpatient). For inpatients, the ward type and hospitalization days will be summarized by treatment.

The frequency and percentage of subjects with multiple AUR or BPH-related surgery events will be summarized by treatment. The frequencies of subjects with 2 events, 3 events, or ≥4 events will be summarized. Among subjects with both events, the pattern of occurrence (AUR/Surgery or Surgery/AUR) will be summarized.

The above described summaries and analyses of AUR or BPH-related surgery will be repeated, when applicable, for the individual components 1) AUR and 2) BPH-related surgery.

All AUR and surgical intervention data will be listed by treatment and subject. Time to first AUR or BPH-related event will be listed for each subject along with the dates used in the computation of these values.

8.1.6. Other Efficacy Measures

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

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

Each of the three 'other efficacy measures' will be summarized by treatment group for number of subjects with at least one post-randomization event across the 2-year period. The crude rate of each measure will be calculated using the Intent-to-Treat population of each treatment as the denominator; the associated 95% confidence interval will be output. No formal treatment comparisons will be performed.

Data collected in terms of these other efficacy measures will be listed by treatment and subject.

8.2. Safety Analyses

Safety summaries and analyses are reported in terms of the following data classifications: adverse events, clinical laboratory assessments (haematology and clinical chemistry), total serum prostate specific antigen (PSA), qualitative breast examination, digital rectal examination, vital signs, suicidality, and post void residual volume.

All safety analyses will be performed using the ITT population unless otherwise specified in text or data display shells. Applicable safety analysis and reporting definitions and presentations within "Program Safety Analysis Plan (PSAP) for GI198745 (dutasteride) and GSK2285985 (fixed dose combination of dutasteride [GI198745] and tamsulosin [GI138525]" are utilized within this RAP, with any deviations noted.

8.2.1. Overview of Adverse Event Tabular Summaries

Table 5 provides an overview of the planned adverse event tabular summaries. A list of planned data displays is in Appendix 15: List of Data Displays.

Reference Section 4 (Analysis Populations) and Appendix 6 (Derived and Transformed Data) for supporting definitions on all below subsections.

Table 5 Overview of Planned Adverse Event Tabular Summaries

Adverse Event Types, High Level							
	Any	Drug-Related	Non-Serious	Serious	Leading to W/D from Study	Perm. D/C of Study Drug	Fatal
By Type	---------- 3.1 (6 above categories, excluding Non-serious) ----------						
Overall	3.2 3.3 [1] 3.4 [2] 3.13 [3]	3.18 3.19 [1] 3.20 [2]	3.5	3.25 3.26 [1] 3.27 [2]	3.35	3.38	3.33
By 6-Month Onset Period	3.6 3.14 [3]	3.21		3.28			
By Age (<65, ≥65)	3.7	3.22		3.29			
By Age (<75, ≥75)	3.8	3.23		3.30			
By Country	3.9	3.24		3.31			
By Descending Frequency	3.10		3.12	3.11			
By Maximum Intensity	3.15						
Most Common	3.16		3.17				

Adverse Event Types, Two Levels						
	Drug-Related and Serious	Drug-Related and Fatal	Drug-Related and Leading to W/D from Study	Serious and Leading to W/D from Study	Drug-Related and Leading to Perm D/C of Study Drug	Serious and Leading to Perm D/C of Study Drug
Overall	3.32	3.34	3.36	3.37	3.39	3.40

Sexual and Breast Adverse Events of Special Interest					
		Altered (Decreased) Libido	Impotence	Ejaculation Disorders	Breast Disorders (includes Enlargement and Tenderness)
MedDRA		----------3.41----------			
Overall		3.42	3.43	3.44	3.45, 3.46 [4], 3.47 [5]
By Baseline Characteristics		3.48	3.49	3.50	3.51, 3.52 [4], 3.53 [5]
By Type		----------3.54----------			
Not Resolved & Leading to Study Withdrawal	Overall	----------3.55----------			
	By Type	3.56	3.57	3.58	3.59

Prostate Cancer Adverse Event of Special Interest	
Prostate Cancer Overall	3.60

Cardiovascular Adverse Events of Special Interest							
	Acute Coronary Syndrome	Ischemic Cerebro-vascular Events	Cardiac Failure	Ischemic Coronary [6]	Cardiac Arrythmia	Peripheral Vascular Disease	Cardio-vascular Events
MedDRA	----------3.61----------						
Overall	3.62	3.63	3.64	3.65	3.66	3.67	3.68

Infrequent Tier 1 Adverse Events of Special Interest	
MedDRA	3.41

Notes: Summaries are in terms of 'Starting Post-Randomization' (defined in Appendix 8) unless otherwise noted as [1] – [3]:

1. Starting On-Treatment; defined in Appendix 8.
2. Starting Post-Treatment; defined in Appendix 8.
3. Starting On-Treatment and in terms of 'Study Drug Exposure Basis" in which [Rate] is the number of subjects per 100 person-years of study drug exposure; adverse events for subjects with missing study drug exposure are excluded.
4. Breast Disorders: subcategory Breast Enlargement
5. Breast Disorders: subcategory Breast Tenderness
6. Ischemic Coronary Artery Disorders / Atherosclerosis

8.2.2. Adverse Events

Adverse events (AEs) will be coded using the MedDRA (Medical Dictionary for Regulatory Activities) coding dictionary. As specified in the protocol, disease related events will not be reported as AEs or serious adverse events (SAEs) unless the investigator assesses the event as more severe than expected for the subject's condition. A mapping of the MedDRA primary system organ class and preferred term to which each verbatim term has been coded will be provided in a listing.

Adverse events (AEs) are to be recorded on the electronic case report form (eCRF) from the start of the placebo run-in phase study treatment until the end of the two year study period. Serious AEs (SAEs) are to be recorded over the same time period as non-serious AEs. However, any SAEs assessed **as related** to study participation or related to a GSK concomitant medication, will be recorded from the time a subject consents to participate in the study up to the end of the two year study period. After discontinuation of study treatment, the investigator will monitor all AEs/SAEs that are ongoing until resolution or stabilization of the event or until the subject is lost to follow-up. Investigators are not required to actively seek information on adverse events occurring after the follow-up contact, but may report any adverse event that they believe may be related to investigational product regardless of when the event occurs. Adverse events summaries will include non-serious as well as serious AEs.

Subjects with sexual function related adverse events leading to study withdrawal, will be followed up for up to 6 months after the last dose of study drug using the sexual function Targeted Follow-Up Questionnaire (TFUQ).

If an AE occurs which, in the investigator's judgment, is possibly related to suicidality, a Possible Suicidality-Related Adverse Event (PSRAE) form should be completed by investigators or their designated staff.

Each AE will be categorized into the following periods according to its onset date: pretreatment, post-randomization, on-treatment, post-treatment. These periods are not mutually exclusive and an AE could be categorized into more than one period. The definitions of these categories are provided in Appendix 8: Adverse Event Time Periods and Special Adverse Event Definitions.

Pre-treatment AEs will not be summarized; they will be included in the AE listing specified later in this section.

The number of post-randomization adverse events, the number and the percentage of subjects reporting any post-randomization AE will be summarized by treatment group for the following:

- All AEs
- Drug-related AEs
- Serious AEs
- AEs leading to study drug discontinuation
- AEs leading to withdrawal from study
- Fatal AEs

Comparisons of treatment groups for each of these sets of AEs will be performed using Fisher's Exact Test.

Total number of adverse events reported in the study as well as the number and percentage of subjects reporting at least one AE will be provided for each treatment group. Total number of AEs as well as the number and percentage of subjects reporting each AE will be reported by treatment group, primary system organ class and preferred term. On-treatment and post-treatment AEs will be summarized separately, as well as together as post-randomization AEs. Non-serious post-randomization AEs will be summarized by treatment group. A summary of post-randomization AEs will be provided by treatment group and six month time period of onset (Months 1-6, Months 7-12, Months 13-18, Months 19-24), by treatment group and age group (<65 years, ≥65 years), by treatment group and age group (<75 years, ≥75 years), and by treatment group and country.

A summary of post-randomization AEs will be provided by treatment group and preferred term by descending frequency of preferred term (regardless of system organ class). In addition, such summaries will be done for serious post-randomization AEs and also for non-serious post-randomization AEs.

For on-treatment AEs, the event rate per 100 person-years of study drug exposure will be summarized by treatment group, primary system organ class and preferred term overall and by time period (Months 1-6, Months 7-12, Months 13-18, Months 19-24).

A summary of post-randomization AEs will also be provided by treatment group and maximum intensity. If the same AE occurs on multiple occasions in the same subject, the AE with the highest intensity will be presented. Intensity will be categorized as mild, moderate, or severe; a category for missing/not applicable intensity will be included.

The most common AEs (Tier 2 events) are defined as those preferred terms occurring in at least 5% of the subjects within any treatment group (non-rounded). The total number of events as well as the number and percentage of subjects reporting at least one most common AE preferred term starting post-randomization will be provided for each treatment group. The number of events, the number and percentage of subjects reporting the most common AE preferred terms starting post-randomization will be provided by treatment group displayed by decreasing frequency of preferred terms (regardless of primary system organ class). For each of these most common AEs, the percentage of

subjects in the treatment groups will be compared using Fisher's exact test. In addition, the percentage of subjects reporting each AE by treatment group along with the corresponding odds ratio and 95% confidence interval for each of the most common AEs will be displayed in a figure sorted by odds ratio in descending order, by treatment group. The above summary will also be provided for the most common non-serious post-randomization AEs.

Total number of drug-related adverse events as well as the number and percentage of subjects reporting at least one drug-related AE will be provided for each treatment group. Total number of drug-related adverse events as well as the number and percentage of subjects reporting each drug-related AE will be reported by treatment group, primary system organ class and preferred term. On-treatment and post-treatment drug-related AEs will be summarized separately, as well as together as post-randomization drug-related AEs. A summary of post-randomization drug-related AEs will be provided by treatment group and time period (Months 1-6, Months 7-12, Months 13-18, Months 19-24), by treatment group and age group (<65 years, ≥65 years), by treatment group and age group (<75 years, ≥75 years) and by treatment group and country.

A listing of all AEs, a listing of AEs by onset period, and a listing of which subjects reported specific AEs will be presented. A listing of Possible Suicidality Related Adverse Event (PSRAE) data will be provided. A listing of the sexual function Targeted Follow-Up Questionnaire (TFUQ) data will be provided.

8.2.3. Deaths and Serious Adverse Events

Total number of serious adverse events as well as the number and percentage of subjects reporting at least one serious AE will be provided for each treatment group. Total number of serious adverse events as well as the number and percentage of subjects reporting each serious AE will be reported by treatment group, primary system organ class and preferred term. On-treatment and post-treatment serious AEs will be summarized separately, as well as together as post-randomization serious AEs. A summary of post-randomization serious AEs will be provided by treatment group and time period (Months 1-6, Months 7-12, Months 13-18, Months 19-24), by treatment group and age group (<65 years, ≥65 years), by treatment group and age group (<75 years, ≥75 years), and by treatment group and country. A summary of all post-randomization drug-related serious AEs, of all post-randomization fatal AEs, and of all post-randomization drug-related fatal AEs will be provided by treatment group. Time to death will be summarized by treatment group using Kaplan-Meier estimates and displayed as Kaplan-Meier plots.

Individual subject listings of all non-fatal serious AEs and a separate listing of all fatal serious AEs will be provided. The listing will indicate the timing of the serious AE with respect to treatment start date.

8.2.4. Adverse Events Leading to Discontinuation of Investigational Product and/or Withdrawal From the Study and Other Significant Adverse Events

8.2.4.1. Adverse Events Leading to Discontinuation of Investigational Product and/or Withdrawal from the Study

A summary of adverse events starting post-randomization and leading to withdrawal from the study will be provided by treatment group for the following categories:

- All AEs
- Drug-related AEs
- Serious AEs

Similar summaries will be provided for adverse events leading to permanent discontinuation of the study medication.

Subject listings of AEs leading to withdrawal from the study and AEs leading to permanent discontinuation of study drug will be provided. The listings will indicate the timing of the AE with respect to treatment start date.

8.2.4.2. Adverse Events of Special Interest

Tier 1 adverse events of special interest are pre-specified adverse event preferred terms for which there are predefined hypotheses about the existence of a potential treatment effect. These events include the following:

- Sexual and breast events
- Prostate cancer
- Cardiovascular events
- Infrequent events

Summaries for these events are specified in the following sections and will be based on post-randomization AEs unless otherwise indicated. A mapping of the MedDRA primary system organ class and preferred term to which each verbatim term in the special interest AE categories has been coded will be provided in a listing.

8.2.4.3. Sexual and Breast Tier 1 Adverse Events of Special Interest

Altered (decreased) libido, impotence, ejaculation disorders, and breast disorders, will be defined as sexual and breast adverse events of special interest. In addition, two subgroups of breast disorders (breast disorders: breast enlargement, and breast disorders: breast tenderness) are of special interest. MedDRA system organ class and preferred terms included in these special interest adverse events are defined in Appendix 8, Table A.

Total number of, as well as number and percentage of the subjects experiencing, sexual and breast adverse events of special interest will be provided by treatment group. In addition, for each of the events of special interest, the number and percentage of subjects by treatment will be provided for the following:

- having an event

- having multiple events
- having an event in 6-month windows, starting from treatment start date

The following categories are related to the occurrence of the first event of the special interest AE; number and percentage of subjects in these categories will be provided by treatment group:

- drug-related AE
- serious AE
- AE leading to withdrawal from the study
- AE leading to permanent discontinuation of study drug
- AE outcome
- AE resolution status (on-therapy vs. off-therapy – see Appendix 8 for definition)
- AE maximum intensity

The number and percentage of the subjects experiencing an adverse event of special interest will be provided by treatment group for the following:

- Overall
- By age group: < 65 years, ≥65 years
- By sexual activity at baseline (Yes, No) based on "sexually active" question.

The number and percentage of subjects experiencing the following types of sexual and breast adverse events of special interest will be provided by treatment group:

- Any Type (Impotence, Decreased Libido, Ejaculation Disorders, or Breast
- Disorders)
- One AE Type
- Two AE Types
- Three AE Types
- All Four AE Types

The time to first onset in days will be summarized by treatment group as a continuous variable as well as by time period of onset. In addition, time to first adverse event of special interest will be summarized by treatment group using estimates calculated by the Kaplan-Meier method and displayed graphically as Kaplan-Meier curves. Time to resolution for the first event in days will be summarized by treatment group.

Duration of adverse events of special interest will be summarized by treatment group for uncensored values, censored values, and all values. It is recognized that summary statistics such as means and medians involving censored values will be biased (low).

The number of sexual and breast adverse events leading to study withdrawal, as well as the number and percentage of subjects reporting at least one such sexual and breast adverse event will be provided for all event types and also by event type for each treatment group.

Resolution status at end of study (resolved, not resolved) and time from treatment stop date to AE resolution will be summarized by treatment group for the sexual and breast

adverse events leading to study withdrawal and not resolved at Month 24 / End of Treatment visit.

Listings of sexual and breast adverse events of special interest will be provided. A listing of sexual and breast adverse event status data will be provided.

A listing of the TFUQ data for sexual and breast adverse events will be provided.

8.2.4.4. Prostate Cancer Tier 1 Adverse Events of Special Interest

Prostate cancer will be defined as an adverse event of special interest. MedDRA preferred terms and codes included in this special interest adverse event are defined in Appendix 8, Table B. Prostate cancer events will be summarized separately following the same format done for sexual and breast special interest AEs described above. Time to first event for prostate cancer events will be summarized separately by treatment group using estimates calculated by the Kaplan-Meier method and displayed graphically as Kaplan-Meier curves.

Listings of prostate cancer adverse events of special interest will be provided.

8.2.4.5. Cardiovascular Tier 1 Adverse Events of Special Interest

Cardiovascular adverse events of special interest will be defined as those included in the following six categories: acute coronary syndrome, ischemic coronary artery disorders/atherosclerosis, ischemic cerebrovascular events, cardiac failure, cardiac arrhythmias, and peripheral vascular disease. MedDRA preferred terms and codes included in these special interest adverse events are defined in Appendix 8, Table C. Total number of cardiovascular events as well as the number and percentage of subjects experiencing cardiovascular events will be provided by treatment group. Each category of cardiovascular events, and all cardiovascular events as one additional category, will be summarized separately following the same format done for sexual and breast special interest AEs described above. Time to first cardiovascular adverse event of special interest will be summarized by treatment group using estimates calculated by the Kaplan-Meier method and displayed graphically as Kaplan-Meier curves.

Listings of cardiovascular adverse events of special interest will be provided.

8.2.4.6. Infrequent Tier 1 Adverse Events of Special Interest

Infrequent Tier 1 adverse events of special interest will be defined as those included in the following categories:

- Breast cancer
- Potential for decreased male fertility due to effects on sperm/semen characteristics
- Interference with formation of external genitalia in a male fetus if a woman carrying a male fetus is exposed to dutasteride

- Hair changes
- Allergic reactions
- Depressed mood
- Testicular pain and swelling
- Intraoperative floppy iris syndrome
- Orthostasis
- Priapism
- Stevens-Johnson syndrome
- Atrial fibrillation, tachycardia, arrhythmias

MedDRA preferred terms and codes included in these special interest adverse events are defined in Appendix 8, Table D. Total number of infrequent Tier 1 events as well as the number and percentage of subjects with infrequent Tier 1 events will be provided by treatment group.

Listings of infrequent Tier 1 adverse events of special interest will be provided.

8.2.5. Pregnancies

A listing of subjects whose female partner become pregnant during the study will be provided if there are any such subjects.

8.2.6. Clinical Laboratory Assessments

Clinical chemistry and hematology parameters are evaluated from samples scheduled at the first screening visit (1a) and at each Month 12 and Month 24 (or end of treatment) visits. The following tests will be performed:

Clinical Chemistry (serum): Alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, total protein, sodium, potassium, albumin, glucose, creatinine, UREA/BUN (blood urea nitrogen)

Hematology: Hemoglobin, platelet count, white blood cell count (WBC), red blood cell count (RBC)

For purposes of statistical analyses the baseline value of a parameter for each subject will be defined as the latest laboratory test value on or before the start of the randomized treatment for that subject.

The final value of a parameter for each subject is defined as the latest post-baseline value available in the study for that subject. A summary of parameter values, including the baseline and final value, will be provided by treatment group and scheduled visit. A

summary of change from baseline in parameter values, including the final value, will also be provided by treatment group and scheduled visit.

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

The number and percentage of subjects with an abnormal laboratory value at baseline among subjects with a baseline laboratory value and at least one post baseline laboratory value will be provided by treatment group and by parameter. The number and percentage of subjects will be summarized by treatment group for each laboratory test for the following shift categories:

- Normal at baseline to abnormal at any time post-baseline
- Normal at baseline to high at any time post-baseline
- Normal at baseline to low at any time post-baseline
- Normal or low at baseline to high at any time post-baseline
- Normal or high at baseline to low at any time post-baseline

Laboratory data transitions from baseline to final assessment will be summarized for each parameter according to the following categories:

- Decrease: High to Low, Normal to Low, High to Normal
- No Change: Low to Low, Normal to Normal, High to High
- Increase: Low to Normal, Normal to High, Low to High

The threshold laboratory values are defined in terms of a multiplicative factor of the testing laboratory's normal range. A laboratory value that is above the upper limit factor multiplied by the upper limit of the normal range is considered a high threshold value. A laboratory value that is below the lower limit factor multiplied by the lower limit of the normal range is considered a low threshold value. Refer to Appendix 9 for a listing of the laboratory threshold factors.

The number and percentage of subjects with a threshold laboratory value at baseline among subjects with a baseline laboratory value and at least one post baseline laboratory value will be provided by treatment group and by parameter. Subjects with threshold values any time post-baseline with a non-threshold baseline laboratory value and at least one post-baseline laboratory value will also be summarized by treatment group and by parameter.

Listings of hematology and clinical chemistry data will be provided, along with listings of hematology and clinical chemistry data exceeding threshold.

The protocol defines possible drug-induced liver injury with hyperbilirubinaemia, for laboratory assessments planned in this study, as:

ALT ≥ 3xULN and Bilirubin ≥ 2xULN.

A listing of subjects meeting this defined liver function abnormality along with the corresponding data will be provided. If no subjects meet the defined criteria, a listing (page) will be produced indicating that no subjects met the criteria.

A blood draw for HBsAg and Hepatitis C Antibody is scheduled for Visit 2 (baseline). These measurements will be included in a data listing.

8.2.7. Serum PSA

Serum PSA samples are scheduled at the screening visit, and at each Month 6, Month 12, and Month 24 (or end of treatment) visits. Total PSA (absolute values, change from baseline values, and percentage change from baseline values) will be summarized by visit and treatment group using both the LOCF and At Visit approaches. Change from baseline total PSA will be compared in terms of combination treatment versus tamsulosin treatment at each scheduled post-baseline assessment using a general linear model with effects for treatment and baseline total PSA.

Listings of PSA data will be produced. A listing of PSA data will be provided, along with a listing of PSA data exceeding the upper limit of normal.

8.2.8. Post Void Residual Volume

Total voided volume (in conjunction with Qmax) is measured at screening (Visit 1a with possible repeat at Visit 1b), baseline, and at each Month 6, Month 12, Month 18, and Month 24 (or end of treatment) visits.

A list of planned data displays is in Appendix 15: List of Data Displays. Baseline, change from baseline, and percentage change from baseline are defined in Appendix 6. Last observation carried forward (LOCF) and At Visit approaches are defined in Appendix 7. Summaries and analyses will be in terms of the ITT population; LOCF approach will be considered primary. Post void residual volume summary statistics will be presented for each scheduled visit; change from baseline and percentage change from baseline will be presented for each scheduled post-baseline visit.

Post void residual volume change from baseline distribution at each scheduled post-baseline assessment will be compared in terms of combination treatment versus tamsulosin treatment using a nonparametric van Elteren test controlling for cluster at the 0.05 level of significance.

A listing of post void residual volume data will be provided.

8.2.9. Gynecomastia Evaluations

A qualitative breast examination is scheduled to be performed at the screening visit, and at each Month 6, Month 12, Month 18, and Month 24 (or end of treatment) visits. The number and percentage of subjects with palpable breast tissue or nipple tenderness and/or clinically significant palpable breast tissue or nipple tenderness at baseline, at each

scheduled post-baseline assessment and the final assessment (the latest post-baseline evaluation available) will be presented by treatment. The number and percentage of subjects changing from 'no' at baseline to 'yes' at any post-baseline assessment for palpable breast tissue and for nipple tenderness will be compared in terms of combination treatment versus tamsulosin treatment using Fisher's exact test.

The number and percentage of subjects changing from 'no' at baseline in clinical significance to 'yes' at any post-baseline assessment in clinical significance for palpable breast tissue and for nipple tenderness will be presented by treatment group.

A listing of gynecomastia data will be provided.

8.2.10. Digital Rectal Examinations

A digital rectal examination (DRE) is scheduled to be performed at the screening visit, and at each Month 6, Month 12, Month 18, and Month 24 (or end of treatment) visits. The results of normal versus focal abnormality will be summarized by treatment group at baseline, at each scheduled post baseline assessment and for the final assessment (the latest post-baseline evaluation available). Among subjects with focal abnormalities, summaries will include yes/no indication of clinical significance and a yes/no indication of biopsy recommendation. The number and percentage of subjects changing from 'normal' at baseline to 'focal abnormality' at any post-baseline assessment will be compared in terms of combination treatment versus tamsulosin treatment using Fisher's exact test.

A listing of digital rectal examination data will be provided.

8.2.11. Vital Signs

Vital signs (blood pressure and heart rate) are scheduled to be assessed at screening, baseline, and at each of the scheduled post-baseline treatment phase visits. Vital signs will be summarized by treatment group for baseline, each scheduled post-baseline assessment through Month 24 as well as for the final assessment (the latest post-baseline value available in the study). Change from baseline vital signs will also be summarized for each post-baseline assessment as well as for the final assessment.

Refer to Appendix 9 for a listing of the vital sign threshold ranges. For threshold vital sign summaries, high threshold, low threshold as well as either threshold will be presented separately. The number and percentage of subjects with a threshold value at baseline among subjects with a baseline and a post baseline value will be presented by treatment group. The number and percentage of subjects with at least one post baseline value in the threshold range will be presented by treatment group. For each systolic blood pressure, diastolic blood pressure, and heart rate, the incidence of exceeding threshold will be compared in terms of combination treatment versus tamsulosin treatment using Fisher's exact test.

A listing of vital signs data and a listing of vital signs data exceeding threshold will be provided.

8.2.12. Prostate Cancer Biopsies

A listing of data for biopsies performed to confirm prostate cancer will be provided.

8.2.13. Suicidality Assessment

Assessment of suicidality will be done using the Columbia Suicide Severity Rating Scale (C-SSRS) and is scheduled to be assessed at each Screening, Month 6, Month 12, and Month 24 (or end of treatment) visits. Tabular summaries of suicidal ideation and suicidal behavior will be produced at each of the scheduled assessments. Along with the aforementioned tabular summary, as well, for all subjects with suicidal ideation or behavior at any assessment, a listing of C-SSRS data will be provided (as a table), along with listings of details of suicidal ideation and suicidal behavior.

In addition a listing of C-SSRS assessments for all subjects will be provided. As noted in the adverse event section of this document, the possible suicidality-related adverse events will be produced.

8.3. Health Outcomes Analyses

Health outcomes analyses will be in terms of: BPH Impact Index (BII), BPH-Related Health Status (BHS), and the Problem Assessment Scale of the Sexual Function Inventory (PAS SFI). Health outcomes analyses will be performed using the ITT population unless otherwise specified in text or data display shells.

A list of planned Health Outcomes data displays is in Appendix 15: List of Data Displays. Baseline and change from baseline are defined in Appendix 6. Last observation carried forward (LOCF) and At Visit approaches are defined in Appendix 7. Reference Appendix 11 for descriptions of handling multiplicity.

8.3.1. BPH Impact Index

The BPH Impact Index (BII) consists of four questions. It is administered at screening, baseline and at each of the scheduled post-baseline treatment phase visits. The BII total score is the sum of the four questions; the total score range is 0 to 13. BII summaries and analyses will be in terms of the total (score); exceptions will be noted such as for supporting summaries of individual questions.

For calculation of the BII total, missing individual responses will be imputed when at least two of the four questions are answered (nonmissing). For the imputation, the average of the nonmissing responses will be calculated and rounded to the nearest integer. This average will be imputed for the original missing response(s). If at least 20% of the subjects have at least one imputed BII then the statistical analyses will be repeated based on non-imputed scores.

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

baseline assessment will be compared in terms of combination treatment versus tamsulosin treatment using t-tests from a general linear model (GLM) with effects for treatment, cluster, and baseline BII. Two-sided tests at 0.05 level of significance will be conducted.

The adjusted mean estimates (mean and standard error), the adjusted mean difference, and the 95% confidence interval in terms of the adjusted mean difference will be presented. The adjusted mean difference will be in terms of combination treatment minus tamsulosin treatment. The model results will be presented on same tabular summary as the arithmetic mean, standard deviation, median, minimum and maximum. The results will be presented by treatment for each scheduled post-baseline assessment.

BII adjusted mean change from baseline will be plotted by treatment for each post-baseline scheduled visit in terms of each LOCF and At Visit approach.

Each of the four BII individual question responses will be summarized at Baseline, Month 12, and Month 24 by treatment group. Month 12 and Month 24 changes from baseline will be summarized by treatment group for each of the four questions. The summaries will be based on the ITT population and presented using both LOCF and At Visit approaches. No statistical testing will be performed.

Listings of BII individual question and total scores will be presented.

8.3.2. BPH-Related Health Status

BPH-Related Health Status (BHS) is collected as Question 8 the IPSS questionnaire and ranges from 0 to 6. The IPSS questionnaire is administered, and thus BHS is collected, at screening, baseline and at each of the scheduled post-baseline treatment phase visits.

Total BHS, change from baseline BHS, and percentage change from baseline BHS will be summarized by treatment group using both the LOCF and At Visit approaches at each scheduled post-baseline assessment. Change from baseline BHS at each scheduled post-baseline assessment will be compared in terms of combination treatment versus tamsulosin treatment using t-tests from a general linear model (GLM) with effects for treatment, cluster, and baseline BHS. Two-sided tests at 0.05 level of significance will be conducted.

The adjusted mean estimates (mean and standard error), the adjusted mean difference, and the 95% confidence interval in terms of the adjusted mean difference will be presented. The adjusted mean difference will be in terms of combination treatment minus tamsulosin treatment. The model results will be presented on same tabular summary as the arithmetic mean, standard deviation, median, minimum and maximum. The results will be presented by treatment for each scheduled post-baseline assessment.

BHS adjusted mean change from baseline will be plotted by treatment for each post-baseline scheduled visit in terms of each LOCF and At Visit approach.

A listing of BHS data will be presented.

8.3.3. Problem Assessment Scale of the Sexual Function Inventory (PAS SFI)

The Problem Assessment Scale of the Sexual Function Inventory (PAS SFI) consists of three questions each with a range of 0 (Big Problem) to 4 (No Problem). It is administered at screening, baseline and at each Month 12 and Month 24 (or end of treatment) visits. The total PAS SFI is the sum of the three questions; the total score range is 0 to 12. PAS SFI summaries and analyses will be in terms of the total (score); exceptions will be noted such as for supporting summaries of individual questions.

For a given subject and visit, calculation of the PAS SFI total will not be performed or imputed if two or all three individual responses are missing. For a given subject and visit, a single missing individual response will be imputed when two of the three questions are answered (nonmissing). For the imputation, the average of the nonmissing responses will be calculated and rounded to the nearest integer. This average will be imputed for the original missing response. If at least 20% of the subjects have at least one imputed PAS SFI then the statistical analyses will be repeated based on non-imputed scores.

Total PAS SFI and change from baseline PAS SFI will be summarized by treatment group using both the LOCF and At Visit approaches at each scheduled post-baseline assessment. Change from baseline PAS SFI at each scheduled post-baseline assessment will be compared in terms of combination treatment versus tamsulosin treatment using t-tests from a general linear model (GLM) with effects for treatment, cluster, and baseline PAS SFI. Two-sided tests at 0.05 level of significance will be conducted.

The adjusted mean estimates (mean and standard error), the adjusted mean difference, and the 95% confidence interval in terms of the adjusted mean difference will be presented. The adjusted mean difference will be in terms of combination treatment minus tamsulosin treatment. The model results will be presented on same tabular summary as the arithmetic mean, standard deviation, median, minimum and maximum. The results will be presented by treatment for each scheduled post-baseline assessment.

Each of the three PAS SFI individual question responses will be summarized at Baseline, Month 12, and Month 24 by treatment group. Month 12 and Month 24 changes from baseline will be summarized by treatment group for each of the three questions. The summaries will be based on the ITT population and presented using both LOCF and At Visit approaches. No statistical testing will be performed.

A listing of PAS SFI data will be presented.

9. COUNTRY-SPECIFIC SUMMARIES AND ANALYSES

Four countries randomized subjects into this trial and include: China, Japan, Korea, and Taiwan. It is anticipated that each of these countries will conduct a regulatory submission using planned summaries and analyses of this ARI114265 study. For primary regulatory filings, summaries and analyses will be in terms of the Intent-to-Treat population which is based on pooled country data. These regulatory filings may also require complete or various sub-levels of data summaries and analyses for (their) specific country.

Each country's regulatory requirements will be fully defined at a time approaching the regulatory filing which will be after RAP finalization. Therefore, to address the *potential* requirements for complete country-specific summaries and analyses, all planned tables and figures, including planned statistical analyses, will be repeated for each of the four countries. Cluster (defined earlier in RAP as equal to country) will be excluded from the model-based within-country analysis. Exceptions will include planned by-country tabular summaries and listings. There will be no across-country multiplicity adjustments. The within-country statistical analyses will be underpowered because of their smaller sample sizes.

The summaries and analyses for each of the four countries will be provided by Clinical Statistics and Programming as part of a secondary (country-based) statistical analysis complete (SAC) package. Then, considering country regulatory filing plans and requirements, GSK regulatory staff of the individual countries will indicate to medical writing staff the summaries, analyses, and formats to be used in final reporting. Non-reporting of some or all country-based summaries and analyses by the individual countries will not result in a RAP revision.

It is anticipated that analysis and reporting of each country will add up to 2 weeks to the initial (Intent-to-Treat Population) SAC. Therefore, the "Country-specific SAC" will be "Primary SAC" plus 8 weeks. The country analysis may be ordered so that the country with earliest regulatory requirements will undergo first analysis and reporting. Changes to the anticipated '8 weeks' as well as action definition of country reporting order will not result in a RAP revision.

10. REFERENCES

GlaxoSmithKline Document Number RM2010/00134/05 Study ID ARI114265. Protocol Amendment 4: A randomized, double-blind, parallel group study to compare the efficacy and safety of combination treatment with dutasteride (0.5mg) and tamsulosin (0.2mg) with tamsulosin (0.2mg) monotherapy, administered once daily for 2 years, on the improvement of symptoms and health outcomes in men with moderate to severe benign prostatic hyperplasia. Report Date 08-JUL-2014.

GlaxoSmithKline Document: Program Safety Analysis Plan (PSAP) for GI198745 (dutasteride) and GSK2285985 (fixed dose combination of dutasteride [GI198745] and tamsulosin [GI138525]); PSAP approval date 09Dec2015. Note: This reflects PSAP version at point of RAP finalization. Any PSAP updates/revisions at point of Statistical Analysis Complete (SAC) may be incorporated without a revision to this RAP; in this event, PSAP updates impacting analysis and reporting will be described in CSR.

Mallinckrodt C, Lane P, Schnell D, Peng Y, Mancuso J. Recommendations for the Primary Analysis of Continuous Endpoints in Longitudinal Clinical Trials. *Drug Information Journal.* 2008; 42: 303-319.

11. APPENDICES

Section	Appendix
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11.1. Appendix 1: Exclusions from the Per-Protocol Population

In accordance with SOP-130050 and the ARI114265 PDMP, deviations which require exclusion from the Per-Protocol population must be identified, when possible, in advance of treatment unblinding. The deviation review and programming processes, as well as spreadsheet and database capabilities, require that deviation identification must be made from two sources:

1. Study Team Assessment of deviations tracked on study team's protocol deviations spreadsheet and then indicated as 'Exclude from Per-Protocol'
and
2. Programmatic Assessment which outputs deviations through Statistics & Programming electronic SAS code execution.

The below table lists the 18 deviations which would exclude a subject from the Per-Protocol population along with identification methods. It is expected that a final analysis dataset will be generated with the two sources pooled. Details on the pooled dataset programming and any adjudication process required to reconcile the two sources will be defined in advance of database freeze through a RAP amendment or a high level note to Study File. If there is inconsistency between the two sources, it is anticipated that the programmatic determination will be considered definitive; this will be outlined through a RAP amendment or a high level note to Study File.

Number	Per-Protocol Deviation	Study Team Assessment	Programmatic Assessment [eCRF Code Note a]
01	Missed placebo run-in phase	Any evidence which implies or documents that subject missed the placebo run-in phase	1) Placebo run-in treatment start and stop dates are missing or 2) Placebo run-in tablets consumed = zero [A5]
02	Incorrect study drug (wrong treatment) consumed	Any evidence which confirms that the incorrect container contains other-than-scheduled study treatment.	Treatment consumed (from incorrect dispensed container) unequal to treatment planned in randomization schedule. Note: this can only be determined after study unblinding. [A5]
03	Randomized but did not consume double-blind study drug	Any evidence which confirms that the zero tablets were consumed in double-blind phase	Final nonmissing cumulative study drug compliance = zero [A5]
04	Cumulative study drug compliance <75%	Study team is unable to calculate RAP-defined study drug compliance. Therefore, deviation will be determined based on programmatic	Final nonmissing cumulative study drug compliance < 75% [A5]

Number	Per-Protocol Deviation	Study Team Assessment	Programmatic Assessment [eCRF Code Note a]
		assessment.	
05	Cumulative study drug compliance >125%	Study team is unable to calculate RAP-defined study drug compliance. Therefore, deviation will be determined based on programmatic assessment.	Final nonmissing cumulative study drug compliance > 125% [A5]
	Violation of Inclusion Criteria (protocol #)		
06	Confirmed BPH clinical diagnosis (Inclusion 2)	Any evidence which confirms inclusion criterion 2 deviation.	Eligibility database indicates violation of inclusion criterion 2 [A1]
07	IPSS ≥12 at Screening (Inclusion 3)	Any evidence which confirms inclusion criterion 3 deviation.	Eligibility database indicates violation of inclusion criterion 3 [A1]
08	Prostate volume ≥30cc by TRUS at Screening (Inclusion 4)	Any evidence which confirms inclusion criterion 4 deviation.	Eligibility database indicates violation of inclusion criterion 4 [A1]
09	PSA ≥1.5ng/ml and ≤10ng/mL at Screening (Inclusion 5)	Any evidence which confirms inclusion criterion 5 deviation.	Eligibility database indicates violation of inclusion criterion 5 [A1]
10	Qmax >5 mL/sec and ≤15mL/sec with Voided Volume ≥125mL/sec at Screening (Inclusion 6)	Any evidence which confirms inclusion criterion 6 deviation.	Eligibility database indicates violation of inclusion criterion 6 [A1]
	Violation of Exclusion Criteria (protocol #)		
11	Any conditions other than BPH, which may in the judgement of the investigator, result in urinary symptoms or changes in flow rate (Exclusion 6)	Any evidence which confirms exclusion criterion 6 deviation.	Eligibility database indicates violation of exclusion criterion 6 [A1]
12	Use of 5ARI within 6 months of Screening or historical TRUS and throughout the study (Exclusion 10a)	Any evidence which confirms exclusion criterion 10a deviation.	Reference Note b. [A1]
13	Use of anabolic steroids within 6 months of Screening and throughout the study (Exclusion 10b)	Any evidence which confirms exclusion criterion 10b deviation.	Reference Note b. [A1]
14	Use of phytotherapy for BPH within 2 weeks of Screening and throughout the study (Exclusion 10c)	Any evidence which confirms exclusion criterion 10c deviation.	Reference Note b. [A1]

Number	Per-Protocol Deviation	Study Team Assessment	Programmatic Assessment [eCRF Code Note a]
15	Use of alpha-adrenoreceptor blockers within 2 weeks of Screening and throughout the study, except study meds (Exclusion 10d)	Any evidence which confirms exclusion criterion 10d deviation.	Reference Note b. [A1]
16	Use of alpha-adrenoreceptor agonists or anticholinegics or cholinergics within 48 hours prior to all uroflowmetry and IPSS assessments (Exclusion 10e)	Any evidence which confirms exclusion criterion 10e deviation.	Reference Note b. [A1]
17	Use of selective beta 3-adrenoreceptor agonist (mirabegron) within 2 weeks prior to all uroflowmetry and IPSS assessments (Exclusion 10f)	Any evidence which confirms exclusion criterion 10f deviation.	Reference Note b. [A1]
	Other		
18	Any condition which should exclude a subject from the Per-Protocol population and is not include above.	Study team identification through review of multiple sources such as protocol deviation log text, study drug compliance outliers, concomitant medication logs, or site/monitor communications.	NA

Notes:
a. Reflects eCRF corresponding code to be applied programmatically; definitions in below table.
b. Exclusion 10 subsets (a – f) are not individually identified in the INFORM and Analysis & Reporting datasets. Therefore, deviation will be determined based on study team assessment.

Important Deviations Categories, Subcategories, and eCRF Codes (eCRF Codes define above indicated programmatic assignment)	
Category / Subcategory	**eCRF Codes**
Assessments and/or procedures	
Biological specimen sample procedures	6E
Equipment procedures	6G
Failure to comply with dosing procedure	6L
Failure to report SAE, pregnancy, or liver function abnormalities per-protocol	6B
Informed consent process	6A
Missed assessment or procedure	6I
Randomization procedures	6H
Study blind / unblind procedures	6C
Study treatment supply procedures	6D
Other	6OT
Eligibility criteria not met	A1
Prohibited medication or device	A3
Received wrong treatment or incorrect dose	A5
Visit, assessment or timepoint window	
Window for dose administration	4C
Window for efficacy assessments	4A
Window for safety assessments	4B
Other	4OT

11.2. Appendix 2: Time & Events

11.2.1. Protocol Defined Time & Events

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

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

Protocol Defined Time & Events, Notes

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

11.3. Appendix 3: Assessment Windows

Boundaries for the scheduled assessments are defined in the protocol. The data will be summarized by nominal visit without regard to window days for all scheduled visits. The efficacy, safety, and health outcomes measures collected at nominal visits include IPSS, prostate volume, Qmax, PSA, post void residual volume, BII, BPH-related Health Status, and PAS-SFI. In order to utilize as much data as possible in these efficacy, safety, and health outcomes summaries and analyses, premature withdrawal visit data will be used as the scheduled visit data when both of the following criteria are met:

- The scheduled visit evaluation is not available, and
- The premature withdrawal visit date falls within 30 days (inclusive) for each of the scheduled post baseline visits (i.e., Months 3, 6, 9, 12, 15, 18, 21, and 24), or within 15 days (inclusive) of the scheduled Baseline visit (Month 0). The scheduled visit day for month k will be calculated as:
  Baseline Date + (k * 365/12) rounded to the nearest integer.

11.4. Appendix 4: Multicenter Studies

11.4.1. Methods for Handling Centers

The 4 countries which randomized subjects into this trial include: China, Japan, Korea, and Taiwan. Forty-six centers across these 4 countries randomized subjects into this trial.

Clusters will be used in the exploration of center effect and treatment-by-center interaction.

As stated in the protocol, it was anticipated that randomized subject accrual would be spread thinly across centers and summaries of data by center would be unlikely to be informative. It was expected that investigative centers would be pooled a priori into clusters based on geographic location. As stated in protocol, these clusters would be identified once randomization was complete and then used in statistical analyses in the exploration of center effects and treatment-by-center interaction.

Based on the actual randomization of sites within countries, it is reasonable and logical to assign each country as a single cluster. Therefore, the 4 clusters are the 4 countries: China, Japan, Korea, and Taiwan. The countries will be used in summaries of randomized subjects, subgroup summaries, and in statistical analyses of efficacy center effect and treatment-by-center interaction; these by-country summaries and analyses are described in relevant sections.

11.5. Appendix 5: Data Display Standards & Handling Conventions

11.5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG [1]		Data Displays for Reporting	
Code	Description	Description	Order [2]
A	Dutasteride 0.5mg once daily + tamsulosin 0.2mg once daily	Dut 0.5mg + Tam 0.2mg	2
B	Dutasteride placebo once daily + tamsulosin 0.2mg once daily	Placebo + Tam 0.2mg	1

NOTES:

1. RandAll NG (Next Generation) is a randomization creation and publishing tool for GSK studies.
2. Order represents treatments being presented in tables, listings, and figures.

Within this RAP, the following additional references may be made for brevity:

--Full Treatment Description--	--Short Treatment Descriptions--
Dutasteride 0.5mg once daily + tamsulosin 0.2mg once daily or	-Combination -Dut 0.5mg + Tam 0.2mg -Dut + Tam
Dutasteride placebo once daily + tamsulosin 0.2mg once daily	-Tamsulosin Monotherapy -Tam 0.2mg -Placebo + Tam 0.2mg -Tam

11.5.2. Reporting Process & Standards

The following reporting process and reporting standards details apply to all RAP defined endpoints.

Reporting Process	
Software	
• SAS software will be used for all analyses except when noted. It is anticipated that the SAS software version 9.3 will be in use at statistical analysis complete; use of a version other than 9.3 will be documented in IMMS Study File.	
Reporting Areas *The following server and areas are identified as of RAP finalization. Revisions to these areas, for example due to platform / server relocation and/or CDISC reporting standards, will be documented in IMMS Study File.*	
HARP Server	US1SALX00259
HARP Area	The high level area is defined as: /arenv/arprod/gi198745/ari114265/final.
QC Documentation Area	QC process and documentation for analysis and reporting will be maintained as a text file on HARP server US1SALX00259 within above noted area.

Reporting Process
Analysis Datasets
• Analysis datasets for international regulatory submissions will be created according to CDISC standards. The SDTM IG Version & AdaM IG Version will be defined in IMMS Study File when CDISC standards are implemented. • For creation of ADaM datasets (ADCM/ADAE), the same version of dictionary datasets will be implemented for conversion from SI to SDTM; changes will be documented in IMMS Study File.
Generation of RTF Files
• RTF files will be generated for all tabular summaries with the reporting efforts described in the RAP unless clearly stated as not required by the assigned Scientific and Medical Writer(s).

Reporting Standards
General
The current GSK Integrated Data Standards Library (IDSL) and GSK IDSL Statistical Principles will be applied for reporting, unless otherwise stated within RAP text or indicated in table, listing, figure shells: • 4.03 to 4.23: General Principles • 5.01 to 5.08: Principles Related to Data Listings • 6.01 to 6.11: Principles Related to Summary Tables • 7.01 to 7.13: Principles Related to Graphics From the above standards and principles as well as to be aligned with historical reporting for this compound and indication, the key reporting standards to be applied are: • All data will be reported according to the actual treatment the subject received unless otherwise stated. • Within listings, numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of decimal places. • Within tabular summaries, the minimum and maximum values are presented with the same number of decimal places as the raw data collected on the eCRF. The mean and percentiles (e.g. median, Q1, and Q3) are presented using one additional decimal place. The standard deviation and standard error are presented using two additional decimal places. • Continuous variables (e.g., age) will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. • Categorical variables will be summarized using the number of subjects (n) and percentage (%) in each category. • P-values greater than 0.10 will be reported to two decimal accuracy. P-values less than or equal to 0.10 will be reported to three decimal accuracy. P-values less than 0.001 will be reported as '<0.001'. • Applicable safety analysis and reporting definitions and presentations within "Program Safety Analysis Plan (PSAP) for GI198745 (dutasteride) and GSK2285985 (fixed dose combination of dutasteride [GI198745] and tamsulosin [GI138525]" will be referenced; any deviations will be oted within this RAP.

11.6. Appendix 6: Derived and Transformed Data

(Placebo) Run-In Start and Stop Dates
• Placebo run-in start date = Start date of (placebo) study treatment recorded for the run-in period. If the recorded start dates for the two study drug containers differ, then select the earlier start date. • Placebo run-in stop date = End date of (placebo) study treatment recorded for the run-in period. If the recorded stop dates for the two study drug containers differ, then select the later stop date. Note: a subject with a nonmissing placebo run-in start date will be considered as included in the Placebo Run-in Phase.
Randomization Date
• Randomization date is the randomization telephone call in date which is recorded in the eCRF. This date is defined here for completeness and no derivations are made. Note: a subject with a nonmissing randomization number recorded in eCRF will be considered Randomized.
(Double-Blind) Treatment Start and Stop Dates
• Treatment start date = Start date of study treatment recorded for the (double-blind) treatment period. If the recorded start dates for the two study drug containers differ, then select the earlier start date. • Treatment stop date = Stop date of study treatment recorded for the (double-blind) treatment period. If the recorded stop dates for the two study drug containers differ, then select the later stop date.

Study Drug Exposure and Compliance

- As explained in the protocol:
  -Dutasteride study treatment is dispensed as capsules within bottles.
  -Tamsulosin study treatment is dispensed as tablets within blister packs.
  Within this RAP, the following general terms are used for exposure and compliance:
  ---"Pill" refers to a capsule or a tablet
  ---"Container" refers to a bottle or a blister pack.
- Study drug exposure (in days) is number of days between (double-blind) treatment start date and (double-blind) treatment stop date, both days inclusive (i.e. Study drug exposure =Treatment Stop Date – Treatment Start Date +1).
- Number of pills consumed during the study is defined for double-blind period as total number of pills dispensed (sum over all containers dispensed) minus total number of pills returned (sum over all containers dispensed) minus total number of pills lost or wasted (sum over all containers dispensed). If any of the containers is not returned or number of pills returned or wasted is missing for any container, number of pills consumed during the study is missing.
- Overall study drug compliance is defined for double-blind period as 100 * (number of pills consumed during the study / study drug exposure) / 2. Division by 2 is required since subjects were scheduled to consume 2 pills per day. Overall study drug compliance is missing if either the number of pills consumed during the study or the study drug exposure is missing.
- Compliance by study drug component: Study drug compliance by component will be output for:
  --Placebo + Tam 0.2mg for each of the two components: Placebo and Tam 0.2mg
  --Dut 0.5mg + Tam 0.2mg for each of the two components: Dut 0.5mg and Tam 0.2mg
  Compliance is defined as 100 * (number of pills consumed during the study / study drug exposure for that drug component) / 1. Note that division by 2 is not applicable for the study drug components. Number of pills and exposure are defined in terms of each drug component and not the overall.

Baseline Date

- A subject's baseline date will be the latest non-missing value of either (double-blind) treatment start date or randomization date. Baseline date will be used in the derivation of study day values and Baseline Values. 'Baseline date' may differ from the Visit 2 (Baseline Visit) date recorded in eCRF.

Baseline Value

- For purposes of data analyses, the subject's baseline value of an assessment will be defined as the latest assessment on or before the Baseline Date.

Change and % Change from Baseline

- Change from Baseline = Post-baseline Value – Baseline
- % Change from Baseline = 100 x [(Post-baseline Value – Baseline) / Baseline]

Study Day

Study Day is calculated as the number of days from Baseline Date:

- Reference Date = Missing → Study Day = Missing
- Reference Date < Baseline Date → Study Day = Reference Date – Baseline Date
- Reference Date ≥ Baseline Date → Study Day = Reference Date – (Baseline Date) + 1

Cut-off Dates

-Month k Cut-off Date (for k= 3, 6, 9, 12, 15, 18, 21, 24): The maximum of [Month k clinic visit date, Month k lab visit date, Baseline Date + (k * 91/3)].

Time Since LUTS First Noted (in years)

-Time Since LUTS First Noted = Baseline Date minus Date LUTS First Noted by Patient / 365

Time Since BPH Clinical Diagnosis (in years)

-Time Since BPH Diagnosis = Baseline Date minus Date of BPH Clinical Diagnosis / 365

Age

Only year of birth is collected in the eCRF. For purposes of calculating age for a given subject, date of birth will be defined as June 30th of the corresponding year of birth. Age is calculated in terms of Screening (Visit 1b) date and output as a truncated integer. Age categories include <65, ≥65, <75, and ≥75 years.

Body Mass Index (BMI) (kg/sq m)

BMI = Weight (kg) / [Height (m)]^2

Race / Ethnicity

Race / ethnicity will be determined based on a subject's reported ethnicity and geographic ancestry as defined in the following table.

	Race / Ethnicity			
	Asian	**White (But Not Hispanic)**	**Hispanic**	**Other**
Ethnicity	Not Hispanic or Latino	Not Hispanic or Latino	Hispanic or Latino	Not Hispanic or Latino
Geographic Ancestry	Any combination of (restricted to the categories below only): - Asian – East Asian Heritage - Asian – Japanese Heritage - Asian - South East Asian Heritage - Asian – Central / South Asian Heritage	Any combination of (restricted to the below categories only): - White – Arabic/ North African Heritage - White – White/ Caucasian/ European Heritage	Any combination	Any combination not considered 'Asian' or 'White (But Not Hispanic)'

IPSS (total score)

IPSS (total score) = Sum of IPSS individual questions 1 – 7. Reference Section 7.1.1 for imputation procedure.

Prostate Volume

Prostate Volume = pi/6 (Anteroposterior Width x Cephalocaudal Width x Transverse Width)

11.7. Appendix 7: Premature Withdrawals & Handling of Missing Data

11.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) is defined as completion of the 4-week placebo run-in and the 104-week study treatment period. • Withdrawn subjects will not be replaced in the study. • All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified. • Number and percent of ITT population completing the study and those withdrawing from the study, along with eCRF recorded reasons for premature withdrawals, will be summarized by treatment and overall.
Note	This section addresses Premature Withdrawals from the study. Premature discontinuation of investigational product, along with reasons, is a separate data collection and is reported separately.

11.7.2. Handling of Missing Data

11.7.2.1. Handling of Missing or Partial Dates

For efficacy time to event endpoints, such as 'Time to AUR or BPH-Related Surgery' the following approach will be used for unknown event dates unless otherwise indicated. If the month and year are known but the day of the month is unknown, then the day of the month will be imputed to be the 15th . If the year is known but the month and day are unknown then the date will be imputed to be July 2 in that year. In all the preceding cases, if it is not definitive that the onset date is on or after the treatment start date based on the non-missing (non-imputed) dates, then the date will be imputed to be the treatment start date. If the year is unknown then the onset date is considered to be prior to treatment start; hence, the event will be excluded from summaries of events on or after treatment start. For subjects without events, the censoring dates will be established using non-missing dates, and using dates with only days missing. Dates with missing months and years will not be used in establishing the censoring dates.

Partial adverse event dates will be handled as described in Appendix 8.

11.7.2.2. Handling of Missing Data for Statistical Analysis

Endpoints measured at specific visits and analyzed in terms of visit numbers include: IPSS, prostate volume, Qmax, PSA, post void residual volume, BPH Impact Index (BII), BPH-Related Health Status, and PAS-SFI. Analysis of the data collected in terms of visit numbers will be performed using two different approaches to account for missing data.

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

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

11.7.3. Questionnaire Total Score Imputation

Calculations of IPSS total and BII total, including imputation for missing responses, are described in the respective RAP sections.

11.8. Appendix 8: Adverse Event Time Periods and Special Adverse Event Definitions

Date-related derivations and transformations related to adverse events (AEs) are described below.

AE Onset Time since First Dose
= AE Onset Date – Treatment Start Date if treatment start date > AE onset date
= AE Onset Date – Treatment Start Date +1 if treatment start date <= AE start date
= missing otherwise

AE Duration (in days) = AE Resolution Date – AE Onset Date + 1

The timing of AEs will be categorized as follows:

- An AE is "Pre-Treatment" if the AE onset date is before the treatment start date.
- An AE is "On Treatment" if the AE onset date is on or after the treatment start date (but on or before the treatment stop date, if that is non-missing), or if the onset date is missing.
- An AE is "Post-Treatment" if the treatment stop date is non-missing, and the AE onset date is after the treatment stop date.
- An AE is "Post-Randomization" if the AE is either On Treatment or Post-Treatment.

Note: Cut-off dates are defined in Appendix 6; definition is repeated here, in terms of 6-month treatment periods, since this is used to determine AE onset period:
Month k Cut-off Date (for k= 6, 12, 18, 24): The maximum of [Month k clinic visit date, Month k lab visit date, Baseline Date + (k * 91/3)].

An on-treatment AE is uniquely identified as having onset within one of the following four time periods: Months 1-6, Months 7-12, Months 13-18, or Months 19-24.

- An AE is considered to have onset in the Months 1-6 time period if it is an on-treatment AE and the onset date is on or before the Month 6 cut-off date.
- An AE is considered to have onset in the Months 7-12 time period if it is an on-treatment AE and the onset date is after the Month 6 cut-off date and is on or before the Month 12 cut-off date.
- An AE is considered to have onset in the Months 13-18 time period if it is an on-treatment AE and the onset date is after the Month 12 cut-off date and is on or before the Month 18 cut-off date.
- An AE is considered to have onset in the Months 19-24 time period if it is an on-treatment AE and the onset date is after the Month 18 cut-off date.

If the AE onset date is partially missing, the timing is determined as follows:
1. If the non-missing parts of the date (either just year or year/month) are unambiguously before the start of treatment, the AE is considered Pre-Treatment.

2. If the non-missing parts of the date are unambiguously after the stop of treatment, the AE is considered Post-Treatment.
3. If #1 or #2 above cannot be assigned, then the AE is considered On-Treatment.

If an on-treatment AE onset date is partially missing, then, for the purpose of assigning the 6-month treatment period referenced above, the onset date will be imputed according to the algorithm described in the second paragraph below, and the imputed date will be used to assign the period.

An AE is considered drug-related if the relationship variable indicates so, or the variable value is missing. When an AE has an outcome of Resolved/Recovered with or without sequelae, it may be categorized for resolution status as follows: if resolution date is on or before treatment stop date, the AE is considered resolved on-therapy, or if either the resolution date or the treatment stop date is missing and the action taken is not 'investigational product withdrawn', the AE is considered resolved on-therapy. If a resolved AE is not resolved on-therapy, it is considered resolved off-therapy.

For the purpose of Kaplan-Meier estimates for Special Interest AEs, and for categorizing AEs by time intervals, the following algorithm will be used:

1) If an AE start date is partial, it will be imputed as follows:
    a. If all components of the date (day, month and year) are missing, then the date will not be imputed, but the AE will be categorized in the first 6-month time period.
    b. If both day and month are missing, then the day and month will be imputed as 01 January.
    c. If only day is missing, then the day will be imputed as 01.
    d. Any imputation described in items 1b and 1c above will be revised if it is in conflict with the treatment start date: if the month and year of treatment start date is same as those in the imputed date, the imputed date will be changed to the treatment start date.
2) A subject not having the particular AE will be censored at the latter of the following two dates: date of last clinic visit, latest AE start date.
3) If an AE end date is partial, it will be imputed as follows:
    a. If all components of the date (day, month and year) are missing, then the end date will be missing.
    b. If both day and month are missing, then the day and month will be imputed as 31 December.
    c. If only day is missing, then the day will be imputed as the last day of the corresponding month.

For computing AE duration, partial AE start and end dates will be imputed as previously described, and events with completely unknown (missing) end dates will be censored at the latter of the following two dates: date of last clinic visit, latest AE start date. AE duration is the total number of non-overlapping days for all events per subject, and will be considered censored if any contributing event is censored.

Time to death is defined as (date of death – treatment start date +1). For subjects who do not experience death, time to death is censored at the date of last clinic visit (if missing, the subject will be censored at the treatment start date).

Special interest adverse events, including MedDRA preferred terms and codes, are presented below in Table A - Table D:

Table A: Sexual and Breast Adverse Events of Special Interest
Table B: Prostate Cancer Adverse Events of Special Interest
Table C: Cardiovascular Adverse Events of Special Interest
Table D: Infrequent Tier 1 Adverse Events of Special Interest

Table A. Sexual and Breast Adverse Events of Special Interest: MedDRA Preferred Terms and Codes

Special Interest Event	MedDRA Preferred Term	PT_Code
Altered (Decreased) Libido	Sexual dysfunction	10040477
	Male sexual dysfunction	10057672
	Libido decreased	10024419
	Loss of libido	10024870
	Libido disorder	10061221
Impotence	Erectile dysfunction	10061461
	Organic erectile dysfunction	10052004
	Disturbance in sexual arousal	10058929
	Psychogenic erectile dysfunction	10052005
Ejaculation Disorders	Ejaculation delayed	10014325
	Ejaculation disorder	10014326
	Ejaculation failure	10014328
	Retrograde ejaculation	10038967
	Anorgasmia	10002652
	Orgasm abnormal	10031085
	Premature ejaculation	10036596
	Male orgasmic disorder	10025513
	Orgasmic sensation decreased	10052449
	Semen volume decreased	10039944
Breast Disorders	Breast hyperplasia	10006256
	Breast enlargement	10006242
	Gynaecomastia	10018800
	Nipple disorder	10029417
	Breast engorgement	10006240
	Breast swelling	10006312
	Breast pain	10006298
	Breast tenderness	10006313
	Nipple pain	10029421
	Nipple swelling	10058680
	Breast discomfort	10049872
Breast Disorders: Breast Enlargement	Breast hyperplasia	10006256
	Breast enlargement	10006242
	Gynaecomastia	10018800
	Nipple disorder	10029417
	Breast engorgement	10006240
	Breast swelling	10006312
Breast Disorders: Breast Tenderness	Breast pain	10006298
	Breast tenderness	10006313
	Nipple pain	10029421
	Nipple swelling	10058680
	Breast discomfort	10049872

Table B. Prostate Cancer Adverse Events of Special Interest: MedDRA Preferred Terms and Codes		
Special Interest Event	**MedDRA Preferred Term**	**PT_Code**
Prostate Cancer	Prostate cancer	10060862
	Prostate cancer stage 0	10036912
	Prostate cancer stage I	10036917
	Prostate cancer stage II	10036918
	Prostate cancer stage III	10036919
	Prostate cancer stage IV	10036920
	Prostate cancer recurrent	10036911
	Prostate cancer metastatic	10036909

Table C. Cardiovascular Adverse Events of Special Interest: MedDRA Preferred Terms and Codes		
Special Interest Event	**MedDRA Preferred Term**	**PT_Code**
Acute Coronary Syndrome	Acute myocardial infarction	10000891
	Myocardial infarction	10028596
	Silent myocardial infarction	10049768
	Sudden cardiac death	10049418
	Angina unstable	10002388
	Cardiac arrest	10007515
	Cardio-respiratory arrest	10007617
	Cardiac death	10049993
	Acute coronary syndrome	10051592
Ischemic Cerebrovascular Events	Cerebrovascular accident	10008190
	Transient ischemic attack	10044390
	Cerebral infarction	10008118
	Cerebrovascular disorder	10008196
	Cerebral artery embolism	10008088
	Cerebral artery occlusion	10008089
	Cerebral artery thrombosis	10008092
	Ischemic stroke	10061256
	Cerebral circulatory failure	10008097
	Cerebellar infarction	10008034
	Thalamic infarction	10064961
	Reversible ischemic neurologic deficit	10050496
	Thrombotic stroke	10043647
	Embolic stroke	10014498
	Vertebral artery occlusion	10048965
	Carotid arterial embolus	10007684
	Carotid artery occlusion	10048964
	Carotid artery stenosis	10007687
	Carotid artery thrombosis	10007688
	Thrombotic cerebral infarction	10067347
	Brain stem infarction	10006147
	Embolic cerebral infarction	10060839
	Lacunar infarction	10051078
	Brain stem stroke	10068644
	Stroke in evolution	10059613
	Ischaemic cerebral infarction	10060840

Table C. Cardiovascular Adverse Events of Special Interest: MedDRA Preferred Terms and Codes (continued)		
Special Interest Event	**MedDRA Preferred Term**	**PT_Code**
Cardiac Failure	Cardiac failure congestive	10007559
	Cardiac failure	10007554
	Left ventricular failure	10024119
	Cardiac failure acute	10007556
	Cardiogenic shock	10007625
	Left ventricular failure acute	10063081
	Right ventricular failure	10039163
	Right ventricular failure acute	10063082
	Ventricular failure	10060953
	Cardiopulmonary failure	10051093
	Congestive cardiomyopathy	10056370
Ischemic Coronary Artery Disorders/ Atherosclerosis	Coronary artery embolism	10011084
	Coronary artery occlusion	10011086
	Coronary artery stenosis	10011089
	Coronary artery thrombosis	10011091
	Myocardial ischemia	10028600
	Coronary artery disease	10011078
	Arteriosclerosis coronary artery	10003211
Cardiac Arrhythmias	Ventricular extrasystoles	10047289
	Torsade de Pointes	10044066
	Ventricular fibrillation	10047290
	Cardiac Fibrillation	10061592
	Pulseless electrical activity	10058151
	Ventricular asystole	10047284
	Long QT syndrome	10024803
	Ventricular tachycardia	10047302
	Ventricular Arrhythmia	10047281
	Ventricular flutter	10047294
Peripheral Vascular Disease	Deep Vein Thrombosis	10051055

Table D. Infrequent Tier 1 Adverse Events of Special Interest: MedDRA Preferred Terms and Codes		
Special Interest Event	**MedDRA Preferred Term**	**PT_Code**
Relevant for dutasteride:		
Allergic reactions	Anaphylactic reaction	10002198
	Anaphylactic shock	10002199
	Anaphylactic transfusion reaction	10067113
	Anaphylactoid reaction	10002216
	Anaphylactoid shock	10063119
	Circulatory collapse	10009192
	First use syndrome	10068158
	Kounis syndrome	10069167
	Shock	10040560
	Type I hypersensitivity	10045240
	Allergic oedema	10060934
	Angioedema	10002424
	Circumoral oedema	10052250
	Conjunctival oedema	10010726
	Corneal oedema	10011033
	Epiglottic oedema	10015029
	Eye oedema	10052139
	Eye swelling	10015967
	Eyelid oedema	10015993
	Face oedema	10016029
	Gingival oedema	10049305
	Gingival swelling	10018291
	Gleich's syndrome	10066837
	Hereditary angioedema	10019860
	Idiopathic angioedema	10073257
	Idiopathic urticaria	10021247
	Laryngeal oedema	10023845
	Laryngotracheal oedema	10023893
	Limbal swelling	10070492
	Lip oedema	10024558
	Lip swelling	10024570
	Mouth Swelling	10075203
	Oculorespiratory syndrome	10067317
	Oedema mouth	10030110
	Oropharyngeal swelling	10031118
	Palatal oedema	10056998
	Palatal swelling	10074403
	Periorbital oedema	10034545
	Pharyngeal oedema	10034829
	Scleral oedema	10057431
	Small bowel angioedema	10051401
	Swelling face	10042682
	Swollen tongue	10042727
	Tongue oedema	10043967
	Tracheal oedema	10044296
	Urticaria	10046735
	Urticaria cholinergic	10046740
	Urticaria chronic	10052568
	Urticaria papular	10046750
	Acquired epidermolysis bullosa	10056508
	Blister	10005191
	Blister rupture	10073385
	Bullous impetigo	10006563
	Conjunctivitis	10010741
	Corneal exfoliation	10064489
	Drug eruption	10013687
	Epidermolysis	10053177
	Epidermolysis bullosa	10014989

	Genital ulceration	10018180
	HLA-B*1502 assay positive	10074771
	HLA-B*5801 assay positive	10074774
	Lip exfoliation	10064482
	Mouth ulceration	10028034
	Mucocutaneous ulceration	10028084
	Mucosa vesicle	10028103
	Mucosal erosion	10061297
	Mucosal exfoliation	10064486
	Mucosal necrosis	10067993
	Mucosal ulceration	10028124
	Nikolsky's sign	10029415
	Noninfective conjunctivitis	10074701
	Oral mucosal blistering	10030995
	Oral mucosal exfoliation	10064487
	Oral papule	10031010
	Oropharyngeal blistering	10067950
	Pemphigoid	10034277
	Pemphigus	10034280
	Penile exfoliation	10064485
	Skin erosion	10040840
	Skin exfoliation	10040844
	Staphylococcal scalded skin syndrome	10041929
	Stomatitis	10042128
	Tongue exfoliation	10064488
	Vaginal exfoliation	10064483
	Vaginal ulceration	10046943
	Vulval ulceration	10047768
	Vulvovaginal rash	10071588
	Vulvovaginal ulceration	10050181
	Application site pruritus	10003053
	Aquagenic pruritus	10003071
	Injection site pruritus	10022093
	Pruritus	10037087
	Pruritus genital	10037093
	Rash pruritic	10037884
	Senile pruritus	10039986
	Itching scar	10050818
	Eyelids pruritus	10051627
	Catheter site pruritus	10052270
	Pruritus generalised	10052576
	Infusion site pruritus	10053664
	Vulvovaginal pruritus	10056530
	Incision site pruritus	10059386
	Uraemic pruritus	10060875
	Pruritus allergic	10063438
	Instillation site pruritus	10063763
	Implant site pruritus	10063785
	Cholestatic pruritus	10064190
	Polymorphic eruption of pregnancy	10066100
	Vessel puncture site pruritus	10067254
	Vaccination site pruritus	10068881
	Brachioradial pruritus	10071443
	Notalgia paraesthetica	10072643
Breast Cancer	Apocrine breast carcinoma	10066206
	Invasive breast carcinoma	10075713
	Triple negative breast cancer	10075566
	Breast cancer	10006187
	Breast cancer female	10057654
	Breast cancer in situ	10006189
	Breast cancer male	10061020

	Breast cancer metastatic	10055113
	Breast cancer recurrent	10006198
	Breast cancer stage I	10006199
	Breast cancer stage II	10006200
	Breast cancer stage III	10006201
	Breast cancer stage IV	10006202
	Breast sarcoma	10068582
	Breast sarcoma metastatic	10068583
	Breast sarcoma recurrent	10068584
	Contralateral breast cancer	10054784
	Electron radiation therapy to breast	10014437
	Extended radical mastectomy	10015721
	Gamma radiation therapy to breast	10017677
	HER-2 positive breast cancer	10065430
	Inflammatory carcinoma of breast recurrent	10021977
	Inflammatory carcinoma of breast stage III	10021978
	Inflammatory carcinoma of breast stage IV	10021979
	Inflammatory carcinoma of the breast	10021980
	Intraductal papillary breast neoplasm	10073540
	Intraductal proliferative breast lesion	10073094
	Invasive ductal breast carcinoma	10073095
	Invasive lobular breast carcinoma	10073096
	Invasive papillary breast carcinoma	10073098
	Lobular breast carcinoma in situ	10073099
	Malignant nipple neoplasm	10062051
	Malignant nipple neoplasm female	10053129
	Malignant nipple neoplasm male	10053128
	Mastectomy	10026878
	Medullary carcinoma of breast	10027095
	Metaplastic breast carcinoma	10073100
	Modified radical mastectomy	10027799
	Mucinous breast carcinoma	10073101
	Neuroendocrine breast tumour	10073103
	Oestrogen receptor assay positive	10054054
	Oestrogen receptor positive breast cancer	10070577
	Paget's disease of nipple	10033364
	Photon radiation therapy to breast	10034949
	Postmastectomy lymphoedema syndrome	10036390
	Progesterone receptor assay positive	10054057
	Radical mastectomy	10037773
	Radiotherapy to breast	10062090
	Simple mastectomy	10040700
	Tubular breast carcinoma	10073104
	X-ray therapy to breast	10048199
	Antioestrogen therapy	10002816
	Breast reconstruction	10006305
	Breast neoplasm	10006279
	Nipple neoplasm	10056286
	Phyllodes tumour	10071776
	Biopsy breast abnormal	10004745
	Breast calcifications	10048782
	Breast dysplasia	10006237
	Breast prosthesis implantation	10006303
	Computerised tomogram breast abnormal	10074534
Depressed mood	Activation syndrome	10066817
	Adjustment disorder with depressed mood	10001297
	Columbia suicide severity rating scale abnormal	10075616
	Adjustment disorder with mixed anxiety and depressed mood	10001299

	Agitated depression	10001496
	Anhedonia	10002511
	Antidepressant therapy	10054976
	Childhood depression	10068631
	Decreased interest	10011971
	Depressed mood	10012374
	Depression	10012378
	Depression postoperative	10012390
	Depressive symptom	10054089
	Dysphoria	10013954
	Dysthymic disorder	10013982
	Electroconvulsive therapy	10014404
	Feeling guilty	10049708
	Feeling of despair	10016344
	Feelings of worthlessness	10016374
	Major depression	10057840
	Menopausal depression	10067371
	Post stroke depression	10070606
	Postictal depression	10071324
	Postpartum depression	10056393
	Completed suicide	10010144
	Depression suicidal	10012397
	Intentional overdose	10022523
	Intentional self-injury	10022524
	Poisoning deliberate	10036000
	Self injurious behaviour	10063495
	Self-injurious ideation	10051154
	Suicidal behaviour	10065604
	Suicidal ideation	10042458
	Suicide attempt	10042464
Hair changes	Alopecia	10001760
	Alopecia areata	10001761
	Alopecia scarring	10001764
	Alopecia syphilitic	10001765
	Alopecia totalis	10001766
	Alopecia universalis	10001767
	Hypotrichosis	10021126
	Progeria	10036794
	Madarosis	10051235
	Follicular mucinosis	10056506
	Application site alopecia	10059046
	Androgenetic alopecia	10068168
	Satoyoshi syndrome	10070579
	Radiation alopecia	10072045
	Diffuse alopecia	10073736
	Hypertrichosis	10020864
Interference with formation of external genitalia in a male fetus	Congenital vas deferens absence	10010670
	Cryptorchism	10011498
	Epispadias	10015088
	Hypospadias	10021093
	Reproductive tract hypoplasia, male	10057858
	Testicular dysplasia	10059271
	Congenital genital malformation male	10059492
	Penoscrotal fusion	10064951
	Sertoli-cell-only syndrome	10066833
	Buried penis syndrome	10067131
	Penoscrotal transposition	10067287
	Penile torsion	10070235
	Infertility tests	10021931
	pH semen	10034784
	pH semen decreased	10034786

Potential for decreased male fertility	pH semen increased	10034788
	pH semen normal	10034790
	Red blood cells semen	10038176
	Red blood cells semen negative	10038179
	Red blood cells semen positive	10038180
	Semen liquefaction	10039931
	Semen liquefaction normal	10039933
	Semen liquefaction prolonged	10039934
	Semen liquefaction shortened	10039935
	Semen viscosity	10039936
	Semen viscosity decreased	10039938
	Semen viscosity increased	10039940
	Semen viscosity normal	10039942
	Semen volume abnormal	10039943
	Semen volume decreased	10039944
	Semen volume increased	10039946
	Semen volume normal	10039948
	Sperm analysis	10041476
	Sperm analysis abnormal	10041477
	Sperm analysis normal	10041478
	Spermatozoa abnormal	10041498
	Spermatozoa morphology	10041501
	Spermatozoa morphology abnormal	10041502
	Spermatozoa morphology normal	10041503
	Spermatozoa progressive motility abnormal	10041504
	Spermatozoa progressive motility decreased	10041506
	Spermatozoa progressive motility normal	10041507
	White blood cells semen	10047956
	White blood cells semen negative	10047959
	White blood cells semen positive	10047960
	Fructose semen decreased	10052476
	Fructose semen increased	10052477
	Prostatic fluid leukocytes increased	10053866
	Infertility tests abnormal	10062020
	Infertility tests normal	10062021
	pH semen abnormal	10062074
	Semen liquefaction abnormal	10062159
	Semen viscosity abnormal	10062160
	Semen analysis normal	10062238
	Semen analysis	10068482
	Semen analysis abnormal	10068483
	Sperm concentration decreased	10070925
	Sperm concentration increased	10070926
	Sperm concentration abnormal	10070927
	Sperm concentration normal	10070928
	Sperm concentration	10070929
	Sperm concentration zero	10070930
	Total sperm count	10070931
	Total sperm count decreased	10070932
	Infertility	10021926
	Infertility male	10021929
Testicular pain and swelling	Anorchism	10002641
	Eunuchoidism	10015532
	Hypogonadism male	10021011
	Testicular atrophy	10043298
	Testicular disorder	10043306
	Testicular failure	10043315
	Testicular failure postoperative	10043317
	Testicular failure primary	10043318
	Testicular hyperfunction	10043334
	Testicular infarction	10043337

	Testicular pain	10043345
	Testicular retraction	10043348
	Testicular swelling	10043354
	Testicular torsion	10043356
	Testicular necrosis	10049572
	Spermatic cord mass	10049792
	Testicular appendage torsion	10050476
	Spermatic cord pain	10051221
	Testicular injury	10051872
	Testicular haemorrhage	10051877
	Epididymal calculus	10052321
	Epididymal enlargement	10052322
	Epididymal tenderness	10052323
	Testis discomfort	10052531
	Monorchidism	10055002
	Epididymal disorder	10055045
	Spermatic cord disorder	10056348
	Testicular mass	10058901
	Testotoxicosis	10063654
	Spermatic cord haemorrhage	10065742
	Spermatic cord obstruction	10065805
	Spermatic cord perforation	10065806
	Spermatic cord stenosis	10065807
	Testicular perforation	10065808
	Testicular hypertrophy	10066101
	Testicular oedema	10066769
	Sperm granuloma	10067802
	Testicular microlithiasis	10067829
	Congenital monorchidism	10069505
	Testicular autoimmunity	10071574
Relevant for tamsulosin:		
Atrial fibrillation, tachycardia, arrhythmias	Arrhythmia	10003119
	Heart alternation	10058155
	Heart rate irregular	10019304
	Pacemaker generated arrhythmia	10053486
	Pacemaker syndrome	10051994
	Paroxysmal arrhythmia	10050106
	Pulseless electrical activity	10058151
	Reperfusion arrhythmia	10058156
	Withdrawal arrhythmia	10047997
	Arrhythmia supraventricular	10003130
	Atrial fibrillation	10003658
	Atrial flutter	10003662
	Atrial parasystole	10071666
	Atrial tachycardia	10003668
	Junctional ectopic tachycardia	10074640
	Sinus tachycardia	10040752
	Supraventricular extrasystoles	10042602
	Supraventricular tachyarrhythmia	10065342
	Supraventricular tachycardia	10042604
	ECG P wave inverted	10057526
	Electrocardiogram P wave abnormal	10050384
	Retrograde p-waves	10071187
	Anomalous atrioventricular excitation	10002611
	Cardiac flutter	10052840
	Extrasystoles	10015856
	Tachyarrhythmia	10049447
	Accelerated idioventricular rhythm	10049003
	Cardiac fibrillation	10061592
	Parasystole	10033929
	Rhythm idioventricular	10039111

	Torsade de pointes	10044066
	Ventricular arrhythmia	10047281
	Ventricular extrasystoles	10047289
	Ventricular fibrillation	10047290
	Ventricular flutter	10047294
	Ventricular parasystole	10058184
	Ventricular pre-excitation	10049761
	Ventricular tachyarrhythmia	10065341
	Ventricular tachycardia	10047302
Floppy Iris Syndrome	Floppy iris syndrome	10066373
Orthostasis	Dizziness	10013573
	Dizziness postural	10013578
	Orthostatic hypotension	10031127
	Hypotension	10021097
	Syncope	10042772
	Presyncope	10036653
	Blood pressure orthostatic abnormal	10053354
	Blood pressure orthostatic decreased	10053356
Priapism	Priapism	10036661
Stevens-Johnson syndrome	Acute generalised exanthematous pustulosis	10048799
	Cutaneous vasculitis	10011686
	Dermatitis bullous	10012441
	Dermatitis exfoliative	10012455
	Dermatitis exfoliative generalised	10012456
	Drug reaction with eosinophilia and systemic symptoms	10073508
	Epidermal necrosis	10059284
	Erythema multiforme	10015218
	Exfoliative rash	10064579
	Oculomucocutaneous syndrome	10030081
	Skin necrosis	10040893
	Stevens-Johnson syndrome	10042033
	Toxic epidermal necrolysis	10044223
	Toxic skin eruption	10057970

11.9. Appendix 9: Threshold Factors for Clinical Laboratory Tests and Vital Signs

Hematology and Clinical Chemistry Laboratory Tests, Codes and Threshold Factors				
LABORATORY TEST	Database LBTESTCD	Unit	Multiplicative Factors[1]	
			Low (x LLN)	High (x ULN)
HEMATOLOGY				
-Hemoglobin	HB_BLC	G/L	0.75	-
-Platelet count	PLT_BLC	GI/L	0.75	1.5
-WBC count	WBC_BLC	GI/L	0.5	3.0
-RBC count	RBC_BLC	GI/L	0.5	-
CLINICAL CHEMISTRY				
-Albumin	ALB_PLC	G/L	0.9	1.2
-ALT	ALT_PLC	IU/L	-	3.0
-Alkaline Phosphatase	ALP_PLC	IU/L	-	1.5
- AST	AST_PLC	IU/L	-	3.0
-Creatinine	CRT_PLC	UMOL/L	0.5	3.0
-Glucose	GLUC_PLC	MMOL/L	0.7	1.75
-Potassium	K_PLC	MMOL/L	0.75	1.4
-Sodium	NA_PLC	MMOL/L	0.9	1.15
-Total Bilirubin	BILT_PLC	UMOL/L	-	2.5
-Total Protein	TP_PLC	G/L	0.8	1.15
-Urea/BUN	UREA_PLC	MMOL/L	0.5	2.0

1. A laboratory value that is above the upper limit factor multiplied by the upper limit of the normal range is considered a high threshold value. A laboratory value that is below the lower limit factor multiplied by the lower limit of the normal range is considered a low threshold value.

Threshold Ranges for Vital Signs			
		Threshold Ranges	
Vital Sign	Unit	Lower	Upper
Systolic Blood Pressure	mmHg	<80	>165
Diastolic Blood Pressure	mmHg	<40	>105
Heart Rate	bpm	<40	>100

11.10. Appendix 10: Examination of Covariates and Subgroups

Endpoint(s)	IPSS change from baseline
Analysis	Subgroup Summaries and General Linear Model

A list of subgroups of interest for the primary efficacy endpoint is below. If the categorization defining the subgroups results in overly sparse data or if some baseline subgroups are homogeneous in response, then particular subgroups may be combined or not reported.

For each subgroup, IPSS change from baseline summaries will be output by treatment group at Month 12 and at Month 24 for the ITT population using both LOCF and At Visit approaches. No statistical comparisons will be performed.

The effects of baseline subgroups and their interactions with treatment will be assessed. As a minimum, these subgroups will include those in the below table except for country and center. These effects will be individually explored in terms of: 1) addition of subgroup effect to the model* and 2) addition of subgroup effect and subgroup effect by treatment interaction to the model*.

*Refers to primary efficacy General Linear Model (GLM):
Change from Baseline IPSS = treatment + cluster + baseline IPSS.

In these analyses, continuous variables will be treated as continuous and not as dichotomous subgroups. These assessments will focus on Month 24 LOCF, and separately Month 24 At Visit, and will be output as listings. Other analyses based on other time points will not be output unless substantive finding dictate.

Subgroups Summarized for Primary Efficacy Endpoint	
Subgroup	**Categorization for Tabular Summary Display**
Baseline Age 65	<65, ≥65 years
Baseline Age 75	<75, ≥75 years
Baseline IPSS	<20, ≥20
Baseline BPH-Related Health Status	<4, ≥4
Baseline Prostate Volume	<40, ≥40cc
Baseline Qmax	<10, ≥10ml/sec
Alpha Blocker History	Yes, No
5-Alpha-Reductase Inhibitor History	Yes, No
Phytotherapy History	Yes, No
Baseline PSA	<3, ≥3ng/ml
Country (cluster)	China, Japan, Korea, Taiwan
Center	Each center with at least one randomized subject.

11.11. Appendix 11: Multiple Comparisons and Multiplicity

Results of all planned statistical analyses and thus all planned p-values will be reported. P-values ≤0.05 will be considered formally statistically significant if the below described conditions are satisfied for multiple endpoints and multiple time points. Otherwise p-values ≤0.05 will be considered nominally significant.

The comparisons are in terms of two treatment arms, Combination and Tamsulosin, so no multiplicity adjustment for treatment is necessary.

Multiplicity adjustment for multiple endpoints is described in this paragraph. For the primary efficacy endpoint, IPSS change from baseline at Month 24, if the Month 24 two-sided p-value is ≤0.05 and the treatment difference supports Combination superiority versus Tamsulosin, then formal statistical significance is declared and testing of each secondary endpoint may occur. For secondary endpoints evaluated at multiple time points, then the testing will begin at Month 24. For purposes of statistical testing, there is no hierarchical order assigned to the set of secondary endpoints at Month 24.

Multiplicity adjustment for multiple time points is described in this paragraph. For any endpoint that is tested over different visits, a step-down procedure for interpreting the p-values will be adopted. The final time point (Month 24) will be tested first. If the Month 24 two-sided p-value is ≤0.05 and the treatment difference supports Combination superiority versus Tamsulosin, the time point immediately preceding it will be interpreted for formal statistical significance; otherwise formal interpretation of significance will stop, but interpretation of nominal significance will continue for preceding endpoints. The interpretation of formal statistical significance will continue this way in a stepwise manner through all time points.

As an example, the time point testing visit sequence for the primary efficacy endpoint is: Month 24, Month 21, Month 18, Month 15, Month 12, Month 9, Month 6, and (last) Month 3.

11.12. Appendix 12: Model Checking and Diagnostics for Statistical Analyses

Endpoint(s)	IPSS change from baseline
Analysis	General Linear Model

- Assessments of the general linear model residuals will be performed. These assessments will include reviews of residual by predicted value plots and normal probability plots on residuals. This will be in terms of the change from baseline IPSS at Month 24 using the LOCF and At Visit approaches. Similar assessments of other time periods will not be reported unless dictated by substantive findings.

- If these assumptions are not met, appropriate non-parametric analyses will be performed to test the robustness of the results of the parametric analyses. If non-parametric analyses are performed further detailed information will be provided in the Statistical Appendix for the Clinical Report.

- The interaction of cluster with treatment will be assessed by adding the (interaction) term to the above planned analysis model at Month 24.

- The interaction of baseline IPSS with treatment will be assessed by adding the (interaction) term to the above stated model at Month 24.

- The effects of baseline subgroups and their interactions with treatment will also be assessed. This is described in Appendix 10, Examination of Covariates and Subgroups

11.13. Appendix 13: Mixed-Model Repeated-Measures Analysis

Mixed-Model Repeated-Measures (MMRM) Analysis: As a supportive analysis, IPSS change from baseline will be analyzed using a mixed-model repeated-measures (MMRM) analysis including data from the scheduled post-baseline assessments [Mallinckrodt, 2008]. Analyses will include the fixed, categorical effects of treatment, cluster, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline IPSS and baseline IPSS-by-visit interaction. An unstructured covariance structure will be used to model the within-patient errors, shared across treatments. PROC MIXED in SAS [Littell, 1996] will be used to fit the model, using the restricted maximum likelihood estimation method and the Kenward-Roger option to estimate denominator degrees of freedom and standard errors.

Corresponding SAS output will be provided as a listing. The treatment comparison will be the contrast between treatments (Combination minus Tamsulosin) at the Month 24 visit using the two-sided p-value from the corresponding t-test at α=0.05. In this supportive analysis, superiority of the Combination vs. Tamsulosin treatment will be declared if the two-sided p-value for the contrast is less than or equal to 0.05 and the observed treatment effect supports superiority. A two-sided 95% confidence interval for the estimated treatment difference in the change from baseline at each scheduled visit will be computed. Estimated mean change from baseline and standard errors will be computed by treatment group and visit. If the model-fitting algorithm fails to converge then alternative initial parameter values and/or covariance structures will be considered.

11.14. Appendix 14 – Abbreviations & Trade Marks

11.14.1. Abbreviations

Abbreviation	Description
5ARI	5 Alpha-Reductase Inhibitor
ADaM	Analysis Data Model
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUR	Acute Urinary Retention
A&R	Analysis and Reporting
BHS	BPH-related Health Status
BII	BPH Impact Index
BPH	Benign Prostatic Hyperplasia
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating
DOB	Date of Birth
DRE	Digital Rectal Examination
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
FDC	Fixed Dose Combination
ICH	International Conference on Harmonization
IMMS	International Modules Management System
IP	Investigational Product
ITT	Intent-To-Treat
GUI	Guidance
LOCF	Last Observation Carried Forward
LUTS	Lower urinary tract symptoms
MMRM	Mixed-Model Repeated- Measures
PAS SFI	Problem Assessment Scale Sexual Function Inventory
PDE-5	Phosphodiesterase-5
PDMP	Protocol Deviation Management Plan
PGx	Pharmacogenetic
PPK	Population Pharmacokinetics
PP	Per-Protocol
PPSM	Patient Perception of Study Medication
PSA	Prostate Specific Antigen
PSAP	Program Safety Analysis Plan
PSRAE	Possible Suicidality Related Adverse Event
QC	Quality Control
Qmax	Maximum (peak) urinary flow rate
RAMOS	Randomization & Medication Ordering System

Abbreviation	Description
RandAll NG	RandAll is a randomization creation and publishing tool for GSK studies. NG represents Next Generation version.
RAP	Reporting & Analysis Plan
RBC	Red Blood Cell
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings
TFUQ	Targeted Follow-Up Questionnaire
TRUS	Transrectal ultrasound
UTI	Urinary Tract Infection
WBC	White Blood Cell

11.14.2. Trademarks

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11.15. Appendix 15: List of Data Displays

11.15.1. Data Display Numbering

The following numbering will be applied for RAP generated displays.

Section	Tables	Figures
Study Population	1.1 to 1.32	NA
Efficacy	2.1 to 2.152	2.1 to 2.9
Safety	3.1 to 3.104	3.1 to 3.18
Health Outcomes	4.1 to 4.56	4.1 to 4.4
Section	**Listings**	
ICH Listings (Study Population)	1.1 to 1.14	
ICH Listings (Efficacy)	2.1 to 2.8	
ICH Listings (Safety)	3.1 to 3.23	
ICH Listings (Health Outcomes)	-	
Other Listings includes Non-ICH listings	5.1 to 5.52	

11.15.2. Study Population Tables

Study Population Tables (Population=ITT except when noted)	
No.	**Title**
Subject Accountability	
1.1.	Summary of Subject Accountability *Note: Population = All Enrolled Subjects*
Subject Disposition	
1.2.	Summary of Subject Withdrawals During Placebo Run-in Phase *Note: Population = Subjects Who Entered Placebo Run-In*
1.3.	Summary of Randomized Subjects by Country and Center
1.4.	Summary of Subject Disposition
1.5.	Summary of Subject Discontinuation by Visit
1.6.	Summary of Primary Reason for Study Withdrawal, by Period of Discontinuation
1.7.	Summary of Inclusion/Exclusion Criteria Deviations
1.8.	Summary of Important Protocol Deviations
1.9.	Summary of Deviations which Require Exclusion from the Per-Protocol Population
Demographic and Baseline Characteristics	
1.10.	Summary of Baseline and Demographic Characteristics
1.11.	Summary of Baseline and Demographic Characteristics by Country
1.12.	Summary of Race and Racial Combinations
1.13.	Summary of Race and Racial Combination Details
1.14.	Summary of Selected Safety Measures at Baseline
1.15.	Summary of Selected Safety Measures at Baseline by Country
1.16.	Summary of Selected Efficacy and Health Outcome Measures at Baseline
1.17.	Summary of Selected Efficacy and Health Outcome Measures at Baseline by Country
Medical Conditions and Concomitant Medications	
1.18.	Summary of Medical Conditions at Screening, by Body System

Study Population Tables (Population=ITT except when noted)	
No.	**Title**
1.19.	Summary of Specific Medical Conditions at Screening
1.20.	Summary of BPH History
1.21.	Summary of Alpha-Blocker Use
1.22.	Summary of 5-Alpha-Reductase Inhibitor Use
1.23.	Summary of Alpha-Blocker and 5-Alpha-Reductase Inhibitor Use
1.24.	Summary of Phytotherapy for BPH Use
1.25.	Summary of Sexual Function at Screening
1.26.	Summary of Family History of Premature Coronary Artery Disease
1.27.	Summary of Family History of Breast Cancer
1.28.	Summary of Family History of Prostate Cancer
1.29.	Summary of Concomitant Medications
1.30.	Summary of Investigational Product Discontinuation
1.31.	Summary of Study Drug Exposure
1.32.	Summary of Compliance to Study Drug

11.15.3. Efficacy Tables

Efficacy Tables (Population=ITT)	
No.	**Title**
IPSS Overview and Primary Analysis	
2.1.	Summary of IPSS Imputations
2.2.	Summary of IPSS at Screening and Baseline *includes Visit 1a, Visit 2, Baseline, Baseline for Subjects with IPSS at each Month n (3, 6, …24)*
2.3.	Summary of IPSS at Each Post-Baseline Visit (LOCF)
2.4.	Summary of IPSS at Each Post-Baseline Visit (At Visit)
2.5.	Summary of IPSS Change from Baseline (LOCF)
2.6.	Summary of IPSS Change from Baseline (At Visit)
IPSS MMRM	
2.7.	Summary of IPSS MMRM Analysis
IPSS Change from Baseline Subgroup Summaries *presented for each Month 12 and Month 24*	
2.8.	Summary of IPSS Change from Baseline, by Age (<65, ≥65 years) (LOCF)
2.9.	Summary of IPSS Change from Baseline, by Age (<65, ≥65 years) (At Visit)
2.10.	Summary of IPSS Change from Baseline, by Age (<75, ≥75 years) (LOCF)
2.11.	Summary of IPSS Change from Baseline, by Age (<75, ≥75 years) (At Visit)
2.12.	Summary of IPSS Change from Baseline, by Baseline IPSS (<20, ≥20) (LOCF)
2.13.	Summary of IPSS Change from Baseline, by Baseline IPSS (<20, ≥20) (At Visit)
2.14.	Summary of IPSS Change from Baseline, by Baseline BPH-Related Health Status (<4, ≥4) (LOCF)
2.15.	Summary of IPSS Change from Baseline, by Baseline BPH-Related Health Status (<4, ≥4) (At Visit)
2.16.	Summary of IPSS Change from Baseline, by Baseline Prostate Volume (<40, ≥40cc) (LOCF)
2.17.	Summary of IPSS Change from Baseline, by Baseline Prostate Volume (<40, ≥40cc) (At Visit)
2.18.	Summary of IPSS Change from Baseline, by Baseline Qmax (<10, ≥10ml/sec) (LOCF)
2.19.	Summary of IPSS Change from Baseline, by Baseline Qmax (<10, ≥10ml/sec) (At Visit)

Efficacy Tables (Population=ITT)	
No.	**Title**
2.20.	Summary of IPSS Change from Baseline, by Alpha-Blocker History (yes, no) (LOCF)
2.21.	Summary of IPSS Change from Baseline, by Alpha-Blocker History (yes, no) (At Visit)
2.22.	Summary of IPSS Change from Baseline, by 5-Alpha-Reductase Inhibitor History (yes, no) (LOCF)
2.23.	Summary of IPSS Change from Baseline, by 5-Alpha-Reductase Inhibitor History (yes, no) (At Visit)
2.24.	Summary of IPSS Change from Baseline, by Phytotherapy History (yes, no) (LOCF)
2.25.	Summary of IPSS Change from Baseline, by Phytotherapy History (yes, no) (At Visit)
2.26.	Summary of IPSS Change from Baseline, by Baseline PSA (<3, ≥3ng/ml) (LOCF)
2.27.	Summary of IPSS Change from Baseline, by Baseline PSA (<3, ≥3ng/ml) (At Visit)
2.28.	Summary of IPSS Change from Baseline, by Country (LOCF)
2.29.	Summary of IPSS Change from Baseline, by Country (At Visit)
	Note: IPSS change from baseline summaries by center are output in Non-ICH Listings rather than in Tables.
Individual IPSS Questions 1 - 7	
2.30.	Summary of IPSS at Screening and Baseline: Question 1 *includes Visit 1a, Visit 2, Baseline, Baseline for Subjects with IPSS at each Months 12 and 24*
2.31.	Summary of IPSS: Question 1 (LOCF) *each of the below individual question summaries is in terms of Months 12 and 24 only*.
2.32.	Summary of IPSS: Question 1 (At Visit)
2.33.	Summary of IPSS Change from Baseline: Question 1 (LOCF)
2.34.	Summary of IPSS Change from Baseline: Question 1 (At Visit)
2.35.	Summary of IPSS at Screening and Baseline: Question 2
2.36.	Summary of IPSS: Question 2 (LOCF)
2.37.	Summary of IPSS: Question 2 (At Visit)
2.38.	Summary of IPSS Change from Baseline: Question 2 (LOCF)
2.39.	Summary of IPSS Change from Baseline: Question 2 (At Visit)
2.40.	Summary of IPSS at Screening and Baseline: Question 3

Efficacy Tables (Population=ITT)	
No.	**Title**
2.41.	Summary of IPSS: Question 3 (LOCF)
2.42.	Summary of IPSS: Question 3 (At Visit)
2.43.	Summary of IPSS Change from Baseline: Question 3 (LOCF)
2.44.	Summary of IPSS Change from Baseline: Question 3 (At Visit)
2.45.	Summary of IPSS at Screening and Baseline: Question 4
2.46.	Summary of IPSS: Question 4 (LOCF)
2.47.	Summary of IPSS: Question 4 (At Visit)
2.48.	Summary of IPSS Change from Baseline: Question 4 (LOCF)
2.49.	Summary of IPSS Change from Baseline: Question 4 (At Visit)
2.50.	Summary of IPSS at Screening and Baseline: Question 5
2.51.	Summary of IPSS: Question 5 (LOCF)
2.52.	Summary of IPSS: Question 5 (At Visit)
2.53.	Summary of IPSS Change from Baseline: Question 5 (LOCF)
2.54.	Summary of IPSS Change from Baseline: Question 5 (At Visit)
2.55.	Summary of IPSS at Screening and Baseline: Question 6
2.56.	Summary of IPSS: Question 6 (LOCF)
2.57.	Summary of IPSS: Question 6 (At Visit)
2.58.	Summary of IPSS Change from Baseline: Question 6 (LOCF)
2.59.	Summary of IPSS Change from Baseline: Question 6 (At Visit)
2.60.	Summary of IPSS at Screening and Baseline: Question 7
2.61.	Summary of IPSS: Question 7 (LOCF)
2.62.	Summary of IPSS: Question 7 (At Visit)
2.63.	Summary of IPSS Change from Baseline: Question 7 (LOCF)

Efficacy Tables (Population=ITT)	
No.	**Title**
2.64.	Summary of IPSS Change from Baseline: Question 7 (At Visit)
IPSS Percentage Change from Baseline	
2.65.	Summary of IPSS Percentage Change from Baseline (LOCF)
2.66.	Summary of IPSS Percentage Change from Baseline (At Visit)
IPSS Non-Imputed Score Analysis	
	Performed only if RAP Section 7.1 imputation conditions are met; thus, table numbers are not listed.
IPSS Per-Protocol Population Analysis	
	Performed only if RAP Section 4 per-protocol conditions are met; thus, table numbers are not listed.
IPSS Change-from-Baseline Improvement Levels	
2.67.	Summary of IPSS Change-from-Baseline Categories (LOCF)
2.68.	Summary of IPSS Change-from-Baseline Categories (At Visit)
IPSS Percentage Change-from-Baseline Improvement Levels	
2.69.	Summary of IPSS Percentage Change-from-Baseline Categories (LOCF)
2.70.	Summary of IPSS Percentage Change-from-Baseline Categories (At Visit)
Prostate Volume	
2.71.	Summary of Prostate Volume at Screening and Baseline
2.72.	Summary of Prostate Volume at Each Post-Baseline Visit (LOCF)
2.73.	Summary of Prostate Volume at Each Post-Baseline Visit (At Visit)
2.74.	Summary of Prostate Volume Change from Baseline (LOCF)
2.75.	Summary of Prostate Volume Change from Baseline (At Visit)
2.76.	Summary of Prostate Volume Percentage Change from Baseline (LOCF)
2.77.	Summary of Prostate Volume Percentage Change from Baseline (At Visit)
2.78.	Summary of Prostate Volume Percentage Change-from-Baseline Categories (LOCF)
2.79.	Summary of Prostate Volume Percentage Change-from-Baseline Categories (At Visit)
2.80.	Summary of Prostate Volume Percentage Change from Baseline, by Age (<65, ≥65 years) (LOCF)

Efficacy Tables (Population=ITT)	
No.	**Title**
2.81.	Summary of Prostate Volume Percentage Change from Baseline, by Age (<65, ≥65 years) (At Visit)
2.82.	Summary of Prostate Volume Percentage Change from Baseline, by Age (<75, ≥75 years) (LOCF)
2.83.	Summary of Prostate Volume Percentage Change from Baseline, by Age (<75, ≥75 years) (At Visit)
2.84.	Summary of Prostate Volume Percentage Change from Baseline, by Baseline IPSS (<20, ≥20) (LOCF)
2.85.	Summary of Prostate Volume Percentage Change from Baseline, by Baseline IPSS (<20, ≥20) (At Visit)
2.86.	Summary of Prostate Volume Percentage Change from Baseline, by Baseline BPH-Related Health Status (<4, ≥4) (LOCF)
2.87.	Summary of Prostate Volume Percentage Change from Baseline, by Baseline BPH-Related Health Status (<4, ≥4) (At Visit)
2.88.	Summary of Prostate Volume Percentage Change from Baseline, by Baseline Prostate Volume (<40, ≥40cc) (LOCF)
2.89.	Summary of Prostate Volume Percentage Change from Baseline, by Baseline Prostate Volume (<40, ≥40cc) (At Visit)
2.90.	Summary of Prostate Volume Percentage Change from Baseline, by Baseline Qmax (<10, ≥10ml/sec) (LOCF)
2.91.	Summary of Prostate Volume Percentage Change from Baseline, by Baseline Qmax (<10, ≥10ml/sec) (At Visit)
2.92.	Summary of Prostate Volume Percentage Change from Baseline, by Alpha-Blocker History (yes, no) (LOCF)
2.93.	Summary of Prostate Volume Percentage Change from Baseline, by Alpha-Blocker History (yes, no) (At Visit)
2.94.	Summary of Prostate Volume Percentage Change from Baseline, by 5-Alpha-Reductase Inhibitor History (yes, no) (LOCF)
2.95.	Summary of Prostate Volume Percentage Change from Baseline, by 5-Alpha-Reductase Inhibitor History (yes, no) (At Visit)
2.96.	Summary of Prostate Volume Percentage Change from Baseline, by Phytotherapy History (yes, no) (LOCF)
2.97.	Summary of Prostate Volume Percentage Change from Baseline, by Phytotherapy History (yes, no) (At Visit)
2.98.	Summary of Prostate Volume Percentage Change from Baseline, by Baseline PSA (<3, ≥3ng/ml) (LOCF)
2.99.	Summary of Prostate Volume Percentage Change from Baseline, by Baseline PSA (<3, ≥3ng/ml) (At Visit)
2.100.	Summary of Prostate Volume Percentage Change from Baseline, by Country (LOCF)
2.101.	Summary of Prostate Volume Percentage Change from Baseline, by Country (At Visit)
Note: Prostate volume percentage change from baseline summaries by center are output in Non-ICH Listings rather than in Tables.	
Qmax	

Efficacy Tables (Population=ITT)	
No.	**Title**
2.102.	Summary of Qmax at Screening and Baseline
2.103.	Summary of Qmax at Each Post-Baseline Visit (LOCF)
2.104.	Summary of Qmax at Each Post-Baseline Visit (At Visit)
2.105.	Summary of Qmax Change from Baseline (LOCF)
2.106.	Summary of Qmax Change from Baseline (At Visit)
2.107.	Summary of Qmax Change from Baseline Categories (LOCF)
2.108.	Summary of Qmax Change from Baseline Categories (At Visit)
2.109.	Summary of Qmax Percentage Change from Baseline (LOCF)
2.110.	Summary of Qmax Percentage Change from Baseline (At Visit)
2.111.	Summary of Qmax Percentage Change from Baseline Categories (LOCF)
2.112.	Summary of Qmax Percentage Change from Baseline Categories (At Visit)
2.113.	Summary of Qmax Change from Baseline, by Age (<65, ≥65 years) (LOCF)
2.114.	Summary of Qmax Change from Baseline, by Age (<65, ≥65 years) (At Visit)
2.115.	Summary of Qmax Change from Baseline, by Age (<75, ≥75 years) (LOCF)
2.116.	Summary of Qmax Change from Baseline, by Age (<75, ≥75 years) (At Visit)
2.117.	Summary of Qmax Change from Baseline, by Baseline IPSS (<20, ≥20) (LOCF)
2.118.	Summary of Qmax Change from Baseline, by Baseline IPSS (<20, ≥20) (At Visit)
2.119.	Summary of Qmax Change from Baseline, by Baseline BPH-Related Health Status (<4, ≥4) (LOCF)
2.120.	Summary of Qmax Change from Baseline, by Baseline BPH-Related Health Status (<4, ≥4) (At Visit)
2.121.	Summary of Qmax Change from Baseline, by Baseline Prostate Volume (<40, ≥40cc) (LOCF)
2.122.	Summary of Qmax Change from Baseline, by Baseline Prostate Volume (<40, ≥40cc) (At Visit)
2.123.	Summary of Qmax Change from Baseline, by Baseline Qmax (<10, ≥10ml/sec) (LOCF)
2.124.	Summary of Qmax Change from Baseline, by Baseline Qmax (<10, ≥10ml/sec) (At Visit)

Efficacy Tables (Population=ITT)	
No.	**Title**
2.125.	Summary of Qmax Change from Baseline, by Alpha-Blocker History (yes, no) (LOCF)
2.126.	Summary of Qmax Change from Baseline, by Alpha-Blocker History (yes, no) (At Visit)
2.127.	Summary of Qmax Change from Baseline, by 5-Alpha-Reductase Inhibitor History (yes, no) (LOCF)
2.128.	Summary of Qmax Change from Baseline, by 5-Alpha-Reductase Inhibitor History (yes, no) (At Visit)
2.129.	Summary of Qmax Change from Baseline, by Phytotherapy History (yes, no) (LOCF)
2.130.	Summary of Qmax Change from Baseline, by Phytotherapy History (yes, no) (At Visit)
2.131.	Summary of Qmax Change from Baseline, by Baseline PSA (<3, ≥3ng/ml) (LOCF)
2.132.	Summary of Qmax Change from Baseline, by Baseline PSA (<3, ≥3ng/ml) (At Visit)
2.133.	Summary of Qmax Change from Baseline, by Country (LOCF)
2.134.	Summary of Qmax Change from Baseline, by Country (At Visit)
	Note: Qmax change from baseline summaries by center are output in Non-ICH Listings rather than in Tables.

AUR or BPH-Related Surgery	
2.135.	Summary of Time to AUR or BPH-Related Surgery
2.136.	Summary of Time to AUR or BPH-Related Surgery by Quarter
2.137.	Summary of AUR or BPH-Related Surgery
2.138.	Summary of Effect of Various Factors on Time to AUR or BPH-Related Surgery
2.139.	Summary of Hospitalization for AUR or BPH-Related Surgery
2.140.	Summary of Time from Treatment Stop to AUR or BPH-Related Surgery
2.141.	Summary of Time to First AUR
2.142.	Summary of Time to First AUR by Quarter
2.143.	Summary of AUR
2.144.	Summary of Hospitalization for AUR
2.145.	Summary of Time to BPH-Related Surgery
2.146.	Summary of Time to BPH-Related Surgery by Quarter
2.147.	Summary of BPH-Related Surgery
2.148.	Summary of Hospitalization for BPH-Related Surgery
2.149.	Summary of Prostatic Surgery
Other Efficacy Measures	
2.150.	Summary of Urinary Tract Infection / Urosepsis
2.151.	Summary of Urinary Incontinence
2.152.	Summary of Renal Insufficiency

11.15.4. Efficacy Figures

Efficacy Figures (Population=ITT)	
No.	**Title**
IPSS	
2.1.	Figure of IPSS Adjusted Mean Change from Baseline (LOCF)
2.2.	Figure of IPSS Adjusted Mean Change from Baseline (At Visit)
Prostate Volume	
2.3.	Figure of Prostate Volume Adjusted Mean Percentage Change from Baseline (LOCF)
2.4.	Figure of Prostate Volume Adjusted Mean Percentage Change from Baseline (At Visit)
Qmax	
2.5.	Figure of Qmax Adjusted Mean Change from Baseline (LOCF)
2.6.	Figure of Qmax Adjusted Mean Change from Baseline (At Visit)
AUR or BPH-Related Surgery	
2.7.	Plot of Kaplan-Meier Estimates of Time to First AUR or BPH-Related Surgery
2.8.	Plot of Kaplan-Meier Estimates of Time to First AUR
2.9.	Plot of Kaplan-Meier Estimates of Time to First BPH-Related Surgery

11.15.5. Safety Tables

Safety	
3.1	Summary of Adverse Events Starting Post-randomization by Type
3.2	Summary of Adverse Events Starting Post-randomization
3.3	Summary of Adverse Events Starting On-Treatment
3.4	Summary of Adverse Events Starting Post-Treatment
3.5	Summary of Non-serious Adverse Events Starting Post-randomization
3.6	Summary of Adverse Events Starting Post-randomization by Time Period of Onset
3.7	Summary of Adverse Events Starting Post-randomization by Age Group (<65, ≥65)
3.8	Summary of Adverse Events Starting Post-randomization by Age Group (<75, ≥75)

3.9	Summary of Adverse Events Starting Post-randomization by Country
3.10	Summary of Adverse Events Starting Post-randomization by Descending Frequency
3.11	Summary of Serious Adverse Events Starting Post-randomization by Descending Frequency
3.12	Summary of Non-serious Adverse Events Starting Post-randomization by Descending Frequency
3.13	Summary of Adverse Events Starting On-Treatment (Study Drug Exposure Basis)
3.14	Summary of Adverse Events Starting On-Treatment by Time Period (Study Drug Exposure Basis)
3.15	Summary of Adverse Events Starting Post-Randomization by Maximum Intensity
3.16	Summary of Most Common Adverse Events Starting Post-Randomization
3.17	Summary of Most Common Nonserious Adverse Events Starting Post-Randomization
3.18	Summary of Drug-related Adverse Events Starting Post-randomization
3.19	Summary of Drug-related Adverse Events Starting On-treatment
3.20	Summary of Drug-related Adverse Events Starting Post-treatment
3.21	Summary of Drug-related Adverse Events Starting Post-randomization by Time Period of Onset
3.22	Summary of Drug-related Adverse Events Starting Post-randomization by Age Group (<65, ≥65)
3.23	Summary of Drug-related Adverse Events Starting Post-randomization by Age Group (<75, ≥75)
3.24	Summary of Drug-related Adverse Events Starting Post-randomization by Country
3.25	Summary of Serious Adverse Events Starting Post-randomization
3.26	Summary of Serious Adverse Events Starting On-treatment
3.27	Summary of Serious Adverse Events Starting Post-treatment
3.28	Summary of Serious Adverse Events Starting Post-randomization by Time Period of Onset
3.29	Summary of Serious Adverse Events Starting Post-randomization by Age Group (<65, ≥65)
3.30	Summary of Serious Adverse Events Starting Post-randomization by Age Group (<75, ≥75)
3.31	Summary of Serious Adverse Events Starting Post-randomization by Country

3.32	Summary of Drug-related Serious Adverse Events Starting Post-randomization
3.33	Summary of Fatal Adverse Events Starting Post-randomization
3.34	Summary of Drug-related Fatal Adverse Events Starting Post-randomization
3.35	Summary of Adverse Events Starting Post-randomization Leading to Withdrawal from the Study
3.36	Summary of Drug-related Adverse Events Starting Post-randomization Leading to Withdrawal from the Study
3.37	Summary of Serious Adverse Events Starting Post-randomization Leading to Withdrawal from the Study
3.38	Summary of Adverse Events Starting Post-randomization Leading to Permanent Discontinuation of the Study Drug
3.39	Summary of Drug-related Adverse Events Starting Post-randomization Leading to Permanent Discontinuation of the Study Drug
3.40	Summary of Serious Adverse Events Starting Post-randomization Leading to Permanent Discontinuation of the Study Drug
3.41	Summary of Sexual and Breast Adverse Events of Special Interest Starting Post-randomization
3.42	Summary of Special Interest Adverse Events Starting Post-randomization: Altered (Decreased) Libido
3.43	Summary of Special Interest Adverse Events Starting Post-randomization: Impotence
3.44	Summary of Special Interest Adverse Events Starting Post-randomization: Ejaculation Disorders
3.45	Summary of Special Interest Adverse Events Starting Post-randomization: Breast Disorders
3.46	Summary of Special Interest Adverse Events Starting Post-randomization: Breast Disorders: Breast Enlargement
3.47	Summary of Special Interest Adverse Events Starting Post-randomization: Breast Disorders: Breast Tenderness
3.48	Summary of Special Interest Adverse Events Starting Post-randomization By Baseline Characteristics: Altered (Decreased) Libido
3.49	Summary of Special Interest Adverse Events Starting Post-randomization By Baseline Characteristics: Impotence

3.50	Summary of Special Interest Adverse Events Starting Post-randomization By Baseline Characteristics: Ejaculation Disorders
3.51	Summary of Special Interest Adverse Events Starting Post-randomization By Baseline Characteristics : Breast Disorders
3.52	Summary of Special Interest Adverse Events Starting Post-randomization By Baseline Characteristics: Breast Disorders: Breast Enlargement
3.53	Summary of Special Interest Adverse Events Starting Post-randomization By Baseline Characteristics: Breast Disorders: Breast Tenderness
3.54	Summary of Special Interest Sexual and Breast Adverse Events Starting Post-randomization
3.55	Summary of Sexual and Breast Adverse Events of Special Interest Leading to Study Withdrawal
3.56	Summary of Sexual and Breast Adverse Events of Special Interest Leading to Study Withdrawal: Altered (Decreased) Libido
3.57	Summary of Sexual and Breast Adverse Events of Special Interest Leading to Study Withdrawal: Impotence
3.58	Summary of Sexual and Breast Adverse Events of Special Interest Leading to Study Withdrawal: Ejaculation Disorders
3.59	Summary of Sexual and Breast Adverse Events of Special Interest Leading to Study Withdrawal: Breast Disorders
3.60	Summary of Special Interest Adverse Events Starting Post-randomization: Prostate Cancer
3.61	Summary of Cardiovascular Adverse Events of Special Interest Starting Post-randomization
3.62	Summary of Special Interest Cardiovascular Adverse Events Starting Post-randomization: Acute Coronary Syndrome
3.63	Summary of Special Interest Cardiovascular Adverse Events Starting Post-randomization: Ischemic Cerebrovascular Events
3.64	Summary of Special Interest Cardiovascular Adverse Events Starting Post-randomization: Cardiac Failure
3.65	Summary of Special Interest Cardiovascular Adverse Events Starting Post-randomization: Ischemic Coronary Artery Disorders/Atherosclerosis

3.66	Summary of Special Interest Cardiovascular Adverse Events Starting Post-randomization : Cardiac Arrythmia
3.67	Summary of Special Interest Cardiovascular Adverse Events Starting Post-randomization: Peripheral Vascular Disease
3.68	Summary of Special Interest Cardiovascular Adverse Events Starting Post-randomization: Cardiovascular Events
3.69	Summary of Infrequent Tier 1 Adverse Events of Special Interest Starting Post-randomization
3.70	Summary of Laboratory Data
3.71	Summary of Change from Baseline Laboratory Data
3.72	Summary of Baseline Abnormal Laboratory Values
3.73	Summary of Shift in Laboratory Values: Normal at Baseline to Abnormal at Any Time Post-baseline
3.74	Summary of Shift in Laboratory Values: Normal at Baseline to High at Any Time Post-baseline
3.75	Summary of Shift in Laboratory Values: Normal at Baseline to Low at Any Time Post-baseline
3.76	Summary of Shift in Laboratory Values: Normal or Low at Baseline to High at Any Time Post-baseline
3.77	Summary of Shift in Laboratory Values: Normal or High at Baseline to Low at Any Time Post-baseline
3.78	Summary of Laboratory Data Transitions: Change From Baseline to Final Assessment
3.79	Summary of Baseline Threshold Laboratory Values
3.80	Summary of Threshold Laboratory Values at Any Time Post-baseline
3.81	Summary of Baseline Total PSA Values (ng/ml)
3.82	Summary of Total PSA (ng/ml) at Post-Baseline Visits (LOCF)
3.83	Summary of Total PSA (ng/ml) at Post-Baseline Visits (At Visit)
3.84	Summary of Total PSA Change From Baseline (ng/ml) (LOCF)
3.85	Summary of Total PSA Change From Baseline (ng/ml) (At Visit)
3.86	Summary of Total PSA Percentage Change From Baseline (LOCF)
3.87	Summary of Total PSA Percentage Change From Baseline (At Visit)
3.88	Summary of Post Void Residual Volume at Screening and Baseline

3.89	Summary of Post Void Residual Volume at Each Post-Baseline Visit (LOCF)
3.90	Summary of Post Void Residual Volume at Each Post-Baseline Visit (At Visit)
3.91	Summary of Post Void Residual Volume Change from Baseline (LOCF)
3.92	Summary of Post Void Residual Volume Change from Baseline (At Visit)
3.93	Summary of Post Void Residual Volume Percentage Change from Baseline (LOCF)
3.94	Summary of Post Void Residual Volume Percentage Change from Baseline (At Visit)
3.95	Summary of Gynecomastia Evaluation
3.96	Summary of Change from Baseline Gynecomastia Evaluation
3.97	Summary of Digital Rectal Examination
3.98	Summary of Change from Baseline Digital Rectal Examination
3.99	Summary of Vital Signs
3.100	Summary of Change from Baseline Vital Signs
3.101	Summary of Vital Signs Exceeding Threshold at Baseline
3.102	Summary of Vital Signs Exceeding Threshold at Any Post-Baseline Visit
3.103	Summary of C-SSRS Data
3.104	Listing of C-SSRS Data for Subjects With Suicidal Ideation and/or Behavior

11.15.6. Safety Figures

3.1	Plot of Study Drug Exposure
3.2	Plot of Power to Detect a Difference in Adverse Event Rate for Combination versus Tamsulosin
3.3	Most Common Adverse Events Sorted by Odds Ratio
3.4	Plot of Kaplan-Meier Estimates of Time to First Altered (Decreased) Libido Adverse Event
3.5	Plot of Kaplan-Meier Estimates of Time to First Impotence Adverse Event
3.6	Plot of Kaplan-Meier Estimates of Time to First Ejaculation Disorder Adverse Event
3.7	Plot of Kaplan-Meier Estimates of Time to First Breast Disorder Adverse Event
3.8	Plot of Kaplan-Meier Estimates of Time to First Breast Disorder: Breast Enlargement Adverse Event
3.9	Plot of Kaplan-Meier Estimates of Time to First Breast Disorder: Breast Tenderness Adverse Event
3.10	Plot of Kaplan-Meier Estimates of Time to First Prostate Cancer Adverse Event
3.11	Plot of Kaplan-Meier Estimates of Time to First Acute Coronary Syndrome Adverse Event
3.12	Plot of Kaplan-Meier Estimates of Time to First Ischemic Cerebrovascular Adverse Event
3.13	Plot of Kaplan-Meier Estimates of Time to First Cardiac Failure Adverse Event
3.14	Plot of Kaplan-Meier Estimates of Time to First Ischemic Coronary Artery Disorders/Atherosclerosis Adverse Event
3.15	Plot of Kaplan-Meier Estimates of Time to First Cardiac Arrythmia Adverse Event
3.16	Plot of Kaplan-Meier Estimates of Time to First Peripheral Vascular Disease Adverse Event

3.17	Plot of Kaplan-Meier Estimates of Time to First Cardiovascular Adverse Event
3.18	Plot of Kaplan-Meier Estimates of Time to Death

11.15.7. Health Outcome Tables

Health Outcomes Tables (Population=ITT)	
No.	**Title**
BII Overview and Primary Analysis	
4.1	Summary of BII Imputations
4.2	Summary of BII at Screening and Baseline *includes Visit 1a, Visit 2, Baseline, Baseline for Subjects with BII at each Month n (3, 6, …24)*
4.3	Summary of BII at Each Post-Baseline Visit (LOCF)
4.4	Summary of BII at Each Post-Baseline Visit (At Visit)
4.5	Summary of BII Change from Baseline (LOCF)
4.6	Summary of BII Change from Baseline (At Visit)
Individual BII Questions 1 - 4	
4.7	Summary of BII at Screening and Baseline: Question 1 *includes Visit 1a, Visit 2, Baseline, Baseline for Subjects with BII at each Months 12 and 24*
4.8	Summary of BII: Question 1 (LOCF) *each of the below individual question summaries is in terms of Months 12 and 24 only*.
4.9	Summary of BII: Question 1 (At Visit)
4.10	Summary of BII Change from Baseline: Question 1 (LOCF)
4.11	Summary of BII Change from Baseline: Question 1 (At Visit)
4.12	Summary of BII at Screening and Baseline: Question 2
4.13	Summary of BII: Question 2 (LOCF)
4.14	Summary of BII: Question 2 (At Visit)
4.15	Summary of BII Change from Baseline: Question 2 (LOCF)
4.16	Summary of BII Change from Baseline: Question 2 (At Visit)
4.17	Summary of BII at Screening and Baseline: Question 3
4.18	Summary of BII: Question 3 (LOCF)
4.19	Summary of BII: Question 3 (At Visit)
4.20	Summary of BII Change from Baseline: Question 3 (LOCF)

Health Outcomes Tables (Population=ITT)	
No.	**Title**
4.21	Summary of BII Change from Baseline: Question 3 (At Visit)
4.22	Summary of BII at Screening and Baseline: Question 4
4.23	Summary of BII: Question 4 (LOCF)
4.24	Summary of BII: Question 4 (At Visit)
4.25	Summary of BII Change from Baseline: Question 4 (LOCF)
4.26	Summary of BII Change from Baseline: Question 4 (At Visit)
BII Percentage Change from Baseline	
4.27	Summary of BII Percentage Change from Baseline (LOCF)
4.28	Summary of BII Percentage Change from Baseline (At Visit)
BII Non-Imputed Score Analysis	
	Performed only if RAP Section 11.7 imputation conditions are met; thus, table numbers are not listed.
BPH-Related Health Status	
4.29	Summary of BPH-Related Health Status at Screening and Baseline *includes Visit 1a, Visit 2, Baseline, Baseline for Subjects with BII at each Month n (3, 6, …24)*
4.30	Summary of BPH-Related Health Status at Each Post-Baseline Visit (LOCF)
4.31	Summary of BPH-Related Health Status at Each Post-Baseline Visit (At Visit)
4.32	Summary of BPH-Related Health Status Change from Baseline (LOCF)
4.33	Summary of BPH-Related Health Status Change from Baseline (At Visit)
4.34	Summary of BPH-Related Health Status Percentage Change from Baseline (LOCF)
4.35	Summary of BPH-Related Health Status Percentage Change from Baseline (At Visit)
PAS SFI Overview and Primary Analysis	
4.36	Summary of PAS SFI Imputations
4.37	Summary of PAS SFI at Screening and Baseline *includes Visit 1b, Visit 2, Baseline, Baseline for Subjects with PAS SFI at each Month n (12 and 24)*
4.38	Summary of PAS SFI at Each Post-Baseline Visit (LOCF)

Health Outcomes Tables (Population=ITT)	
No.	**Title**
4.39	Summary of PAS SFI at Each Post-Baseline Visit (At Visit)
4.40	Summary of PAS SFI Change from Baseline (LOCF)
4.41	Summary of PAS SFI Change from Baseline (At Visit)
Individual PAS SFI Questions 1 - 3	
4.42	Summary of PAS SFI at Screening and Baseline: Question 1 *includes Visit 1a, Visit 2, Baseline, Baseline for Subjects with PAS SFI at each Months 12 and 24*
4.43	Summary of PAS SFI: Question 1 (LOCF) *each of the below individual question summaries is in terms of Months 12 and 24 only.*
4.44	Summary of PAS SFI: Question 1 (At Visit)
4.45	Summary of PAS SFI Change from Baseline: Question 1 (LOCF)
4.46	Summary of PAS SFI Change from Baseline: Question 1 (At Visit)
4.47	Summary of PAS SFI at Screening and Baseline: Question 2
4.48	Summary of PAS SFI: Question 2 (LOCF)
4.49	Summary of PAS SFI: Question 2 (At Visit)
4.50	Summary of PAS SFI Change from Baseline: Question 2 (LOCF)
4.51	Summary of PAS SFI Change from Baseline: Question 2 (At Visit)
4.52	Summary of PAS SFI at Screening and Baseline: Question 3
4.53	Summary of PAS SFI: Question 3 (LOCF)
4.54	Summary of PAS SFI: Question 3 (At Visit)
4.55	Summary of PAS SFI Change from Baseline: Question 3 (LOCF)
4.56	Summary of PAS SFI Change from Baseline: Question 3 (At Visit)

11.15.8. Health Outcomes Figures

Health Outcomes Figures (Population=ITT)	
No.	**Title**
4.1	Plot of BII Adjusted Mean Change from Baseline (LOCF)
4.2	Plot of BII Adjusted Mean Change from Baseline (At Visit)
4.3	Plot of BPH-Related Health Status Adjusted Mean Change from Baseline (LOCF)
4.4	Plot of BPH-Related Health Status Adjusted Mean Change from Baseline (At Visit)

11.15.9. ICH and Non-ICH Listings

The following categorizes data listings as ICH (International Conference on Harmonization) used to support critical analyses or non-ICH. The two classifications are assigned with consideration for general regulatory requirements across countries at point of RAP finalization. Changes to these classifications may occur at point of reporting as a result of specific country requirements or requests and will not result in a RAP revision.

ICH	Non-ICH	Title
Study Population		
-	5.1	Listing of Subject Withdrawals During Placebo Run-in Phase
1.1		Listing of Randomized and Actual Treatments
1.2		Listing of Subject Accountability
1.3		Listing of Reasons for Study Withdrawal
1.4		Listing of Subjects with Inclusion/Exclusion Criteria Deviations
1.5		Listing of Important Protocol Deviations
1.6		Listing of Deviations which Require Exclusion from the Per-Protocol Population
1.7		Listing of Demographic Characteristics

ICH	Non-ICH	Title
1.8		Listing of Race Details
	5.2	Listing of Substance Use at Screening
	5.3	Listing of Medical Conditions at Screening
	5.4	Listing of Sexual Function at Screening
	5.5	Listing of Family History of Premature Coronary Artery Disease
	5.6	Listing of Electrocardiogram Results
	5.7	Listing of BPH History
	5.8	Listing of Alpha-Blocker, 5-Alpha-Reductase Inhibitor, and Phytotherapy Usage History
	5.9	Listing of Family History of Breast Cancer and Prostate Cancer
1.9		Listing of Concomitant Medications
1.10		Listing of Relationship Between ATC Level 1, Ingredient, and Verbatim Text
1.11		Listing of Investigational Product Discontinuation
1.12		Listing of Exposure to Study Drug
	5.10	Listing of Study Drug Dispensing
1.13		Listing of Study Drug Compliance
1.14		Listing of Subjects for Whom the Treatment Blind was Broken During the Study

ICH	Non-ICH	Title
Efficacy Listings		
IPSS		
2.1		Listing of IPSS
	5.11	Listing of IPSS MMRM Analysis: SAS Output
	5.12	Listing of IPSS Change from Baseline GLM and Diagnostics: SAS Output for Month 24 (LOCF)
	5.13	Listing of IPSS Change from Baseline GLM and Diagnostics: SAS Output for Month 24 (At Visit)
	5.14	Listing of IPSS Change from Baseline Subgroup Analyses: SAS Output for Month 24 (LOCF)
	5.15	Listing of IPSS Change from Baseline Subgroup Analyses: SAS Output for Month 24 (At Visit)
	5.16	Summary of IPSS Change from Baseline by Center for Months 12 and 24 (LOCF) *Note, this LOCF table and below At Visit table are in Non-ICH listing rather than a table due to high number of centers, many with low enrollment. Output can be moved at point of CSR if necessary.*
	5.17	Summary of IPSS Change from Baseline by Center for Months 12 and 24 (At Visit)
Prostate Volume		
2.2		Listing of Prostate Volume
	5.18	Listing of Prostate Volume Percentage Change from Baseline GLM and Diagnostics: SAS Output for Month 24 (LOCF)
	5.19	Listing of Prostate Volume Percentage Change from Baseline GLM and Diagnostics: SAS Output for Month 24 (At Visit)
	5.20	Listing of Prostate Volume Percentage Change from Baseline Subgroup Analyses: SAS Output for Month 24 (LOCF)
	5.21	Listing of Prostate Volume Percentage Change from Baseline Subgroup Analyses: SAS Output for Month 24 (At Visit)
	5.22	Summary of Prostate Volume Percentage Change from Baseline by Center for Months 12 and 24 (LOCF)
	5.23	Summary of Prostate Volume Percentage Change from Baseline by Center for Months 12 and 24 (At Visit)
Qmax		

ICH	Non-ICH	Title
2.3		Listing of Subjects with Voided Volume less than 125ml
2.4		Listing of Qmax and Voided Volume
	5.24	Listing of Qmax Change from Baseline GLM and Diagnostics: SAS Output for Month 24 (LOCF)
	5.25	Listing of Qmax Change from Baseline GLM and Diagnostics: SAS Output for Month 24 (At Visit)
	5.26	Listing of Qmax Change from Baseline Subgroup Analyses: SAS Output for Month 24 (LOCF)
	5.27	Listing of Qmax Change from Baseline Subgroup Analyses: SAS Output for Month 24 (At Visit)
	5.28	Summary of Qmax Change from Baseline by Center for Months 12 and 24 (LOCF)
	5.29	Summary of Qmax Change from Baseline by Center for Months 12 and 24 (At Visit)
2.5		Listing of Biannual Follow-Up Telephone Contacts
2.6		Listing of Subjects with AUR
2.7		Listing of Subjects with Prostatic Surgery
2.8		Listing of Subjects with Non-Surgical Intervention for BPH
	5.30	Listing of Time to First AUR or BPH-Related Surgery Event
	5.31	Listing of Analysis of Time to First AUR or BPH-Related Surgery: SAS Output
	5.32	Listing of Time to First AUR
	5.33	Listing of Analysis of Time to First AUR: SAS Output
	5.34	Listing of Time to First BPH-Related Surgery Event
	5.35	Listing of Analysis of Time to First BPH-Related Surgery: SAS Output
	5.36	Listing of Subjects With Urinary Tract Infection / Urosepsis
	5.37	Listing of Subjects With Urinary Incontinence
	5.38	Listing of Subjects With Renal Insufficiency

ICH	Non-ICH	Title
Safety		
3.1		Listing of Relationship between System Organ Class and Verbatim Text
3.2		Listing of All Adverse Events
3.3		Listing of All Adverse Events by Onset Period
3.4		Listing of Subject Numbers for Specific Adverse Events
3.5		Listing of Fatal Adverse Events
3.6		Listing of Non-Fatal Serious Adverse Events
3.7		Listing of Adverse Events Leading to Permanent Discontinuation of Study Drug
3.8		Listing of Adverse Events Leading to Withdrawal from the Study
3.9		Listing of Possible Suicidality-Related Adverse Event Data: Event and Description (Section 1 - Section 2)
3.10		Listing of Possible Suicidality-Related Adverse Event Data: Possible Cause(s) (Section 3)
3.11		Listing of Possible Suicidality-Related Adverse Event Data (Section 4)
3.12		Listing of Possible Suicidality-Related Adverse Event Data (Section 5 – Section 8)
3.13		Listing of Relationship between Special Interest Adverse Events and Verbatim Text
3.14		Listing of Adverse Events of Special Interest
	5.39	Listing of Sexual and Breast Adverse Events of Special Interest Leading to Study Withdrawal
	5.40	Listing of Targeted Followup Questionnaire Data
3.15		Listing of Pregnancies in Female Partners of Male Study Participants
	5.41	Listing of Clinical Chemistry Data
	5.42	Listing of Hematology Data
3.16		Listing of Clinical Chemistry Data Exceeding Threshold
3.17		Listing of Hematology Data Exceeding Threshold
	5.43	Listing of Baseline HBsAg and Hepatitis C Antibody Data
	5.44	Listing of Serum PSA Data

ICH	Non-ICH	Title
3.18		Listing of Serum PSA Data Exceeding Upper Limit of Normal
3.19		Listing of Subjects with ALT ≥ 3 times ULN and Bilirubin ≥ 2 times ULN
	5.45	Listing of Post Void Residual Volume
	5.46	Listing of Gynecomastia Data
	5.47	Listing of Digital Rectal Examination Data
	5.48	Listing of Vital Signs Data
3.20		Listing of Vital Signs Exceeding Threshold
3.21		Listing of For-Cause Biopsy Results
	5.49	Listing of C-SSRS Data
3.22		Listing of C-SSRS Suicidal Behavior Details for Subjects With Suicidal Behavior
3.23		Listing of Details of Most Severe Suicidal Ideation at Each C-SSRS Assessment for Subjects With Suicidal Ideation
Health Outcomes		
	5.50	Listing of BPH Impact Index (BII)
	5.51	Listing of BPH-Related Health Status
	5.52	Listing of Problem Assessment Scale of the Sexual Function Inventory (PAS SFI)

11.16. Appendix 16: Mock Shells for Data Displays

Mock table shells are stored in IMMS, within same directory/cabinet as RAP, as separate documents.