treatment period of 16 weeks and 3) a 4-week follow-up period. The trial will be conducted at up to approximately 35 sites in the US.

Study Population:
Approximately 115 subjects will be randomized to treatment.

Inclusion criteria.
Subjects are eligible if they meet the following criteria:
1. Present with BPH-LUTS based on disease diagnostic criteria at visit 1
2. Are men aged 45 years or older at visit 1
3. [redacted]
4. Have a PSA >1.5 and <10.0 ng/mL at visit 1. This PSA blood draw must be performed at least 1 week after any DRE [redacted]
5. Subjects with a PSA ≥4.0 and <10.0 ng/mL must have documentation of a negative histologic biopsy of carcinoma of the prostate within 12 months of screening (visit 1). For subjects aged ≤80 years and who have not undergone any invasive urological procedure within 6 months, if biopsy has not been performed, then 4Kscore Test value must be <7.5% at visit 1
6. Have laboratory tests within normal limits (with the exception of total serum or free testosterone). If laboratory test results are outside normal limits they are determined to be not clinically significant at visit 1
7. Have not received prior treatment with 5-ARIs (finasteride, dutasteride) within the past one year for any indication
8. Have not received herbal BPH preparations within 1 week of visit 1. If the subject is currently on such treatment, a 1-week washout period will be required
9. Agree not to use any 5-ARIs, herbal or experimental treatments for BPH at any time during the study. Subjects on daily PDE5i's, alpha-blockers or anticholinergic medications for BPH should remain on a stable dose during the study, unless a change in dose is medically warranted. Occasional-use PDE5i's for erectile dysfunction (ED) are also permitted at a stable dose and frequency, however should not be taken within 72 hours prior to a study visit
10. Agree to use an acceptable method of birth control during the study and for 60 days after the last dose of IP, unless the female partner is postmenopausal. Postmenopausal is defined as a female >50 years of age and 12 months of amenorrhea, or surgically postmenopausal
11. Are reliable and willing to make themselves available for the duration of the study, and who will comply with the required study and dosing visits and abide by the Clinical Research Site policy and procedure and study restrictions
12. Have given written informed consent

Exclusion criteria.
Subjects are not eligible to participate if they meet any of the following criteria at visit 1:
1. History of any of the following pelvic conditions:
   - radical prostatectomy, pelvic surgery for removal of malignancy, or bowel resection
   - pelvic radiotherapy
   - any pelvic surgical procedure on the urinary tract, including transurethral resection of the prostate (TURP), penile implant surgery
   - lower urinary tract malignancy or trauma

PP	Per Protocol (population)
PSA	prostate-specific antigen
CCI	[redacted]
QoL	quality of life
SAE	serious adverse event
SAP	statistical analysis plan
SARM	selective androgen receptor modulator
TEAE	treatment-emergent adverse event
CCI	[redacted]

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

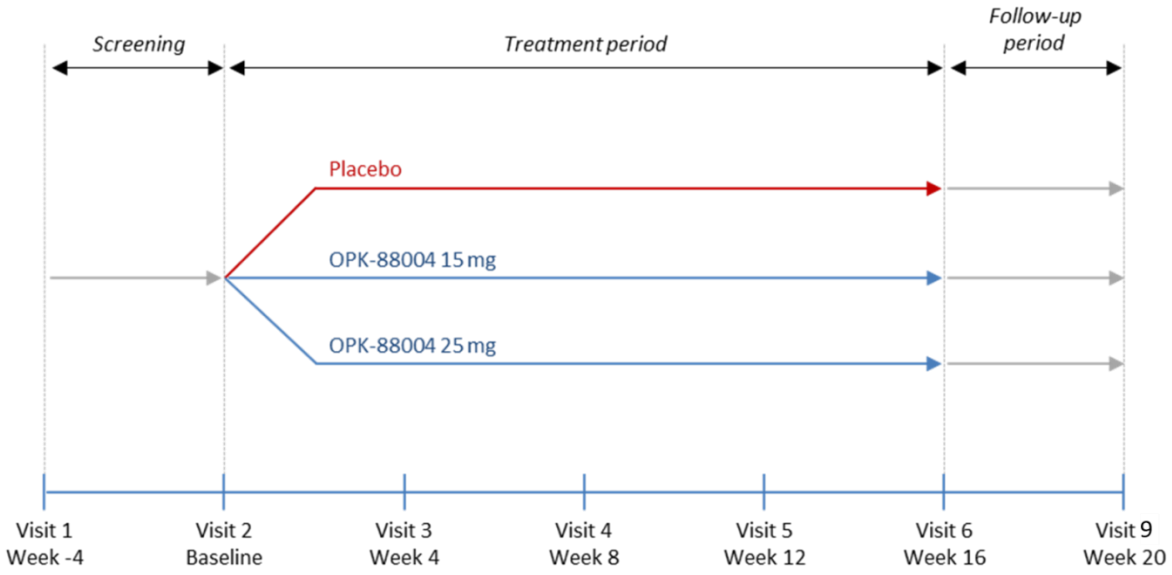
Study SAR-202 is a phase 2 multicenter, placebo-controlled, double-blind trial to evaluate the effect of OPK-88004 doses (OPK-88004 15 mg, or OPK-88004 25 mg) on serum PSA compared to placebo in men with BPH. Approximately 115 men with BPH will be enrolled in the study, randomized 1:1:1 across three arms (placebo, OPK-88004 15 mg, or OPK-88004 25 mg). The trial will be conducted at approximately up to 35 sites within the US.

The study duration for individual subjects will be up to 24 weeks and will include three phases:

- a screening period (up to 4 weeks, including 1-week washout if required),
- a treatment period (16 weeks), and
- a follow-up period (4 weeks)

The design for study SAR-202 is illustrated in Figure 1.

Figure 1 Study Design for SAR-202



* Visit 7 (4 days post final dose) and 8 (7 days post final dose) are for PK blood draw only

Study procedures and timing are outlined in the Study Event Schedule (Appendix 1). Subjects will be randomized and receive their first dose of study drug at visit 2. They will begin the once daily oral dosing regimen and return every 4 weeks to the study site during the 16-week treatment period. Assessments during the study period will include vital signs, laboratory testing, weight, adverse events (AEs), concomitant drugs, and study drug compliance. Efficacy assessments will include serum PSA, LBM and fat mass by DXA scans, CCI [redacted]

3.2 Rationale for Study Design and Control Group

The study is designed to evaluate the effect on PSA, safety and PK of OPK-88004 doses for 16 weeks. Prostate volume will be assessed indirectly by PSA level. Results from the MTOPS (Medical Therapy of Prostatic Symptoms) and CombAT studies [McVary 2005; Roehrborn et al 2010] suggest that men with larger prostate volume may experience earlier LUTS improvement with 5-ARI therapy, so subjects with prostate volume >40 and <80 cm^3 will be investigated in this phase 2 trial. Safety measures including AEs, clinical laboratory measurements (lipids, chemistry, hematology, coagulation, HbA1c, fasting glucose and insulin, hormone panel, CRP, and urinalysis), physical examinations, vital signs, ECGs and semen analysiswill be obtained. A sparse sampling strategy is employed to assess the PK of OPK-88004 in this patient population.

The primary efficacy endpoint in this trial is PSA levels, an indirect measure of prostate volume, after 16 weeks treatment. Size is the most sensitive marker for an effect on the prostate, and reduction in prostate volume is believed to underlie improvement in urinary flow and associated symptoms. This study has been designed to provide over 80% power to detect a 30% reduction of PSA from baseline for any OPK-88004 dose when compared with placebo. Experience with the ARIs finasteride and dutasteride suggest that a reduction in prostate size may be measurable within three months after starting treatment, and that the effect increases further and is thereafter maintained with continued treatment, therefore assessment after 16 weeks treatment is appropriate in this initial study to assess effects on PSA. CCI [redacted] The 16-week treatment period may also provide data on a variety of secondary and other efficacy endpoints, including measures of body composition CCI [redacted].

Androgenic effects of OPK-88004 will be assessed by measurements of LBM and fat mass (by DXA). The selected dose levels may have a positive effect on CCI [redacted] measurements of body composition. CCI [redacted]

3.3 Study Duration and Dates

The study duration for individual subjects will be up to 24 weeks, and will include a screening phase of up to 4 weeks (including 1-week washout if required), a 16-week treatment period and a 4-week follow-up period.

The trial is expected to commence recruitment during 4Q 2017.

4 STUDY POPULATION SELECTION

4.1 Study Population

The trial will be conducted in generally healthy men at least 45 years of age at screening with a medical history of BPH, an enlarged prostate (>40 cm^3 and <80 cm^3 as assessed byTRUS) and an increased serum PSA level.

Eligibility for study enrollment will be based on the results of a screening medical history, physical examination, vital signs, and clinical laboratory tests. Any conditions present at the time of the physical examination and any pre-existing conditions will be documented.

If, in the opinion of the investigator, an ineligible lab test result is due to an error or unexpected circumstance then that parameter can be re-tested once. Subjects who do not initially meet the criteria for participation in this study (screen failures) may be rescreened only at the discretion of the investigator in consultation with the designated medical monitor. The interval between re-screenings should be at least 1 week. Subjects who rescreen must sign a new consent and complete all screening tests under a new subject number to confirm eligibility.

4.2 Inclusion Criteria

Subjects are eligible if they meet the following criteria:

1. Present with BPH-LUTS based on disease diagnostic criteria at visit 1

2. Are men aged 45 years or older at visit 1

[redacted] CCI [redacted]

4. Have a PSA >1.5 and <10.0 ng/mL at visit 1. This PSA blood draw must be performed at least 1 week after any digital rectal exam (DRE) CCI [redacted]

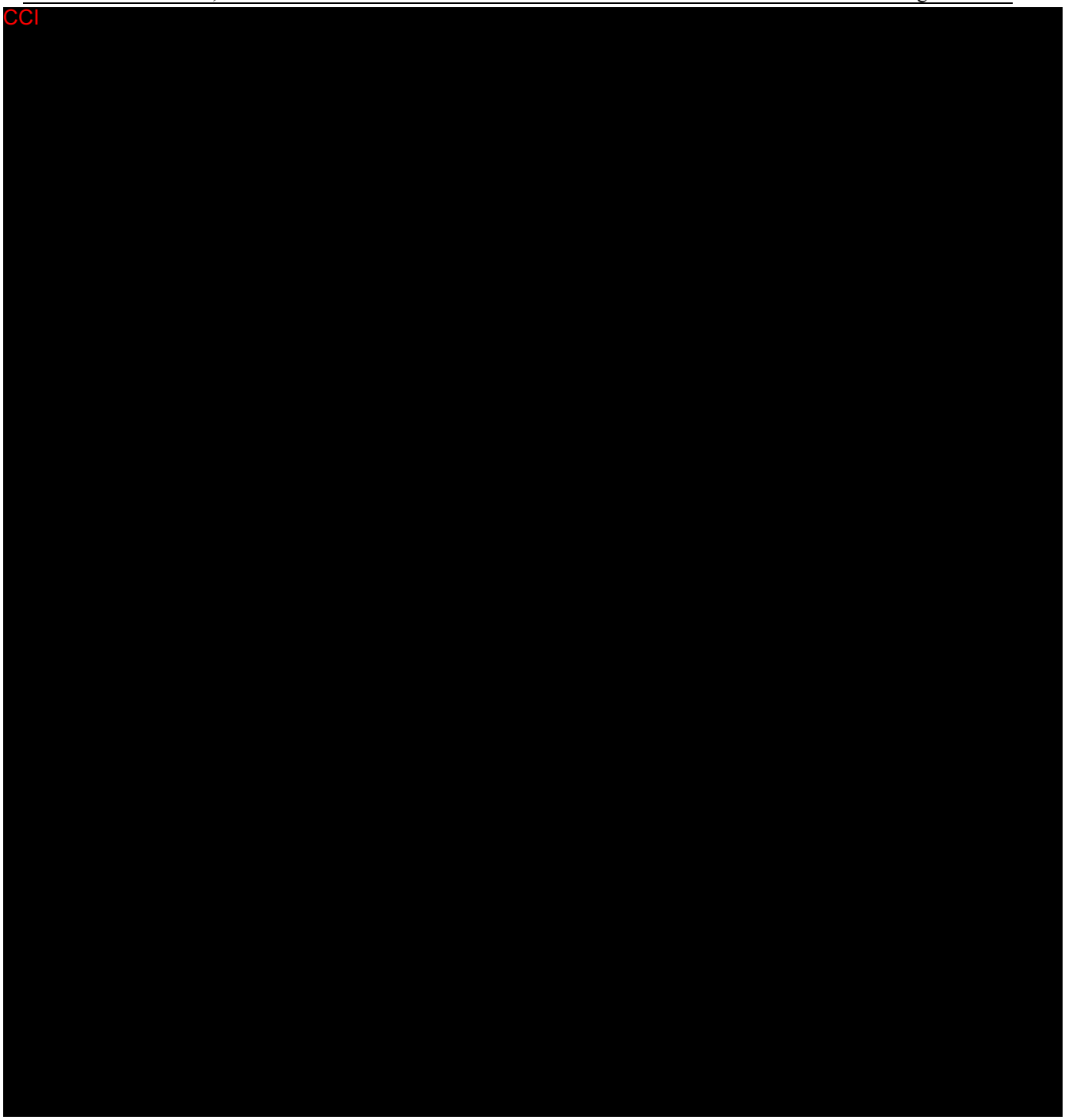
5. Subjects with a PSA ≥4.0 and <10.0 ng/mL must have documentation of a negative histologic biopsy of carcinoma of the prostate within 12 months of screening (visit 1). For subjects aged ≤80 years and who have not undergone any invasive urological procedure within 6 months, if biopsy has not been performed, then CCI [redacted] value must be <7.5% at visit 1

6. Have laboratory tests within normal limits (with the exception of total serum or free testosterone). If laboratory test results are outside normal limits they are determined to be not clinically significant at visit 1

7. Have not received prior treatment with 5-ARIs (finasteride, dutasteride) within the past one year for any indication

8. Have not received herbal BPH preparations within 1 week of visit 1. If the subject is currently on such treatment, a 1-week washout period will be required

CCI



6.8.4 LBM and Fat Mass

LBM and fat mass will be measured by DXA. DXA scans should be obtained in the morning if possible, with the subject fasting at least two hours prior to the scan is recommended. The technologist must confirm that the subject has not undergone and radiologic procedures within the last two weeks (14 days) that required the use of contrast agents. All clothing should be removed (including jewelry) with the exception of undergarments, unless there is the potential they could cause artifact. The subject should be positioned supine on the imaging table, lying

straight, within the field of view. It is important that all repeat DXA scans be performed on the same DXA machine as was used on the previous scan.

A detailed overview of the DXA procedures, as well as training on image acquisition, will be provided by the imaging core lab.

CCI [redacted]

6.9 Appropriateness of Measurements

PSA levels are recognized to reflect prostate size, thus changes in PSA may be used to monitor effects on prostate volume in this trial. CCI [redacted]

Comprehensive safety parameters are assessed in this trial.

6.10 Concomitant Medication Assessments

Medications ongoing at the time of visit 1 as well as any new medication added during the course of the study will be recorded as concomitant medications.

The study coordinator or designee will record concomitant medication history in the source document and eCRF at each visit.

7 DISCONTINUATION

7.1 Discontinuation of Subjects

The criteria for enrollment must be followed explicitly. If a subject who does not meet enrollment criteria is inadvertently enrolled, that subject is discontinued from the trial, and the sponsor or its designee must be contacted and reported to the site's IRB as appropriate.

In addition, subjects will be permanently discontinued from the study drug after consultation with the sponsor-designated medical monitor in the following circumstances:

1. The investigator decides that the subject should be withdrawn. If this decision is made because of a serious adverse event (SAE) or a clinically significant laboratory value, the study drug is to be discontinued and appropriate measures are to be taken

2. Increase in QTc >60 msec above baseline or absolute QTc >500 msec

3. Hematocrit >54% (confirmed by repeat testing within 1 week).

4. When a subject meets one of the following criteria:

    - Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) >8X upper limit of normal (ULN).

    - ALT or AST >5X ULN for more than 2 weeks.

    - ALT or AST >3X ULN and (total bilirubin levels >2X ULN or INR >1.5).

    - ALT or AST >3X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

In addition, subjects will be discontinued from the trial in the following circumstances:

- The sponsor or its designee stops the study or stops the subject's participation in the trial for medical, safety, regulatory or other reasons consistent with applicable laws, regulations and good clinical practice (GCP).

- The subject requests to be withdrawn from the trial.

7.2 Discontinuation of Study Sites

Study site participation may be discontinued if the sponsor, the investigator, or the investigational review board (IRB) of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

7.3 Discontinuation of the Trial

The trial will be discontinued if the sponsor or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations and GCP.

The maximum severity attained for each AE reported will be recorded in the eCRFs.

8.1.2 Relationship

The investigator decides whether they interpret the observed AEs as either related to disease, to the study medication, study procedure or other concomitant treatment or pathologies. To assess the relationship of the AE to the study drug, the following terminologies are defined:

- Definitely related: a direct cause and effect relationship between the study treatment and the AE is likely. The AE follows a reasonable temporal sequence from drug administration, abates on discontinuation of the drug (dechallenge), and/or is confirmed by reappearance of the reaction on repeat exposure (rechallenge)

- Probably related: the AE follows a reasonable temporal sequence from drug administration, abates on discontinuation of the drug (dechallenge), and/or cannot be reasonably explained by the known characteristics of the subject's clinical state

- Possibly related: a cause and effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probable, but is also not impossible. The AE follows a reasonable temporal sequence from drug administration but could have been produced by the subject's clinical state or by other therapies administered to the subject.

- Unrelated: the AE is definitely produced by the subject's clinical state or by other therapies administered to the subject.

All "related", "probably related" and "possibly related" AEs and SAEs will be defined as related to study drug.

8.2 AEs of Special Interest (AESI)

The following Adverse Events of Special Interest (AESIs) of varying clinical significance will be used to determine the tolerability of OPK-88004 doses selected for this clinical trial. All AESIs should be captured and reported via eCRF. All AESIs that meet the definition of an SAE (Section 8.4) must be reported as an SAE.

8.2.1 Clinical Laboratory Testing for Hematology and Lipids

Clinical laboratory testing will be conducted on all subjects as per Schedule of Events (Appendix 1). New abnormal findings or worsening of the baseline conditions detected following treatment visits (visit 2 or later visit) will be recorded as AESIs on the appropriate eCRF page.

8.2.1.1 Hematology

Increase in total number of RBC count will be monitored for potential androgen-induced erythrocytosis. Blinded hematocrit values >54% will be flagged to the investigator and may lead to subject discontinuation (see Section 7.1).

- death,
- life-threatening AE,
- hospitalization or prolongation of existing hospitalization,
- a persistent or significant disability/incapacity,
- a congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.5 Reporting Serious Adverse Events

8.5.1 Initial Report

All SAEs occurring from the time of signed informed consent until 30 days following the last administration of study drug must be reported to Medpace Clinical Safety **within 24 hours** of the knowledge of the occurrence (this refers to any AE that meets any of the aforementioned serious criteria). All SAEs that the investigator considers related to study drug *occurring after the 30-day follow-up period* must be reported to the sponsor.

To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, Medpace Safety personnel will be notified electronically and will retrieve the form.

If the event meets serious criteria and it is not possible to access the EDC system, send an email to Medpace Safety (email address listed below) or call the Medpace SAE hotline (phone number listed below), and fax the completed paper SAE form to Medpace (fax number listed below) within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

Safety Contact Information:

Medpace SAE Reporting Phone Line:
Telephone: CCI [redacted]
Facsimile CCI [redacted]

e-mail: medpace-safetynotification@medpace.com

The investigator is responsible for informing his or her IRB of any SAEs at that site.

A subject experiencing one or more SAEs will receive treatment and follow-up evaluations by the investigator, or they will be referred to another appropriate physician for treatment and

follow-up. Withdrawal from the study and all therapeutic measures will be at the discretion of the investigator at the site.

The investigator must continue to follow the subject until resolution or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment) or the subject dies. The subject will be followed for a minimum of 30 days after study drug administration and subsequently all events will be closed. Female partner pregnancies will be followed until 6 weeks following delivery to determine the outcome.

8.5.2 Follow-up Reports

Within 24 hours of receipt of follow-up information, the investigator must update the SAE form electronically within the EDC system and submit any supporting documentation (e.g., subject discharge summary or autopsy report) to Medpace Clinical Safety using the contacts listed above for initial reporting.

- Blood samples (fasting serum chemistry excluding 25-hydroxyvitamin D, including lipids, hematology and coagulation, HbA1c, fasting glucose, fasting insulin, hormone panel, CRP, PSA and CCI
- CCI
- Urinalysis
- LBM and fat mass (DXA). This assessment should be done within 14 days prior to visit 2. If necessary, DXA rescan can occur up to 7 days after dosing
- Semen analysis. Semen collection can occur any time after screening (visit 1) but must be more than 48 hours prior to PSA CCI on visit 2
- Randomization
- IP dispensed. The first dose must occur at the investigational site and be witnessed for 10 minutes to ensure that an allergic reaction does not occur

9.2.2 Visit 3 (Week 4 ±2 Days) Procedures

The subject will be reminded not to take their daily dose at home on the day of this visit; this will be taken at the site and the actual time of dosing noted

- AE assessment
- Concomitant medication review
- Vital signs
- 12-lead ECG (Obtain after 10 minutes supine rest)
- Blood samples (fasting serum chemistry excluding 25-hydroxyvitamin D and including lipids, hematology and coagulation, HbA1c, fasting glucose, fasting insulin, CRP)
- Urinalysis
- Drug accountability/treatment compliance
- IP dispensed, daily dose taken
- CCI

9.2.3 Visit 4 (Week 8 ± 2 Days) Procedures

- AE assessment
- Concomitant medication review

- Blood samples (fasting serum chemistry including lipids, hematology and coagulation, HbA1c, fasting glucose, fasting insulin, hormone panel, PSA, CCI and CRP)
- PK sample
- Urinalysis

CCI

- Semen analysis. Semen collection should not occur within 48 hours prior to PSA and CCI blood draws and may occur up to 7 days after PSA and CCI blood draws
- Drug accountability

a. Includes medication history
b. Includes weight; height will be measured only at screening
c. Fasting serum chemistry (sodium, potassium, total bilirubin, direct bilirubin, ALP, ALT, AST, GGT, BUN, CK, creatinine, calcium, 25-hydroxyvitamin D (at visits 1 and 6/ET only), albumin, phosphorus) includes fasting lipid panel at visits 1, 2, 3, 4, 6, 9/ET (total cholesterol, TG, HDL cholesterol, direct LDL cholesterol, apolipoproteins A1, A2, B, C3 and A5, lipoprotein (a))
d. When a washout period is required, all lab tests, CCI [redacted] will be conducted after the washout period
e. Hormone panel includes total testosterone, free testosterone (calculated), SHBG, LH, FSH, estradiol and TSH
f. Semen collection can occur any time after screening (visit 1) but must be more than 48 hours prior to PSA and CCI [redacted] on visit 2
g. Additional semen analysis to be conducted 3 months post final dose in those subjects with a decrease in sperm concentration >50% from baseline.
h. Not required if sample not obtained at visit 2
i. CCI [redacted] may be performed at visit 1 in subjects ≤80 years old with PSA ≥4 ng/mL who have not undergone an invasive urological procedure within 6 months and without biopsy within 12 months, per inclusion criterion 5.
j. DXA scans can occur within ±7 days
k. C [redacted] samples: visit 2 : single pre-dose sample (within 1 hour); visit 3, two samples: 1-2 h and 3-5 h post dose; visit 5, single pre-dose (within 1 hour),visit 6: two samples: 3-5 h and 8-10 h post-dose; visit 7: single sample 4 days post final dose; visit 8: single sample 7 days post final dose; ET, single sample

Signature Page for Protocol SAR-202 v8.0

Approval	PPD 12-Nov-2018 15:39:15 GMT+0000

Signature Page for CCI [redacted]

- pelvic surgery or any other pelvic procedure less than 6 months prior to visit 1

2. Lower urinary tract instrumentation (including prostate biopsy) within 6 weeks prior to screening PSA blood draw
3. History of urinary retention or lower urinary tract (bladder) stones within 1 month of visit 1
4. Minimally invasive procedures for BPH, such as prostatic stent, high intensity focused ultrasound (HIFU), holmium laser enucleation of prostate (HoLEP), interstitial laser coagulation (ILC), transurethral electroevaporation of the prostate (TUVP), transurethral microwave thermotherapy (TUMT), transurethral needle ablation (TUNA), photoselective vaporization (PVP), UroLift, within 6 weeks
5. Clinical evidence of urinary tract infection or urinary tract inflammation (including prostatitis)
6. Intravesical obstruction (eg, intravesical median lobe of the prostate)
7. Current neurologic disease or condition associated with neurogenic bladder (eg, Parkinson's disease, multiple sclerosis)
8. History of significant renal insufficiency, defined as receiving renal dialysis or having an estimated creatinine clearance <45 mL/min
9. Active hepatobiliary disease or serologic evidence of active hepatitis A, B, C, hepatitis E or HIV
10. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 2X the upper limit of normal (ULN)
11. Glycosylated hemoglobin (HbA1c) >9%
12. Hematocrit ≥50%
13. HDL-C <35 mg/dL and LDL-C >130 mg/dL
14. QTcB interval >450 msec. For heart rates over 75, the ECG may be repeated after 5 minutes of resting quietly
15. Abnormality in ECG (eg, left bundle branch block, complete right bundle branch block, or delayed intraventricular conduction with a QRS interval >120 msec) that in the opinion of the investigator places the subject at an unacceptable risk for study participation, or subject has implanted pacemaker
16. History of any of the following cardiac/coronary conditions within 90 days:
    - history of myocardial infarction or coronary artery bypass graft
    - percutaneous coronary intervention
    - stroke
17. Any evidence of heart disease (NYHA ≥Class II, Appendix 4) within 6 months, or receiving treatment for congestive heart failure (CHF)
18. Any supraventricular or ventricular arrhythmia with uncontrolled ventricular response (mean heart rate >100 bpm) at rest despite medical therapy
19. Systolic blood pressure >160 or <90 mm Hg or diastolic blood pressure >100 or <50 mm Hg as determined by a sitting measurement (if stress is suspected, retest up to two times under basal conditions), or malignant hypertension
20. Have a history or presence of prostatic carcinoma, as well as any conditions that may be exacerbated by androgenic medications such as (but not limited to) epilepsy, seizures, convulsions, migraine or polycythemia
21. History of cancer within the previous 5 years, except for excised superficial lesions (such as basal cell carcinoma and squamous cell carcinoma of the skin)

1 INTRODUCTION

1.1 Background

Benign prostatic hyperplasia (BPH), characterized by an increase in the size of the prostate, is a complex and progressive disease common in aging men. An estimated 50% of men have BPH by the age of 60 years, and 90% by age 85 [Berry et al 1984; Roehrborn 2005]. Men with BPH have increased prevalence of lower urinary tract symptoms (LUTS) which may require treatment and potentially surgery. In addition, a very large proportion of this patient population with symptomatic BPH have other symptoms such as sexual dysfunction that have been shown to increase with advancing age [Rosen et al 2005].

Mechanical obstruction by the enlarged prostate, dynamic obstruction caused by the tone of the prostatic smooth muscle and the reaction of the bladder are thought to contribute to the symptoms of BPH [Roehrborn 2005]. Men with BPH may experience lower urinary tract symptoms and serious complications of urethral obstruction [Hollingsworth & Wilt 2014]. Histologically, BPH is characterized by an increased number of both epithelial and stromal cells in the periurethral area of the prostate. It is understood that androgens, growth factors, neurotransmitters and other cell interactions play a role in the development of this condition [Cunha et al 2004]. Approved medical therapies for the treatment of the signs and symptoms of BPH include three drug classes: (1) selective alpha-blockers such as terazosin, tamsulosin, doxazosin, and silodosin (2) 5-α-reductase inhibitors (5-ARIs) finasteride and dutasteride 3) phosphodiesterase 5 inhibitor (PDE5i), tadalafil.

While alpha-blockers and PDE5i's provide rapid relief in the form of improved urinary flow rate, their effects do not reduce the overall risk of BPH-related complications. It is known that androgen receptor (AR) signaling plays a key role in development of BPH, and that blockade of this signaling decreases prostate volume and BPH related urinary tract symptoms. 5-ARIs (finasteride and dutasteride) impact the underlying disease by affecting dihydrotesterone, the primary androgen involved in normal and abnormal prostate growth. Through this inhibition, prostate size is decreased, thereby reducing the risk of acute urinary retention and BPH-related surgery while providing symptom control [Andriole et al 2004; Smith & Carlson 2009]. Therefore, actively decreasing the size of the prostate through reduction of androgen signaling arguably plays an important role in the reduction of long-term risks associated with BPH progression. Targeting the AR may therefore provide a reasonable therapeutic approach for treatment of BPH.

OPK-88004 acts as an oral, tissue-selective androgen receptor modulator (SARM), with antagonist effects on the prostate while providing anabolic effects on body composition. In vitro research studies have demonstrated tissue selectivity of OPK-88004 on the human AR (hAR). The proposed mechanisms for the tissue selectivity of SARMs include the role of 5α-reductase, tissue-specific expression of co-regulators, differences in the complexes formed by the AR in anabolic and androgenic tissues, and the tissue-specific role of intracellular signaling cascades [Narayanan et al 2008].

Nonclinical and clinical data supports the use of OPK-88004 to treat the signs and symptoms of BPH in men. In vitro and animal data support that OPK-88004 serves as a potential antagonist to testosterone on the prostate and at similar doses provides anabolic activity on muscle and bone.

9. Agree not to use 5-ARIs, herbal or experimental treatments for BPH, at any time during the study. Subjects on daily PDE5i's, alpha-blockers or anticholinergic medications for BPH should remain on a stable dose during the study, unless a change in dose is medically warranted. Occasional-use PDE5i's for ED are permitted at a stable dose and frequency, however should not be taken within 72 hours prior to a study visit

10. Agree to use an acceptable method of birth control during the study and for 60 days after the last dose of IP, unless the female partner is postmenopausal. Postmenopausal is defined as a female >50 years of age and 12 months of amenorrhea, or surgically postmenopausal

11. Are reliable and willing to make themselves available for the duration of the study, and who will comply with the required study and dosing visits and abide by the Clinical Research Site policy and procedure and study restrictions

12. Have given written informed consent

4.3 Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria at visit 1:

1. History of any of the following pelvic conditions:
   - radical prostatectomy, pelvic surgery for removal of malignancy, or bowel resection
   - pelvic radiotherapy
   - any pelvic surgical procedure on the urinary tract, including transurethral resection of the prostate (TURP), penile implant surgery
   - lower urinary tract malignancy or trauma
   - pelvic surgery or any other pelvic procedure less than 6 months prior to visit 1

2. Lower urinary tract instrumentation (including prostate biopsy) within 6 weeks prior to screening PSA blood draw

3. History of urinary retention or lower urinary tract (bladder) stones within 1 month of visit 1

4. Minimally invasive procedures for BPH, such as prostatic stent, high intensity focused ultrasound (HIFU), holmium laser enucleation of prostate (HoLEP), interstitial laser coagulation (ILC), transurethral electroevaporation of the prostate (TUVP), transurethral microwave thermotherapy (TUMT), transurethral needle ablation (TUNA), photoselective vaporization (PVP), UroLift, within 6 weeks

5. Clinical evidence of urinary tract infection or urinary tract inflammation (including prostatitis)

6. Intravesical obstruction (eg, intravesical median lobe of the prostate)

7. Current neurologic disease or condition associated with neurogenic bladder (eg, Parkinson's disease, multiple sclerosis)

8 SAFETY EVALUATIONS

Investigators are responsible for monitoring the safety of subjects who have entered this trial and for alerting the sponsor or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject. Laboratory values blinded to the investigator (see Section 5.6 and Table 1) will be reviewed by sponsor medical monitor(s) and periodically by the DSMB.

The investigator is responsible for the appropriate medical care of subjects during the study.

The investigator remains responsible for following through an appropriate health care option, AEs that are serious, considered related to the study treatment or the study, or that caused the patient to discontinue before completing the study. The subject should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

In addition to records of observations made at specific times, unexpected signs and symptoms and concomitant medications will be recorded in the clinical trial records throughout the study.

8.1 Adverse Events

All AEs, including SAEs occurring after the subject signs the ICF through the subject's final visit will be reported and monitored. AEs that occur following first administration of study drug are treatment emergent AEs (TEAEs). Any clinically significant (CS) abnormal laboratory results, physical examination findings, ECGs, and vital signs will be reported as an AE.

The investigator is not obliged to follow-up with subjects for AEs or SAEs that begin after study completion, however if an SAE is reported to the investigator after a subject has completed the study, and it is 'reasonably related' to the study drug, then the investigator will report it to the sponsor and its IRB.

Investigators will be instructed to report their assessment of the potential relatedness of each AE to protocol procedures or study drug via the eCRF.

8.1.1 Severity

The intensity of the AE will be rated by the investigator as mild, moderate or severe using the following criteria:

- Mild: Symptoms causing no or minimal interference with usual social and functional activities
- Moderate: Symptoms causing greater than minimal interference with usual social and functional activities
- Severe: Symptoms causing inability to perform usual social and functional activities

It should be noted that the clinical severity and seriousness of an AE are not synonymous, eg, a severe headache is not classified as serious until it meets the required elements as an SAE.

8.2.1.2 Lipid Changes

Fasting lipid panel will be monitored for clinically significant changes in lipids (LDL-C, triglycerides, and apolipoprotein A1 etc). HDL-C values are blinded to the investigator.

8.2.2 Cardiovascular Events

Deaths (CV and non-CV), nonfatal MIs, and nonfatal strokes that occur during the treatment period or follow-up period will be reviewed by the sponsor-designated medical monitor. Investigative sites will also be asked to report any cases of transient ischemic attack (TIA) or hospitalization for unstable angina to the sponsor medical monitor as well to ensure that all true stroke and MI events are captured. Cardiovascular event definitions will be based on the Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials and the ESC/ACCF/AHA/WHF Expert Consensus Document Third Universal Definition of Myocardial Infarction [Thygesen et al 2012].

8.2.3 ECG

After enrollment, if a clinically significant increase in the QT/corrected QT (QTc) interval from baseline or other clinically significant quantitative or qualitative change from baseline is identified, the subject will be assessed by the investigator for symptoms (eg, palpitations, near syncope, syncope) and to determine whether the subject can continue in the study. The investigator or qualified designee is responsible for determining if any change in subject management is needed and must document his/her review of the ECG printed at the time of evaluation. ECGs will be stored at the investigation site. Any treatment emergent clinically significant ECG finding should be reported as adverse event in the eCRF.

8.2.4 Semen Analysis

Since androgens can impact sperm counts, semen analysis is being performed as baseline and at visit 6/ET in subjects willing and able to produce a measurable semen sample. A follow-up semen analyses at 3 months post-treatment will be done in those subjects with a decrease in sperm concentration >50% from baseline.

8.2.5 Testosterone and Steroidal Androgen Events

Subjects will be monitored for fluid retention (edema), sleep disturbances, emotional and psychological effects such as depression and anger, breast enlargement and breast pain, increased acne and increased sex drive (libido).

8.3 PSA

Subjects with PSA increase from baseline >1.4 ng/mL should be re-tested immediately, and if confirmed, repeated in 4 weeks. If this value remains elevated, the subject should be referred to a urologist for further evaluation. The subject may remain on study drug, at the discretion of the investigator.

8.4 Serious Adverse Events

An SAE is defined by the investigator or sponsor as any AE occurring at any dose that results in any of the following outcomes:

9 STUDY ACTIVITIES

9.1 Screening/Visit 1 (Week -4 to Day 0) including 1 week washout if required

Subjects will sign informed consent prior to any study procedures being performed. A 1-week washout period during screening is permitted for subjects on previous BPH therapy (see inclusion criterion 8, Section 4.2). All lab tests, CCI [redacted] will be conducted after completion of the washout period, if a washout is required.

- A signed ICF will be obtained prior to any study-related activities
- Review of inclusion/exclusion criteria
- Medical history and demographics
- Medication history
- General physical examination, vital signs, weight and height
- 12-lead ECG (obtain after 10 minutes supine rest)
- Blood samples (fasting serum chemistry including lipids, hematology and coagulation, HbA1c, fasting glucose, fasting insulin; serology, PSA, CCI [redacted], if applicable)
- Urinalysis
- Urine drugs of abuse screen

CCI [redacted]

- Concomitant medications assessment

9.2 Treatment Period (Week 0 to Week 16)

9.2.1 Visit 2 (Day 1) Procedures

- Review of entry criteria
- AE assessment
- Concomitant medication review
- Physical examination including vital signs

- Physical examination
- Vital signs
- 12-lead ECG (Obtain after 10 minutes supine rest)
- Blood samples (fasting serum chemistry excluding 25-hydroxyvitamin D and including lipids, hematology and coagulation, HbA1c, fasting glucose, fasting insulin, hormone panel, PSA)
- Urinalysis
- Drug accountability/treatment compliance
- IP dispensed

9.2.4 Visit 5 (Week 12 ± 2 Days) Procedures

The subject will be reminded not to take their daily dose at home on the day of this visit; this will be taken after pre-dose PK blood sampling, and the time of dosing noted.

- AE assessment
- Concomitant medication review
- Vital signs
- Drug accountability/treatment compliance
- IP dispensed, dose taken

CCI [redacted]

9.3 End of Treatment -Visit 6 (Week 16 ±2 Days) Procedures

- AE assessment
- Concomitant medication review
- Physical examination
- Vital signs
- 12-lead ECG (obtain after 10 minutes supine rest)
- Blood samples (fasting serum chemistry including lipids, hematology and coagulation, HbA1c, fasting glucose, fasting insulin, hormone panel, PSA, CCI [redacted] and CRP)
- Urinalysis

10 QUALITY CONTROL AND ASSURANCE

A quality assurance audit may be performed by the sponsor and/or its designee at selected sites to verify that the study was conducted in accordance with the protocol, ICH/GCP [International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP)], and applicable SOP and regulations, to ensure that the safety and welfare of subjects are addressed, and to confirm that problems reported by study monitors have been resolved. Verification of study documents and study activities (if applicable) will be conducted to confirm accuracy of recorded data and its analysis. Audit observations and findings will be documented and communicated to appropriate study personnel and management. An inspection may be conducted by regulatory authorities. The investigator must allow direct access to study documents during these inspections and audits.

Monitoring visits will be performed to evaluate study conduct, data integrity, protocol, and GCP compliance.

Each investigator is responsible for the accuracy, completeness, legibility, and timeliness of the data reported. All source documents are to be completed in a neat, legible manner to ensure accurate interpretation of data.

Source documents and laboratory reports will be reviewed to ensure that they are accurate and complete.

10.1 Data Quality Assurance

To ensure accurate, complete, and reliable data, the sponsor or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- provide start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate CRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database

In addition, the sponsor or its representatives will periodically check a sample of the subject data recorded against source documents at the study site. Investigators will maintain study records in a secure location on completion of the study and the file archive location will be provided to the sponsor or its representatives.

Appendix 2. Prohibited Concomitant Medications

This is a representative listing of medications that are specifically excluded per protocol. The list is to serve as a guideline only and is not inclusive of all generic, over-the-counter, or nutraceutical products excluded for this study. Enquiries should be addressed with the sponsor or designee.

5-α- Reductase Inhibitors: finasteride (Proscar®, Propecia®), dutasteride (Avodart™)

Androgens: testosterone (Androderm®) Androgel®, Testoderm®, Testim™, Depo-Testosterone®), methyltestosterone (Testred®)

Anabolic Steroids: oxymethalone (Anadrol-50®), oxandrolone (Oxandrin®)

Antiandrogens: bicalutamide (Casodex®), flutamide (Eulexin®), nilutamide (Nilandron®)

Dehydroepiandrosterone (DHEA): Andromon®, Fibrinase®, Tofipan®

Herbal Supplements: red clover, ginkgo biloba, gotu kola, muira puama, tribulus, damiana, maitake, licorice root, ginseng, hawthorn, wild yam, horny goat weed, Cholest-Natural

OTC steroid supplements: Tren, Epi-Tren, Stakabol, Black Mass Tren Stack

Phytotherapies: Saw Palmetto, Prostata, Yohimbine, Pygeum Africanum

Potent CYP3A4 inhibitors: amiodarone, aprepitant (Emend®), cyclosporine (Gengraf®, Neoral®, Sandimmune®), clarithromycin (Biaxin®), conivaptan (Vaprisol®), chlorzoxazone (Parafon Forte DSC®), chlortrimazole, cimetidine, erythromycin, diltiazem (Cardizem®, Cartia XT®, Dilacor XR®, Taztia XT®), fluvoxamine (Luvoz CR®), fluconazole (Diflucan®), grapefruit products, indinavir (Crixivan®), imatinib (Gleevec®), itraconazole (Sporanox®), ketoconazole, mibefradil, nelfinavir (Viracept®), norfloxacin (Noroxin®), nefazodone, posaconazole (Noxafil®), ritonavir (Kaletra®, Norvir®), saquinavir (Fortovase®), schisandra sphenathera extract, starfruit, telithromycin (Ketek®), troleandomycin (Tao®), verapamil (Tarka®), voriconazole (Vfend®)

CLINICAL TRIAL PROTOCOL: SAR-202

Study Title:	A Randomized, Double-blind, Placebo-controlled Dose-ranging Study of OPK-88004 Once-a-day Dosing for 16 Weeks in Men with Signs and Symptoms of Benign Prostatic Hyperplasia
Study Number:	SAR-202
Study Phase:	Phase 2
Product Name:	OPK-88004
IND Number:	CCI [redacted]
Indication:	Benign Prostatic Hyperplasia (BPH)
Investigators:	Multicenter
Sponsor:	Transition Therapeutics Ireland Ltd. (a subsidiary of OPKO Health, Inc.)
Sponsor Contact:	Dr. PPD [redacted] PPD [redacted] Development OPKO Health, Inc. 4400 Biscayne Blvd Miami, FL 33137 Email: PPD [redacted] Phone: PPD [redacted]
Medical Monitor:	Dr. PPD [redacted] Medpace PP [redacted] Medical Department 5375 Medpace Way Cincinnati, OH 45227 Email: PPD [redacted] Phone: PPD [redacted]

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