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.)
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Version Number	Date
1	27 September 2017
2	30 October 2017
3	06 February 2018
4	22 March 2018
5	25 June 2018
6 (not implemented)	19 October 2018
7	09 November 2018

SYNOPSIS

Sponsor:
Transition Therapeutics Ireland Ltd. (a subsidiary of OPKO Health, Inc.)

Name of Finished Product:
OPK-88004 capsules

Name of Active Ingredient:
OPK-88004 (carbamic acid, *N*-[(2S)-7-cyano-1,2,3,4-tetrahydro-4-(2-pyridinylmethyl) cyclopent[*b*]indol-2-yl]-,1-methylethyl ester)

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

Primary Objectives:
1. To evaluate the effect of 15 mg and 25 mg OPK-88004 daily for 16 weeks on serum PSA compared with placebo
2. To evaluate the safety of 15 mg and 25 mg OPK-88004 daily for 16 weeks compared with placebo

Secondary Objectives:
1. To assess the effects of OPK-88004 on body composition by DXA, specifically lean body mass and fat mass
2. CCI

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Study Design:
This is a randomized, double-blind, placebo-controlled phase 2 trial to evaluate the effect of OPK-88004 doses on serum PSA compared to placebo from baseline to week 16. 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). A sample size of 28 completed subjects per treatment group will provide 80% power to detect a 30% reduction of PSA from baseline for any OPK-88004 dose when compared with placebo. The trial consists of three phases: 1) a 4-week screening period, including 1-week washout if required, followed by 2) a

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

- 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)

22. History of drug, alcohol, or substance abuse within 6 months
23. Have an alcohol intake of ≥3 units/day or ≥14 units/week during the study (1 unit = 12 ounces of beer, 5 ounces of wine, 1.5 ounces of distilled spirits)
24. Any condition that would interfere with subject's ability to provide informed consent or comply with study instructions, would impair ability to perform the study assessments, or would place subject at increased risk, or might confound the interpretation of the study results
25. Current treatment with androgens, antiandrogens, estrogens, or anabolic steroids within the prior 1 month. Any prior or current treatment with LHRH agonists/antagonists
26. Current treatment with potent CYP3A4 inhibitors such as itraconazole or ritonavir
27. Have taken prescription or over-the-counter medications to promote weight loss within the prior 3 months
28. Any prior use of OPK-88004
29. Allergic to any component of OPK-88004

Test Product, Dose, and Mode of Administration:
OPK-88004 capsules or matching placebo will be taken orally daily for 16 weeks at 0, 15 or 25 mg.

Duration of Treatment:
Each subject may participate in the study for up to 24 weeks. OPK-88004 will be administered for 16 weeks.

Efficacy Assessments:
1. Serum PSA

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Safety Assessments:
1. AEs
1. Clinical laboratory measurements (lipids, chemistry, hematology, coagulation, HbA1c, fasting glucose and insulin, hormone panel, CRP, and urinalysis)
2. Physical examinations
3. Vital signs
4. ECGs
5. Semen analysis

Statistical Methods:
Approximately 115 subjects will be enrolled in the study, randomized 1:1:1 across three arms (placebo, OPK-88004 15 mg, or OPK-88004 25 mg). The primary efficacy objective is to evaluate the ability of OPK-88004 doses to reduce PSA compared to placebo from baseline to week 16. Based on the historical data, the treatment differences of percent reduction of PSA from baseline to week 16 endpoint between any OPK-88004 dose and placebo is over 30% with common standard deviation <40%. With a sample size of 28 completed subjects per

treatment group, the power for PSA reduction for any OPK-88004 dose compared to placebo is over 80%.

The primary efficacy endpoint will be analyzed in the mITT Population using a mixed-model repeated-measures (MMRM). Sensitivity analysis of the percent change from baseline of PSA to week 16 endpoint will be performed using ANCOVA. Descriptive summary statistics will be provided for all safety variables.

CCI [redacted]

Efficacy analyses will be repeated on the PP Population to test robustness of the analysis on the mITT Population

CCI [redacted]

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.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
AESI	adverse event of special interest
5-ARIs	5-alpha reductase inhibitors
BPH	benign prostatic hyperplasia
BOO	bladder outlet obstruction
CSR	clinical study report
DRE	digital rectal exam
DXA	dual energy X-ray absorptiometry
ECG	electrocardiogram
ET	early termination (visit)
GCP	Good Clinical Practices
hAR	human androgen receptor
HDL-C	high-density lipoprotein cholesterol
ICH	International conference on Harmonisation
IP	investigational product
IPSS	international prostate symptom score
LBM	lean body mass
LDL-C	low-density lipoprotein cholesterol
LHRH	luteinizing hormone releasing hormone
LOAEL	lowest observed adverse effect level
LOCF	last observation carried forward
LUTS	lower urinary tract symptoms
mITT	modified Intent-to-Treat (population)
NOAEL	no observed adverse effect level
P1NP	N-terminal propeptide of procollagen type 1
PD	pharmacodynamics
PDE5i	phosphodiesterase 5 inhibitor
PK	pharmacokinetic

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]

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.

In an orchidectomized rat model treatment with OPK-88004 at 3 to 30 mg/kg/day in the presence of testosterone demonstrate that OPK-88004 antagonizes the androgenic effects of testosterone on the prostate by decreasing prostate and seminal vesical weights. Further, in chronic toxicology studies OPK-88004 decreased prostate weight in naïve, non-orchidectomized rats and dogs. The loss in weight was more pronounced in dogs relative to rats. In dogs treated with doses from 3 to 300 mg/kg/day, a decrease of 60-80% in prostate weight was associated with prostate atrophy at 6 and 12 months. CCI [redacted] These observations were supported in a phase 2 trial, where treatment of elderly men for 12 weeks at 5 mg daily showed a trend of decrease in PSA levels. These data suggest that OPK-88004 acts as a selective androgenic antagonist on the prostate. The treatment with OPK-88004 may be expected to improve lower urinary tract symptoms associated with BPH and reduce the risk of urinary retention by affecting the excessive growth of the prostate.

In a gonadectomized rodent model, OPK-88004 demonstrated anabolic effects on muscle and osteoanabolic properties on bone mass and biomechanical strength. In a multiple dose trial, healthy subjects exposed for 28 days to OPK-88004 demonstrated clinically and statistically significant increases in LBM and calf area. This was accompanied by changes in bone biochemical biomarkers consistent with a bone anabolic increase. In a phase 2 trial in men with ED, OPK-88004 has shown improvement on body composition parameters including lower extremity muscle strength and power, LBM and fat mass after 12 weeks of treatment. The concomitant effect of OPK-88004 on LBM and muscle strength may decrease loss of physical function and fatigue common in older men with BPH.

Human clinical studies show an acceptable safety profile for OPK-88004 in that observed effects were considered monitorable and reversible.

Development of an androgen that can effectively treat the distressing symptoms of BPH and improve body composition changes would be an innovative clinically beneficial therapeutic option for men with moderate to severe BPH-LUTS and enlarged prostate. As the US population ages both the incidence and prevalence of BPH is increasing and subsequently there is a greater need for suitable treatment options [Parsons 2010].

1.2 Nonclinical Studies

OPK-88004 is a potent and selective modulator of the hAR with no significant cross reactivity against other nuclear hormone receptors. In toxicology studies, OPK-88004 was generally well tolerated for up to 6 months in rats and for up to 12 months in dogs, with no compound-related mortality or adverse clinical signs. OPK-88004 demonstrated no drug-related effects at doses up to 1000 mg/kg in gastrointestinal (GI), renal, pulmonary, and cardiovascular function studies.

OPK-88004-induced pharmacological effects are consistent with agonist activity on the AR in repeat-dose toxicological studies. Noteworthy effects of OPK-88004 included reversible changes in the reproductive cycle and in reproductive tissues of males and females. Functional effects related to these changes in rats included reduced sperm count, decreased fertility, and reduced embryo viability. OPK-88004 was teratogenic in mice. Overall, treatment-related findings were, in general, consistent with effects on androgen-responsive tissues and alterations in the hypothalamic-pituitary-gonadal (HPG) axis and reproductive cycling. Safety

pharmacology studies of up to 6-month duration indicate a high safety margin for the drug. OPK-88004 was negative in a battery of genotoxicity tests.

1.3 Previous Human Experience

To date, six clinical trials have been completed with OPK-88004, five phase 1 clinical trials and one phase 2 clinical trial. A total of 353 subjects have been exposed to OPK-88004 of which 200 subjects have received concurrent doses of OPK-88004 and tadalafil (5 mg and 10 mg tablet) once a day. Across these studies, OPK-88004 was well tolerated with a satisfactory safety profile at single doses up to 1000 mg, at multiple doses up to 75 mg for 28 days and at 5 mg for 12 weeks. Once-daily treatment of combination of OPK-88004 with 5 mg and 10 mg tadalafil for 12 weeks was also well tolerated with a satisfactory safety profile.

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Potential reproductive effects were monitored clinically by sperm evaluation in the phase 2 trial. Treatment differences across the treatment groups were not considered to be clinically meaningful.

In clinical studies, OPK-88004 showed improvement on body composition parameters. In a multiple dose study healthy subjects exposed for 28 days to OPK-88004 demonstrated clinically and statistically significant increases in LBM and calf area. This was accompanied by changes in bone biochemical biomarkers consistent with a bone anabolic increase. Empirical pharmacodynamics models demonstrated a positive exposure-response relationship for LBM and N-terminal propeptide of procollagen type 1 (P1NP). In a phase 2 trial, OPK-88004 showed improvement on body composition parameters, lower extremity muscle strength and power, LBM, fat mass and bone mineral density and biochemical biomarkers after 12 weeks of treatment. Significant increase in LBM and lower extremity muscle power (measured by the stair climb) was observed at the 5 mg dose.

Results from clinical studies completed to date suggest that OPK-88004 acts as a selective AR modulator with antagonist effect on the prostate and agonist effects on some tissues, supporting the data generated in animal models.

1.4 Rationale for the Study

OPK-88004 has demonstrated the potential to reduce prostate size that can prevent progression of LUTS secondary to BPH and reduce the risk of urinary retention. Additionally, the

concomitant effect of OPK-88004 on LBM and muscle strength may decrease loss of physical function and fatigue common in older men. Human clinical studies show a favorable safety profile for OPK-88004 in that observed effects were considered monitorable and reversible. These findings formed the basis for the proposed evaluation of OPK-88004 as a treatment for the signs and symptoms associated with BPH.

In this first trial for this indication, the effects of OPK-88004 on PSA will be assessed in a BPH patient population with PSA levels of >1.5 ng/mL and prostate volumes >40 cm^3 and <80 cm^3 and signs and symptoms of BPH. Serum PSA levels and safety parameters will be the primary endpoints. CCI [redacted] The trial will evaluate the safety of two doses of OPK-88004 on this patient population. CCI [redacted] The trial is double-blinded to permit assessment of more subjective markers of safety compared to placebo treatment. Information available for the 5-ARI dutasteride suggests that effects on prostate volume may be observed within three months of treatment. The length of treatment in this trial (16 weeks) is thus adequate to observe changes in PSA, reflecting changes in prostate volume.

1.4.1 Rationale for Dose Selection

Based on nonclinical and clinical data on effect of OPK-88004 on prostate size, clinical doses selected to be administered in this trial are 15 mg or 25 mg daily for 16 weeks. These doses are expected to result in a clinically meaningful reduction in PSA levels and prostate size. A reduction in prostate volume of ≥15% has been reported to be associated with clinically significant improvement in clinical scores and maximum urinary flow rate [Gormley GJ 1992].

Prostate size has not been measured in previous clinical trials with OPK-88004, however PSA data obtained from clinical studies support the selected dose levels. A trend of decrease in PSA levels relative to placebo was observed in healthy males exposed to OPK-88004 at doses of 15 and 25 mg daily for 4 weeks (study GPBC). In study GPEC, treatment of elderly men with OPK-88004 at 5 mg daily showed a trend of decrease in PSA levels in those subjects with baseline levels of PSA ≥2.5 ng/mL, indicative of prostate hyperplasia. There was no effect in this study of 1 mg OPK-88004 following 12 weeks treatment.

Population PK modeling showed that dose levels of 15 and 25 mg will provide sufficiently separated exposure profiles.

For all of the safety pharmacology, general toxicology and reproductive toxicology studies, safety margins of at least 4-fold are in place with the exception of developmental toxicity in mice, which is 0.6-fold.

2 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives of this study are:

1. To evaluate the effect of 15 mg and 25 mg OPK-88004 daily for 16 weeks on serum PSA compared with placebo
2. To evaluate the safety of 15 mg and 25 mg OPK-88004 daily for 16 weeks compared with placebo

2.2 Secondary Objectives

The secondary objectives of this study are:

1. To assess the effect of OPK-88004 on body composition by DXA, specifically LBM and fat mass
2. To assess PK of OPK-88004 based on a sparse sampling strategy

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3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

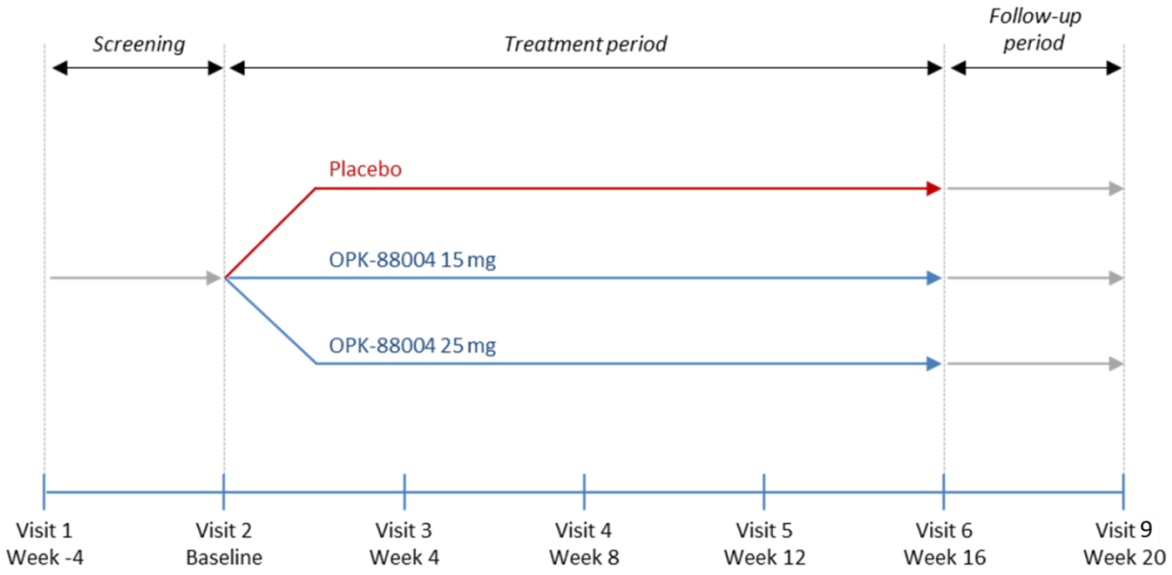
Study SAR-202 is a phase 2 multicenter, placebo-controlled, double-blind trial to evaluate the effect of OPK-88004 doses (OPK-88004 15 mg, or OPK-88004 25 mg) on serum PSA compared to placebo in men with BPH. Approximately 115 men with BPH will be enrolled in the study, randomized 1:1:1 across three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

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. 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 are 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)

22. History of drug, alcohol, or substance abuse within 6 months

23. Have an alcohol intake of ≥3 units/day or ≥14 units/week during the study (1 unit = 12 ounces of beer, 5 ounces of wine, 1.5 ounces of distilled spirits)

24. Any condition that would interfere with subject's ability to provide informed consent or comply with study instructions, would impair ability to perform the study assessments, or would place subject at increased risk, or might confound the interpretation of the study results

25. Current treatment with androgens, antiandrogens, estrogens, or anabolic steroids within the prior 1 month. Any prior or current treatment with LHRH agonists/antagonists

26. Current treatment with potent CYP3A4 inhibitors such as itraconazole or ritonavir

27. Have taken prescription or over-the-counter medications to promote weight loss within the prior 3 months

28. Any prior use of OPK-88004

Allergic to any component of OPK-88004

5 STUDY TREATMENT(S)

5.1 Randomization

Subjects who have completed the screening visit and meet all of the inclusion and none of exclusion criteria are randomized into the study on day 1. Randomized treatment assignment and randomization numbers are assigned via IWRS/IVRS. Randomization is stratified by prostate volume <60 cm^3 or ≥60 cm^3 and LUTS severity (total IPSS [Q1-Q7] of <16 or ≥16). Following randomization, study drug will be dispensed in a double-blind manner. The sponsor and all clinical site personnel (investigator, pharmacist, etc) are blinded to the treatment group for each subject. Subjects also are blinded to the treatment they receive.

5.2 Description of Treatment(s)

OPK-8804 and matching placebo are provided in HDPE bottles with child-resistant closures containing 30 capsules per bottle (see Section 5.9).

5.2.1 OPK-88004

Dosage form: capsule for oral administration

Dose strength: 15 mg and 25 mg per capsule

Description: **s**ize 2 white gelatin capsule

Nonactive components: pregelatinized starch, dimethicone

Storage conditions: room temperature (15 to 30ºC, 59 to 86 ºF)

5.2.2 Placebo

Dosage form: capsule for oral administration

Dose strength: 0 mg per capsule

Description: **s**ize 2 white gelatin capsule

Nonactive components: pregelatinized starch, dimethicone (capsule contents)

Storage conditions: room temperature (15 to 30ºC, 59 to 86 ºF)

5.3 Treatments Administered

Study drug should **NOT** be administered to individuals known to be allergic to any component of the drug. All subjects should be observed for allergic reaction following study drug administration. All allergic reactions will be documented as AEs in the source documents and the electronic case report forms (eCRF).

On day 1 (visit 2), eligible subjects will be randomized 1:1:1 to one of three treatment arms, namely 0 mg (placebo), 15 mg or 25 mg OPK-88004. Subjects will receive one bottle of study drug at visits 2, 3, 4 and 5.

Subjects will be instructed to contact the investigator as soon as possible if he has a complaint or problem with the study drug so that the situation can be assessed.

5.4 Selection and Timing of Dose for Each Patient

Subjects will be instructed to take one dose (1 capsule) of study drug with water at approximately the same time each morning, **except for visits 3 and 5**. The dose may be taken with or without food. At visits 3 and 5, the subject will take the dose of study medication while at the site in order to facilitate PK sampling.

5.5 Method of Assigning Patients to Treatment Groups

Enrollment and assignment to investigational product will be accomplished using IWRS/ IVRS (an automated web randomization system) in a 1:1:1 ratio.

5.6 Blinding

Capsules used in the study will be identical in appearance to maintain double-blind status. Study drug will be managed using IVRS/IWRS. Each user will have a unique username and passcode to access the system. In an emergency, when knowledge of the treatment assignment for the subject is essential for the clinical management or welfare of the subject, the Investigator may unblind the subject. Prior to unblinding, the investigator should make every effort to contact the sponsor or designee before proceeding with the unblinding process if possible. If a subject's treatment assignment is unblinded without sponsor or designee's prior knowledge, the sponsor must be notified immediately.

Each site will be provided with a sealed envelope containing a six-digit code that can be entered into the IVRS/IWRS to unblind a subject's treatment assignment.

To preserve the double-blinding of the study a minimum number of sponsor personnel will have access to the randomization scheme and treatment assignments before the study is complete.

The investigator will be blinded to post-randomization laboratory values for HDL-C, hematocrit, hemoglobin, testosterone (total and free), and PSA. PSA increases from baseline >1.4 ng/mL and hematocrit values >54 % will be flagged to investigators.

5.7 Concomitant Therapy

Treatment with medications that are excluded in the entry criteria is not permitted. None of the excluded medications may be taken during the study without the approval of the investigator and sponsor. Since OPK-88004 is metabolized primarily by CYP3A4, inhibition of this enzyme may result in increased plasma drug concentrations. As such, concomitant use of potent inhibitors of CYP3A4 is prohibited. A list of prohibited medication is provided in Appendix 2.

Doses of other prescription medications for treatment of concurrent medical conditions should remain stable during the study whenever possible.

If the need for additional concomitant medication arises, inclusion or continuation of the patient may be at the discretion of the investigator after consultation with the sponsor- designated medical monitor.

Non-steroidal anti-inflammatory medications (including aspirin and acetaminophen), cough suppressants, antihistamines, vitamin/mineral supplements, antibiotics, and topical ointments may be used on an as-needed basis.

5.8 Restrictions

Meals–Subjects shall fast for at least 8 hours overnight prior to all visits except for visit 5 and PK follow up visits.

Subjects should be instructed to continuing their pre-study diet and activity levels.

Blood donation – Study participants should be instructed not to donate blood or blood products during the study or for 8 weeks following the study.

Calcium Supplements – Subjects should be instructed not to take calcium supplements on the day of the DXA scan.

Contraception – Male subjects or their female partners of child-bearing potential must use acceptable contraception during intercourse throughout the treatment period and for 60 days after the last dose of IP.

Acceptable contraception includes male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate), oral, injected or implanted hormonal methods of contraception, intrauterine device or implant, and barrier methods of contraception (condom or occlusive cap, diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository. The use of barrier contraceptives should always be supplemented with the use of a spermicide.

5.9 Packaging and Labeling

OPK-88004 is supplied for the proposed clinical trial as capsules packaged in 30-count white, induction sealed high density polyethylene (HDPE) bottles with child-resistant closures, and should be stored at room temperature.

Clinical trial materials will be labeled according to regulatory requirements. The labels will include protocol number, name of sponsor, investigational statement, storage conditions and instructions for use. Bottles will be assigned numbers that are linked to the randomization scheme through the IWRS/IVRS.

Bottles should **not** be dispensed if the seal of the primary package appears compromised.

5.10 Storage and Accountability

While at the study site, study drug bottles will be stored at controlled room temperature (15 - 30^{o}C, 59 - 86^{o}F) in the supplied packaging, with access granted to authorized personnel only.

All sites must ensure that study drug has been kept under required conditions prior to dispensing. A temperature log recording the daily storage conditions will be maintained at each site for study drug. In the case of temperature excursions, product should not be dispensed, and the

investigator or designee should contact the clinical monitor as soon as possible to receive further instruction.

Accountability for study drug, from receipt until final reconciliation and return of drug by the monitor or other sponsor designee will be the responsibility of the investigator or designee. The investigator or assigned designee(s), will maintain study drug accountability records for study drug throughout the course of the study. Specifically, the investigator or assigned designee will confirm that all study drug supplies are received intact and in the correct amounts per the shipping forms. This will be documented by signing and dating the shipping forms and providing a copy to the sponsor or designee. A study drug accountability and dispensing log will record the study drug disposition, including dates, quantity of drug received, to whom dispensed (participant-by-participant accounting), and accounts of any drug accidentally destroyed. The site's running inventory of study drug supplies will be verified routinely throughout the course of the study. All opened and unopened containers of study drug are to be retained at the site until the sponsor or designee has performed a complete verification of the dispensation, following which study drug will be returned to the sponsor or designee.

At the conclusion of the study, a final inventory will be performed by the investigator (or designee) and verified by the study monitor. Any discrepancies identified will be indicated, with a specific explanation of each discrepancy. The investigator (or designee) must return all unused medication in accordance with the sponsor's instructions, and a copy of the clinical supplies return documentation will be returned to the sponsor or designee. Drug accountability records, clinical drug supply receipts, and returns must be maintained by the investigator.

5.11 Materials and Supplies

The sponsor or assigned designee will supply vacutainers, blood collection tubes, labels, boxes with labels for storage of serum and plasma samples and all necessary shipping supplies/containers. The investigator will supply all phlebotomy and centrifugation equipment including biohazard and/or safety supplies. The investigator will ensure that all biohazard wastes are disposed of in accordance with investigator site SOPs and local regulations.

6 STUDY PROCEDURES

6.1 Medical History and Physical Examination

The physical examination will be performed by a qualified personnel. A detailed medical history, vital signs (include systolic and diastolic blood pressure, heart rate and respiratory rate), height, weight and 12-lead ECG will be obtained at visit 1.

6.2 ECG Collection and Reporting

For each patient, 12-lead ECGs will be collected according to the schedule of events (Appendix 1). 12-lead digital ECGs will be obtained after 10 minutes in supine rest. Whenever vital signs, 12-lead ECGs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, and then blood draws. Skin preparation should be thorough and electrodes should be placed according to standard 12-lead ECG placement.

ECGs will be digitally recorded and printed on paper. The printed paper ECG will be used for "real time" bedside ECG assessment by the investigator (or designee) who will be responsible for the overall interpretation, determination of the clinical significance, and subject eligibility based on the ECG findings. ECG interpretation categories are: Normal ECG, Abnormal ECG – not clinically significant, Abnormal ECG – clinically significant ECG. The original ECGs will be retained in the subject's records at the site. All digital ECG records will also be submitted to the cardiovascular core lab, which will perform the digital ECG analysis and interpretation in this study using standard methodology. If the central reviewer identifies an abnormality, per the study alert criteria, the investigator will be notified who will review the ECG and report any AEs as necessary.

The following variables will be reported: HR, RR, PR, QRS, QT, QTcB, and QTcF intervals. The investigator may add extra 12-lead ECG safety assessments if there are any abnormal findings or if the investigator considers it is required for any other safety reason.

6.3 Semen Analysis

A semen analysis (total sperm count, sperm concentration, sample volume and pH, sperm motility and morphology) will be performed at baseline (visit 2) and at the end of treatment (visit 6) or early termination (ET) for subjects willing and able to produce a measurable semen sample. Local procedures will be followed. A follow-up semen analysis at 3 months post-treatment will be done in those subjects with a decrease in sperm concentration >50% from baseline.

6.4 Clinical Laboratory Tests

6.4.1 Laboratory Parameters

Clinical laboratory tests to be assessed are indicated in Table 1.

Table 1 List of Laboratory Tests

Hematology:

Hematocrit (Hct)[a]
Hemoglobin (Hgb)[a]
Mean corpuscular hemoglobin (MCH)
Mean corpuscular hemoglobin concentration (MCHC)
Mean corpuscular volume (MCV)
Platelet count
Red blood cell (RBC) count
White blood cell (WBC) count with differential

Urinalysis:

Glucose
Urine leukocyte esterase
Occult blood
Nitrite
pH
Protein
If an abnormal value is observed on the urine dipstick test, the sample may be further analyzed with urine microscopy

Serology:

Hepatitis A (IgM) antibody
Hepatitis B surface antigen
Hepatitis C antibody
Hepatitis E (IgM) antibody
HIV

Sex hormone panel:

Sex hormone binding globulin (SHBG)
Luteinizing hormone (LH)
Follicle-stimulating hormone (FSH)
Total serum testosterone and free serum testosterone, calculated[a]
Estradiol
Thyroid-stimulating hormone (TSH)

Semen Analysis

pH
Volume
Total sperm count
Sperm concentration
Motility
Morphology

Serum Chemistry:

Albumin (ALB)
Alkaline phosphatase (ALK-P)
Alanine aminotransferase (ALT; SGPT)
Aspartate aminotransferase (AST; SGOT)
Blood urea nitrogen (BUN)
Calcium
25-hydroxyvitamin D
Creatinine
Creatine kinase
Gamma-glutamyl transferase (GGT)
Glucose, fasting
Phosphorus
Potassium
Sodium
Total bilirubin
Direct bilirubin

Coagulation:

Prothrombin time (PT)
Activated partial thromboplastin time (PTT)
INR

Lipid Panel (fasting):

Total cholesterol
Triglycerides
HDL cholesterol[a]
Direct LDL cholesterol
Apolipoprotein A1
Apolipoprotein A2
Apolipoprotein A5
Apolipoprotein B
Apolipoprotein C3
Lipoprotein (a)

Miscellaneous

Hemoglobin A1c (HbA1c)
C-reactive protein (CRP)
Prostate-specific antigen (PSA)[a]
Insulin, fasting
Urine drug screen
CCI

a The investigator is blinded to post-randomization values

6.4.2 Sample Collection, Storage, and Shipping

Collection, processing, storage and shipping procedures will be performed in accordance with the instructions provided by the central laboratory. Detailed instructions will be provided separately from this protocol in the laboratory manual. Blood samples will be collected and analyzed for clinical laboratory and PK analysis.

Additional blood draws may be needed for unscheduled visits. Single redraws for samples resulting in values outside eligibility criteria ranges may be performed during screening, and the medical monitor may be consulted as necessary. Missed samples should be drawn whenever possible, and laboratory samples not collected should be noted as a protocol deviations and reported to the site's IRB if necessary (see Section 12.8). The investigator will provide a limited access, temperature monitored space for the study drug and a -20°C or -70°C space for respective serum and plasma aliquots.

Investigators must document their review of each laboratory safety report. Any clinically significant abnormal results will be reported as an AE (see Section 8.1).

Blood samples for PK analyses will be collected from all randomized subjects in accordance with the study schedule. Only samples from subjects assigned to treatment with OPK-88004 will be analyzed for drug concentration. Date and time of each sample and of the last OPK-88004 dose prior to PK blood draw must be clearly recorded. Drug concentration information that would unblind the study will not be reported to study sites or blinded personnel while the study is blinded.

Bioanalytical samples collected to measure investigational product concentration will be retained for a maximum of 1 year following last subject visit for the study.

6.5 Dispensing Study Drug

Study drug will be dispensed to the subject at visits 2, 3, 4, and 5 according to instructions supplied by the IWRS/IVRS. Subjects will be requested to return bottles at each visit.

Sites will maintain records of drug dispensed and returned according to Section 5.10.

6.6 Treatment Compliance

Subjects will return for study treatment visits 3, 4, 5 and 6 or early termination (ET) during which the study coordinator or designee will perform drug accountability and dosing compliance calculations (number of capsules that should have been taken versus actual number taken as evidenced by number of returned capsules). During the treatment period, compliance documented as <80% or >120% should be reported as a protocol deviation.

CCI

6.8 Efficacy Assessments

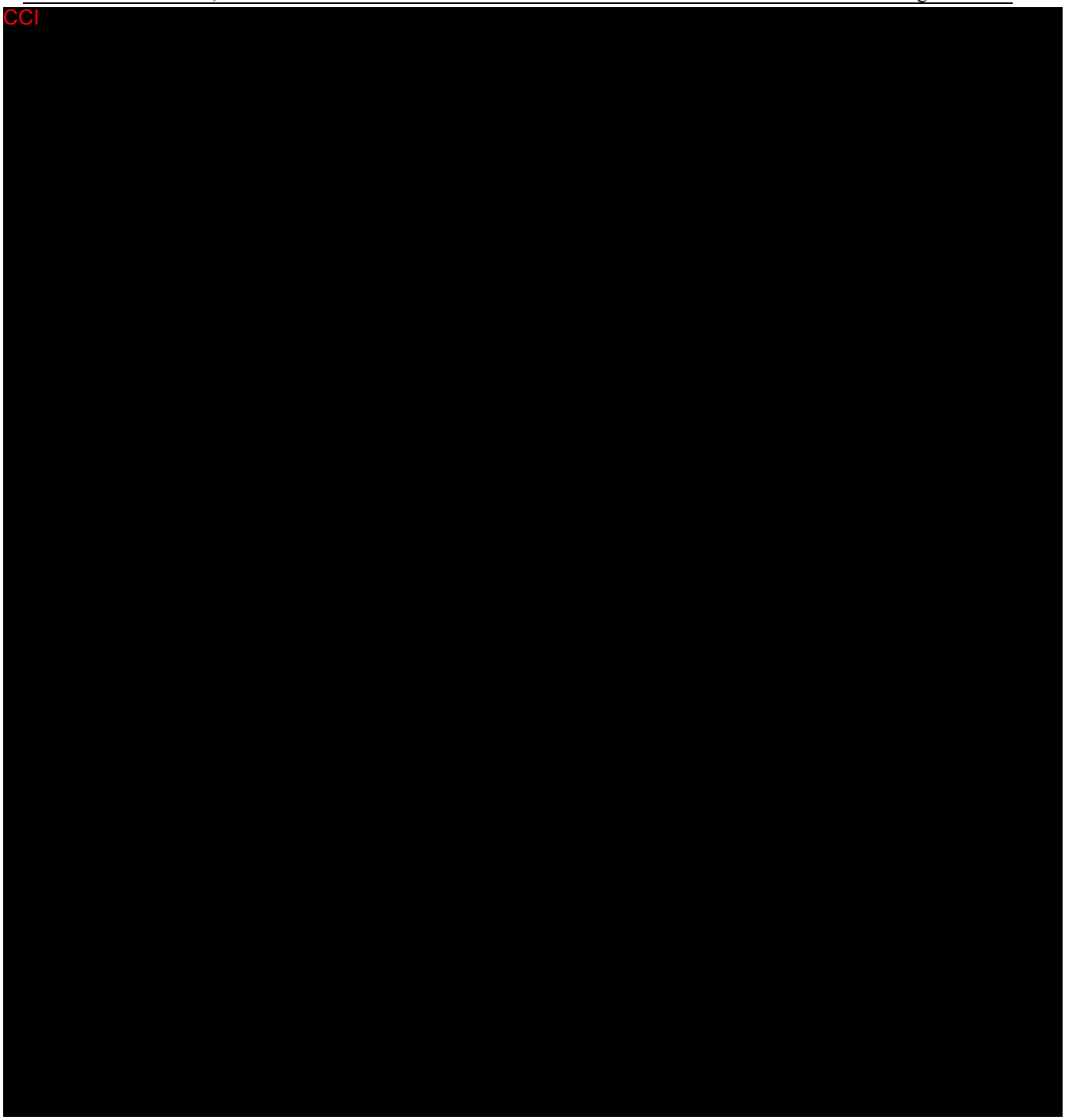
6.8.1 PSA

Blood samples for PSA measurements will be taken prior to, or at least 1 week after, any examination (eg, DRE, CCI likely to result in increased values. Subjects should be requested to abstain from sexual activity that involves ejaculation, or participate in vigorous physical exercise or activity that stimulates the prostate (eg, bicycle or horseback riding) for 48 hours prior to collection of samples for PSA. When a washout period is required during screening, the PSA blood sample will be collected after completion of the washout period.

As part of the study eligibility review, the CCI may be performed at screening for subjects aged ≤80 years with PSA ≥4 ng/mL who have not undergone any invasive urological procedure within 6 months and without biopsy during the previous 12 months (see Inclusion Criteria, Section 4.2) [Punnen et al 2015].

Blood samples for CCI will be taken prior to, or at least 1 week after, any procedures (eg, DRE, CCI likely to result in increased values. Subjects should be requested to abstain from sexual activity that involves ejaculation, or participate in vigorous physical exercise or activity that stimulates the prostate for 48 hours prior to collection of samples for CCI When a washout period is required during screening, the screening CCI sample should be collected after completion of the washout period.

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.

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.

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).

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:

- 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.

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

- 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

- 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

CCI [redacted]

- LBM and fat mass (DXA)
- Semen analysis. Semen collection should not occur within 48 hours prior to PSA CCI [redacted] and may occur up to 7 days after PSA CCI [redacted]
- Drug accountability/treatment compliance

CCI [redacted]

9.4 End of Treatment – Follow up CC Visits 7 and 8

Two additional visits for collection of CC samples will be scheduled 4 and 7 days following administration of final dose of study drug.

9.5 Follow-up- Visit 9 (Week 20 ± 2 Days) Procedures

- AE assessment
- Concomitant medication review
- Physical exam
- Vital signs
- Fasting serum chemistry excluding 25-hydroxyvitamin D, including lipids
- Hematology and coagulation

9.6 Early Termination Visit (ET) Procedures

When a subject terminates early from the trial, the following assessments will be performed, if possible:

- 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 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

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.

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the subject files as original source documents for the study. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable IRBs with direct access to original source documents.

11 PLANNED STATISTICAL METHODS

11.1 General Considerations

Any change to the data analysis methods described in the protocol will require a protocol amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol and the justification for making the change will be described in the statistical analysis plan (SAP) or clinical study report (CSR). CCI [redacted].

The SAP will be finalized before database lock. The clinical SAP will detail the statistical methodology to be used and will outline the statistical programming specifications, tables, and listings. The SAP will describe the variables and populations, anticipated data transformations and manipulations, and other details of the analyses not provided in the protocol.

Data from screen failures will not be presented. Data from enrolled subjects will be presented in data listings by treatment group. A subject who is randomized but does not receive study drug will be included in the data listings but excluded from all data summaries.

All observed assessments, will be included in the data listings.

Continuous data will be presented with number of observations (n), mean, and median, standard deviation (SD), minimum and maximum. Frequencies and percentages will be used for summarizing discrete (categorical) data.

Data that are reported as missing will be presented as missing in the data listings and treated as missing in all data summaries. No imputations for missing data will be made unless otherwise specified for endpoint derivation.

No adjustments for multiplicity will be performed due to the exploratory nature of this study. All tests of treatment effects will be conducted at a two-sided alpha level of 0.05 and/or two-sided 95% confidence interval (CI), unless otherwise stated.

11.2 Determination of Sample Size

Approximately 115 subjects will be enrolled in the study, randomized 1:1:1 across three arms (placebo, OPK-88004 15 mg, or OPK-88004 25 mg). The primary efficacy objective is to evaluate the ability of OPK-88004 doses to reduce PSA compared to placebo from baseline to week 16. CCI [redacted] From historical data, the treatment difference of percent reduction of PSA from baseline to week 16 endpoint between any OPK-88004 dose and placebo is over 30% with common standard deviation <40%. With a sample size of 28 completed subjects per treatment group, the power for the test significance of PSA reduction for any OPK-8804 dose compared to placebo is over 80%. A dropout rate of 10% from randomization to study completion is anticipated

The treatment effect, standard deviation, and dropout rate used in the sample size calculation are based on historical data.

11.3 Analysis Populations and Randomization

11.3.1 Analysis Populations

The Randomized Population will include all subjects who sign the informed consent form and are assigned a randomization number. Baseline and demographic characteristics will be summarized for this population.

The Safety Population will include subjects in the Randomized Population who receive at least 1 dose of randomized study medication. All safety analyses will be conducted based on the Safety Population.

The modified Intent-to-Treat (mITT) Population will include all subjects in the Safety Population who have a baseline efficacy measurement and have at least 1 post-randomization measurement for the appropriate efficacy endpoint. The mITT Population is the primary analysis population, and all efficacy analyses will be performed using the mITT Population.

The Per-Protocol (PP) Population will include all subjects in the mITT Population who complete the 16-week, double-blind treatment period without any significant deviations from the protocol procedures. The PP Population will be used to assess robustness of the primary analysis results. A final listing of all subjects to be excluded from the PP Population will be completed prior to unblinding the study database.

11.4 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group. Categorical variables will be summarized by frequencies and percentages. For categorical variables, comparisons between treatment groups will be assessed using a Pearson Chi-Square test. Continuous variables will be summarized by means and SDs. For continuous variables, comparisons between the treatment groups will be performed using a one-way Analysis of Variance (ANOVA) with treatment as the fixed effect.

11.5 Study Drug Exposure, Compliance, and Concomitant Therapies

Concomitant medication/therapy verbatim terms will be coded using the World Health Organization (WHO) Drug Dictionary version March 2017E or higher. The number and percentage of subjects taking concomitant medications will be summarized by Anatomical & Therapeutic Chemical classification and preferred term for each treatment group. Listings of all prior and concomitant medications will be provided.

Total exposure days to study medication will be summarized by treatment group. Overall percent compliance to study medication, calculated as percent of doses taken relative to doses scheduled to be taken, will be summarized by treatment group.

11.6 Primary Efficacy Analysis

The primary efficacy endpoint of this study is:

- Percent change from baseline PSA levels (visit 2) to week 16 endpoint.

This endpoint will be analyzed based on mITT Population.

Analysis of the percent change from baseline of PSA to week 16 endpoint will be performed using a MMRM, implemented using SAS® Proc Mixed. The factors in the model will be treatment, prostate volume stratification group, and IPSS stratification group, visit, and the treatment group by visit interactions and baseline PSA as a covariate. Treatment difference between OPK-88004 doses and placebo at week 16 will be estimated from the MMRM model, as well as confidence intervals and p-values. Sensitivity analysis of the percent change from baseline of PSA to week 16 endpoint will be performed using ANCOVA modeled with treatment, prostate volume stratification group and IPSS stratification group as fixed effects and baseline PSA as a covariate. Additional covariates may be added and will be detailed in the SAP.

The efficacy analysis of the primary efficacy variable will be repeated on the PP Population to test the robustness of the analysis on mITT Population.

Descriptive statistics by treatment for PSA, and percent change from baseline at the 16-week endpoint will be presented using all observed data with no imputations and no elimination of patients with protocol violations. The descriptive statistics will be presented by visit.

11.7 Safety Analysis

Descriptive summary statistics will be provided for all safety variables, including AEs, clinical laboratory measurements (lipids, chemistry, hematology, coagulation, fasting HbA1c, glucose and insulin, hormone panel, CRP, and urinalysis), vital signs, physical examinations, ECGs, and semen analysis.

Adverse events will be summarized by the MedDRA system organ class and preferred terms, as well as by worst severity. TEAEs will be presented in the CSR, ie, those events occurring following administration of study drug. For each event classification term, the number of subjects experiencing a TEAE with that classification term will be tabulated. The number of subjects experiencing treatment-related TEAEs will also be tabulated. Treatment-related TEAEs are defined as TEAEs that are indicated by the investigator on the CRF to be treatment-related. If a subject reports the occurrence of a particular event more than once, the most severe of those events will be included in the summary tables of TEAEs, and the most severe of the related events will be included in the summary tables of treatment-related events. Discontinuations due to TEAEs and SAEs will be listed by subject and summarized by treatment group.

Analysis comparing the incidence of TEAEs of particular interest and the incidence of treatment-related TEAEs of particular interest will be performed using Fisher's exact tests across all groups in the study.

Summary statistics will provided by treatment group for clinical laboratory measurements, vital signs, ECGs, and semen analysis at baseline and post-baseline visits, including the change from baseline to each visit.

11.8 Secondary Efficacy Analysis

Secondary efficacy endpoints include body composition by DXA, specifically lean body mass and fat mass. Both change and percent change from baseline at the week 16 endpoint will be summarized and analyzed with ANCOVA modeled with treatment, prostate volume stratification group and IPSS stratification group as fixed effects and baseline as a covariate.

The efficacy analysis of the secondary efficacy variables will be repeated on the PP Population to test the robustness of the analysis on the mITT Population.

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12 ADMINISTRATIVE CONSIDERATIONS

12.1 Investigators and Study Administrative Structure

This trial will be performed at up to approximately 35 clinical sites located in the US.

At screening, the subject will be offered notification of their primary care physician that he is participating in a clinical study. If the subject accepts, a brief letter outlining the study and identifying the study drug will be sent once the subject is enrolled.

Table 2 lists contract organizations involved in the trial conduct.

Table 2 CROs

Organization	Responsibility
Medpace 5375 Medpace Way Cincinnati, OH 45227	CRO for the study
Sherpa Clinical Package 6166 Nancy Ridge Dr, San Diego, CA 92121, USA	Drug distribution
InVentiv Health Clinique 2500 rue Einstein Quebec, QC, Canada	Bioanalysis of plasma OPK-88004 and C analysis
BioReference Laboratories 481 Edward H Ross Dr Elmwood Park, NJ 07407, USA	CCI

12.2 Institutional Review Board (IRB) Approval

The investigator will submit all required documentation and obtain IRB approval to implement the study prior to the conduct of any study procedures. At a minimum, the study protocol, protocol amendments, ICF, Investigator's Brochure, and subject-related information, relevant curricula vitae and promotional materials will be submitted.

The sponsor or designee will approve all ICFs before they are used at investigative sites. All ICFs must be compliant with the ICH guideline on GCP.

Documentation of IRB approval of the protocol and the ICF must be provided before the study may begin at the investigative site(s). If it is necessary to amend the protocol during the course of the study, the investigator must ensure that the IRB reviews and approves the amendment. No amendments will be implemented without the agreement of the investigator and the sponsor as well as the IRB, where applicable.

The investigator will comply with requirements for reporting to the IRB.

12.3 Ethical Conduct of the Study

The study will be conducted in accordance with GCP (ICH GCP) and all applicable laws and regulations including the ethical principles of the Declaration of Helsinki (Edinburgh 2000, with Note of Clarification, Tokyo 2004) and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.

In accordance with applicable country-specific regulations, the sponsor will obtain approval from the appropriate regulatory authority(ies) prior to initiating the study in that country.

12.4 Subject Information and Consent

The investigator will obtain a written informed consent form for each subject prior to the performance of any study-related procedures. The investigator is responsible for ensuring that the subject fully understands the nature of the study, potential risks and benefits of participating, including answering any questions the subject may have throughout the study and sharing in a timely manner any new information that may be relevant to the subject's willingness to continue participation in the study.

The investigator will ensure that the ICF is signed and dated by each subject and that documentation of consent being obtained will be recorded in the subject's medical record/source documents.

As used in this protocol, the term "informed consent" includes all consent and assent given by subjects.

12.5 Subject Confidentiality

Subject confidentiality will be strictly held in trust by the study investigators, their staff, the sponsor and their authorized representatives. This confidentiality includes clinical information relating to participating subjects and their biological sample testing.

The study protocol, documentation, data, and all other information will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party, without prior written approval of the sponsor.

Authorized representatives of the sponsor, contract research organizations (if applicable), study monitors, employees of government authorities (eg, US FDA or other), and IRB members may inspect all study-related documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The investigator and clinical study site will permit access to such records.

No information that would permit the identification of a specific individual will be provided for entry into the study database or study report. Study documentation submitted to the sponsor will identify study participants by study code and initials. The investigator will keep a separate confidential enrollment log that matches identifying study codes with the subject names and contact information.

12.6 Case Report Forms and Study Records

This study will utilize an electronic data capture system for the management of clinical data. Data capture and management will be consistent with applicable ICH/GCP guidelines.

All data collected during the study for subjects will be recorded in an individual, subject-specific electronic case report forms (eCRF) as part of an electronic data capture (EDC) system. Access to the electronic system will be restricted and users will only be able to access the system via authorized individual accounts. The sponsor or designee will provide training to the investigative site on the EDC system and eCRFs. All eCRFs will be completed as soon as data are available in the source for each subject. As electronic data capture will be utilized, instructions, training records, and a log will be maintained to identify the designated site personnel who can enter data and/or sign off on an eCRF.

A subject eCRF must be completed for each subject who signs a consent form and undergoes randomization.

To ensure the quality of the clinical data across all subjects and sites, a Clinical Data Management review will be performed by the sponsor or designee on subject data entered or integrated into the EDC system. During the review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol, and ICH/GCP. Moreover, all data from external sources, eg, central laboratory and PD processing/analysis will be reconciled with subject eCRF data. To resolve any questions arising from the Data Management review process, data queries and/or data clarification notifications will be generated via the EDC system for completion and resolution.

The investigator will sign and date the indicated places on the eCRF via the EDC system's electronic signature. These signatures will indicate that the investigator reviewed the data on the eCRF, the data queries, and the data clarifications and agrees with the content.

12.7 Safety Monitoring

A study level safety review will be conducted to monitor and assess safety data collected during the study. Specifically, any signs or trends indicating potential underlying safety issues will be identified. The safety review will be scheduled regularly and reviewed by the sponsor-designated medical monitor. More details will be provided in the safety review team (SRT) plan including the type of safety data, frequency of review, and unblinding plan if necessary.

The sponsor will monitor safety within time frames mandated by company procedures. The medical monitor will periodically review:

- Trends in safety data and laboratory analysis
- Serious and non-serious adverse events including adverse events of special interest (see Section 8.2)

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding the subject or at a group level, the study team will follow the company procedures for unblinding and safety reporting, respectively.

12.7.1 Data Monitoring Committee

An independent Data and Safety Monitoring Committee (DSMB) consisting of one statistician and two clinicians with appropriate expertise will monitor the study at regular intervals, and may make recommendations for changes to the conduct of the trial to reflect safety concerns. Specific responsibilities and activities of the DSMB will be defined in the charter to be ratified at the organizational meeting of the DSMB.

12.8 Protocol Deviations

Protocol deviations are any intentional or unintentional change from an IRB approved protocol that was not approved by the IRB prior to initiation of the change.

The investigator is responsible for ensuring protocol and study compliance by all study staff members. Deviations from protocol will be documented in subjects' study records.

The sponsor requires that all major protocol deviations be reported to the IRB. In addition, the investigator is responsible for adhering to his/her IRB's protocol deviation reporting requirements.

12.9 Retention of Data

The investigator/institution will maintain all CRFs and all source documents that support the subject data collected, and all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial and as specified by the applicable regulatory requirement. The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least two years after the last approval of a marketing application in an ICH region or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the study, the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstances shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

12.10 Publication and Disclosure Policy

Data derived from the study are the exclusive property of the sponsor. Publication rights are outlined in the clinical study agreement.

13 REFERENCE LIST

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Appendix 1. Schedule of Events

Evaluation	Screening	Treatment Period					Follow-up			ET
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	
	-4 weeks to Day 0	Day 1	Week 4 ± 2 days	Week 8 ± 2 days	Week 12 ± 2 days	Week 16 ± 2 days	4 days post final dose	7 days post final dose	Week 20 ± 2 days	
Informed consent	X									
I/E criteria	X	X								
Demographics/medical history[a]	X									
Physical examination[b]	X	X		X		X			X	X
Serology	X									
Vital signs	X	X	X	X	X	X			X	X
Fasting serum chemistry[c]	X[d]	X	X	X		X			X	X
Hematology & coagulation	X[d]	X	X	X		X			X	X
Fasting HbA1c, glucose, insulin	X[d]	X	X	X		X				X
Hormone panel[e]		X		X		X				X
CRP		X	X			X				X
Urinalysis	X[d]	X	X	X		X				X
Urine drug screen	X									
Semen analysis		X[f]				X[g,h]				X
12-lead ECG	X		X	X		X				X
PSA	X[d]	X		X		X				X
CCI [redacted]	X[i]	C				X				C
CCI [redacted]	C									
CCI [redacted]	C					C				C
CCI [redacted]	C					C				C
CCI [redacted]	C					C				C
LBM and fat mass (DXA)		X				X[j]				
Randomization		X								
Drug dispensed		X	X	X	X					
Drug accountability/compliance			X	X	X	X				X
AE Assessment		X	X	X	X	X			X	X
Conmed Assessment	X	X	X	X	X	X			X	X
C [redacted] blood sampling[k]		X[k]	X[k]		X[k]	X[k]	X[k]	X[k]		X[k]

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

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

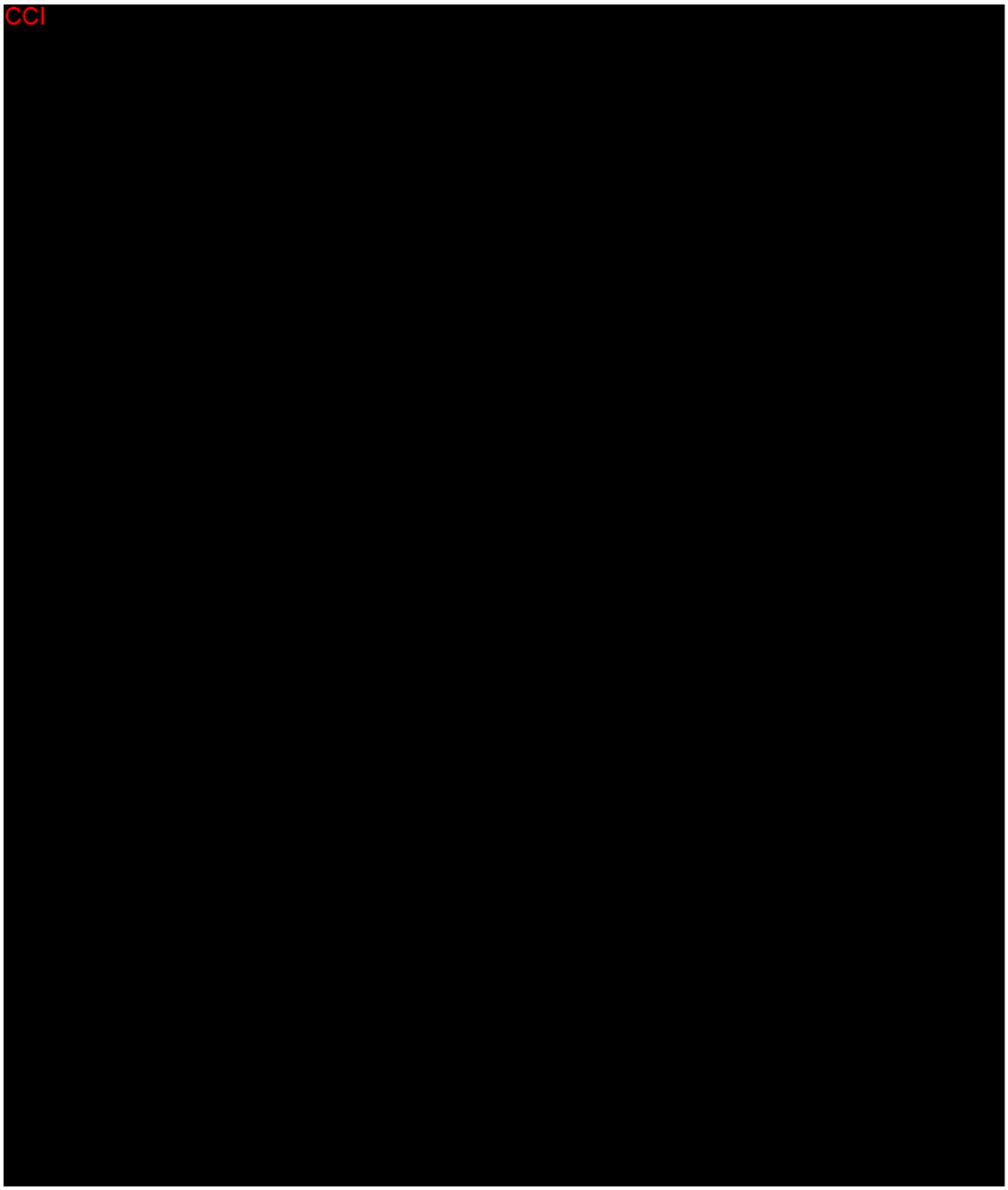
OTC steroid supplements: Tren, Epi-Tren, Stakabol, Black Mass Tren Stack

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®)

CCI [redacted]

CCI [redacted]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Appendix 4. NEW YORK Heart Association Cardiac Disease Classification

Functional Capacity

Class I

Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause fatigue, palpitation, dyspnea, or anginal pain

Class II

Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain

Class III

Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain

Class IV

Patients with cardiac disease resulting in inability to carry on physical activity without discomfort. Symptoms of heart failure or angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort increase.

[CCNYHA] The Criteria Committee of the New York Heart Association, 1994. Nomenclature and criteria for diagnosis of disease of the heart and great vessels. 9th ed. Boston (MA): Little, Brown&co.

Appendix 5. Investigator's Signature

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
Version Date:	x09 November 2018

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, with any future amendments, and with any other written study conduct procedures provided and reviewed and approved by Transition Therapeutics Ireland Ltd. or its designee(s).
- Not to implement any deviations from or changes to the protocol without agreement from the sponsor and prior review and the written approval from IRB/IEC/REB, except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- That I am thoroughly familiar with the appropriate use of the investigational drug, as described in this protocol, and any other information provided by the sponsor including, but not limited to, the following: the current Investigator's Brochure or equivalent document provided by Transition Therapeutics Ireland Ltd. or its designee(s).
- That I am aware of, and will comply with, GCP and all applicable regulatory requirements, including the regulations governing the use of controlled substances.
- To ensure that all persons assisting me with the study are adequately informed about the investigational drug and of their study-related duties and functions as described in the protocol.
- That I have been informed that certain regulatory authorities require the sponsor to obtain and supply details about the investigator's ownership interest in the sponsor or the study drug, and more generally about his/her financial ties with the sponsor. Transition Therapeutics Ireland Ltd. will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence, I:

- Agree to supply Transition Therapeutics Ireland Ltd. with any information regarding ownership interest and financial ties (including those of my spouse and dependent children), including with OPKO Health, Inc., and any of its affiliates.
- Agree to update this information if any relevant changes occur during the course of the study and for one year following completion of the study.
- Agree that Transition Therapeutics Ireland Ltd. may disclose this information about such ownership interests and financial ties to regulatory authorities.

Signed:_____ Date:_____

Printed Name: _____

Signature Page for Protocol SAR-202 v8.0

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

Signature Page for CCI [redacted]