University of Thessaly

School of Medicine

Laboratory of Biomathematics

Director: Professor ZINTZARAS ELIAS

Master of Science program: Biomedical Research Methodology, Biostatistics and Clinical Bioinformatics

.....

Master of science thesis

"A protocol for an observational study for finasteride 5mg in men with moderate Benign Prostatic Hyperplasia"

By

Kalyvas F. Vasileios

Supervisor: DoxaniChrysoula

Evaluator 1: StefanidisIoannis

Evaluator 2:Zintzaras Elias

Larissa, Greece, September 2016

Table of contents

SYNOPSIS

Title of study: A protocol for an observational study for finasteride 5mg in men with moderate Benign Prostatic Hyperplasia

Phase: Observational study

Investigational Product: Finasteride 5mg

Indication:Benign Prostatic Hyperplasia

Primary Efficacy Endpoint :The primary efficacy endpoint of the study will be the change in IPSS from baseline to month 24 because of taking Finasteride 5mg.

Secondary Efficacy Endpoint: The secondary efficacy endpoints will be the categorical improvements in IPSS (>=3 points or >=25%) and the time to, and proportion of, patients with clinical progression of BPH {rise in total IPSS of >=3 points compared with baseline, BPH-related AUR, recurrent UTI, overflow or urge incontinence or renal insufficiency (single >=50% rise from baseline serum creatinine and total value >=1.5mg/dl)}.Health outcomes will be include change in BII score from baseline; rating of IPSS-Q8; and responses to two questions of the PPST questionnaire

Primary Safety Objective: To determine the development of Adverse Events and Serious Adverse Events because of receiving Finasteride.

Study Design and Duration: This is a non-interventional observational study to evaluate the efficacy and safety of finasteride in men with BPH. The study will be event driven thus the number of subjects required and length of treatment are best estimates based on event rates in similar studies. The expected duration of the study, from first subject, first visit through the last follow up phone contact for the last subject is approximately 24 months.

Patients will visit the clinic 1 month after the first visit and then every 4 months until the end of the study period. Patient-reported symptoms, symptom impact, BPH-related QoL (Quality of Life), and treatment satisfaction were

assessed using the IPSS, BPH Impact Index (BII) score, question 8 of the IPSS (IPSS-Q8; 'if you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?'), and patient perception of study treatment (PPST) at every visit.

Data on AEs (Adverse Events) were collected from the time of administration of the first study treatment dose until discontinuation.

Study Population:The study population will be men with particular criteria

Inclusion criteria

1. men aged >=50 years
2. confirmed clinical diagnosis of BPH and moderate LUTS (IPSS 8-19)
3. Prostate Volume >= 30ml by TRUS (at screening)
4. Serum prostate-specific antigen (PSA) level >=1.5 ng/ml

Exclusion criteria

1. Evidence or suggestion of prostate cancer
2. Neurogenic bladder dysfunction
3. History of acute urinary retention necessitating two or more catheterizations in the previous 2 years
4. History of prostate surgery or other invasive procedure (e.g. transurethral microwave thermotherapy, urethral stenting ,balloon urethroplasty)
5. History of condition predisposing patient to urethral strictures
6. Chronic bacterial prostatitis
7. Total serum PSA level of >10ng/ml
8. Use of drugs with antiandrogenic properties
9. Hematuria associated with untreated active urinary tract infection, prostatitis or bladder cancer
10. Current or prior treatment related to BPH
11. Any condition jeopardizing patient's ability to complete the study

Statistical Methods:The statistical test which is going to be used is t-test for dependent data (paired samples t-test) with P-value=0.05 (level of significance) in IBM SPSS Statistics 22. We are going to observe if there is statistically significant difference between mean IPSS in 24th month vs mean IPSS in baseline . In addition, we are going to observe if there is statistically significant difference between mean BII Score 24th month vs BII Score baseline and between mean IPSS Q8 24th month vs IPSS Q8 baseline .

Also ,we are going to observe :

- the percentage of the patients who will show improvement >=3 points in IPSS or >=25% between 24th month and baseline.
- the percentage of the patients (and the cardinal number) who will develop clinical progression of BPH between 24th month and baseline
- the percentage of the patients (and the cardinal number) in each category of PPST questionaire in the baseline and in the 24th month
- the percentage of the patients (and the cardinal number) who will develop AE, SAE and Adverse Events leading to study/drug discontinuation because of receiving Finasteride 5mg

UNIT 1: INTRODUCTION

1.1 Backround -BPH

Benign prostatic hyperplasia (BPH) is characterized by a proliferation of prostatic tissue, particularly in the periurethral zone, leading to anatomic obstruction of the urethra and diverse but characteristic urinary tract symptoms.

The clinical manifestations of BPH fall into two categories: symptoms of obstruction, related to impaired flow (e.g., poor stream, hesitancy or urinary retention), and symptoms of irritation, related to alterations in the bladder response to filling (e.g., frequency, nocturia or urgency).) Although these symptoms are linked to prostate enlargement, the correlation between symptom intensity and the degree of prostate enlargement is complex and poorly understood. The presence of symptoms does not always correlate with objective measurements of voiding function (e.g., maximuin or mean urinary flow rate, prostate volume or residual urine volume).

The natural history of BPH is variable but slowly progressive. Some patients tolerate mild to moderate symptoms for a long time without any treatment. Nonetheless, symptoms affect quality of life: they are bothersome, interfere with daily activities and can affect psychological well-being. Moreover, the serious complications of BPH, such as infection, urinary retention and upper tract sequelae, may constitute medical emergencies.

Until recently, the sole treatment for severe symptoms of BPH involved surgery (e.g. transurethral resection of the prostate [TURP]), with surveillance (watchful waiting) the only alternative. Although TURP is associated with a very low mortality rate (0.2%), the morbidity is substantial (18%) and includes failure to void (6.5%), postoperative bleeding requiring transfusion (3.9%), clot retention (3.3%) and infection (2.3%).9 In addition, following TURP there is a variable incidence of urethral stricture, loss of ejaculation (55%) and impotence (13%).

Therefore, it is not surprising that many patients who seek treatment for their BPH symptoms consider medical therapy before surgery. Two types of medication have proven beneficial: ox-adrenergic blockers and 5a-reductase inhibitors.

1.2 5a-reductase inhibitors (5ARIs)-FINASTERIDE

Of the two commonly used pharmacotherapeutic interventions for men with symptomatic benign prostatic hyperplasia (BPH), the 5a-reductase inhibitors (5ARIs) and a1 blockers, only the 5ARIs have been shown to modify the underlying pathology. Data from three large-scale, randomised clinical studies demonstrate that treatment with the 5ARIs dutasteride or finasteride results in significant reductions in prostate volume associated with improvements in urinary symptoms and flow, and significant reductions in the risks of acute urinary retention (AUR) and BPH-related surgery. In contrast, a1 blockers, which reduce the dynamic elements of BPH but do not reduce prostate volume, are associated with rapid improvements in symptoms and flow, but have not been shown to reduce the long-term risk of AUR or BPH-related surgery in blinded, randomised and placebo-controlled studies.

BPH is a progressive disease in many men, and underlying this progression is continuing prostate growth .Therapy aimed at reducing prostate volume, and the accompanying benefits in improving symptoms and lessening the risk of BPH morbidity, has a logical place in the medical management of men at risk of progressive BPH. However, the long-term nature of BPH requires a therapy that reduces and maintains reductions in prostate volume, has lasting effects on symptoms and minimizes the risks of AUR and BPH-related surgery. A number of studies with the 5ARI finasteride have examined its long-term effect over 4 to 8 years .These studies demonstrate that finasteride treatment is associated with a maximal reduction in prostate volume after 2 years of therapy that is maintained without further reductions over the remaining course of the studies. 5ARIs achieve reductions in prostate volume through the inhibition of the nuclear-bound steroid 5a-reductase (5AR) isoenzymes, which chemically reduce testosterone to dihydrotestosterone (DHT), the principal androgen stimulating prostatic growth. Finasteride suppresses serum DHT by approximately 70%, with only 49% of treated men achieving this reduction in one data series .

1.3 Information about the drug

Treating urinary problems caused by an enlarged prostate gland (benign prostatic hyperplasia [BPH]). It is also used to lower the risk of needing surgery to treat BPH. It may be used with another medicine (doxazosin) to lower the risk of worsening BPH. It may also be used for other conditions as determined by your doctor.

Finasteride is a type of steroid reductase inhibitor. It works by reducing the amount of the hormone dihydrotestosterone (DHT) in the body. This makes the prostate gland smaller, which helps to relieve urinary problems.

Finasteride is a 5α-reductase inhibitor, specifically the type II and III isoenzymes. By inhibiting 5α-reductase, finasteride prevents conversion of testosterone to dihydrotestosterone (DHT) by the type II and III isoenzymes, resulting in a decrease in serum DHT levels by about 65–70% and in prostate DHT levels by up to 85–90%, where expression of the type II isoenzyme dominates. Unlike triple inhibitors of all three isoenzymes of 5α-reductase like dutasteride which can reduce DHT levels in the entire body by more than 99%, finasteride does not completely suppress DHT production because it lacks significant inhibitory effects on the 5α-reductase type I isoenzyme, with 100-fold less affinity for I as compared to II. In addition to blocking the type II and III isoenzymes, finasteride competitively inhibits the 5β-reductase type II isoenzyme, though this is not believed to affect androgen metabolism.

By blocking DHT production, finasteride reduces androgen activity in the scalp. In the prostate, inhibition of 5α-reductase reduces prostate volume, which improves BPH and reduces risk of prostate cancer. Inhibition of 5α-reductase also reduces epididymal weight, and decreases motility and normal morphology of spermatozoa in the epididymis.

DHT helps activate the $GABA_A$ receptor, which functions to tamp down signaling among neurons; because finasteride prevents the formation of DHT, it may contribute to a reduction of $GABA_A$ activity. Reduced $GABA_A$ has been implicated in depression, anxiety, and sexual dysfunction.

1.4 Non-interventional observational studies

In a non interventional observational study which examine the safety of finasteride as used in general medical practice to treat benign prostatic hypertrophy (BPH), the results were impressive. Information was collected on 14 772 patients

who were included in an observational cohort study conducted using Prescription-Event Monitoring. Finasteride was reported to have been effective in 60% of the patients in whom an opinion on efficacy was recorded. Impotence or ejaculatory failure was reported in 2.1% of the patients, decreased libido in 1% and gynaecomastia and related conditions in 0.4%. Impotence was the most frequent reason for stopping treatment with finasteride and was the most commonly reported adverse reaction to the drug. Of the patients included in the elderly cohort involved in this study, 819 (5.5%) died; none of these deaths was attributed to finasteride. As o conclusion impotence or ejaculatory failure, decreased libido and gynaecomastia in a small proportion of patients were associated with the use of finasteride. The results of this study strongly suggest that this drug is acceptably safe when used in accordance with the current prescribing information.

In another multicenter, double-blind, placebo controlled study conducted 25 centers of United States and 5 of Canada they evaluated two doses of finasteride (1mg and 5mg) and placebo, each given once daily for 12 months in 895 men with prostatic hyperplasia. Urinary symptoms, urinary flow, prostatic volume and serum concentrations dihydrotestosterone and PSA were determined periodically during the treatment period. As compared with men in the placebo group, the men treated with 5mg of finasteride daily had a significant decrease in total urinary symptom-scores ($P<0.001$) , an increase of 1.6ml per second (22 percent $P<0.001$) in the maximal urinary flow rate and a 19 percent decrease of prostatic volume ($P<0.001$). The men treated with 1mg of finasteride per day did not have a significant decrease in total urinary symptom-scores , but had an increase of 1.4 ml per second (23 percent) in the maximal flow rate and 18 percent decrease of prostatic volume. The men given placebo had no changes in total urinary symptom-scores , an increase of 0.2 ml per second (8 percent) in the maximal urinary-flow rate and a 3 percent decrease in prostatic volume. The frequency of AE in the tree groups was similar , except of a higher incidence of decreased libido, impotence and ejaculatory disorders in finasteride-treated groups. The treatment of BPH with finasteride 5mg per day results in a significant decrease in symptoms of obstruction, an increase in urinary flow and a decrease in the prostatic volume, but a slightly increased risk of sexual dysfunction.

UNIT 2: STUDY OBJECTIVES

2.1 Primary Objective

To evaluate the efficacy and safety of 2 years treatment of moderate BPH with finasteride.

Efficacy assessments included the International Prostate Symptom Score (IPSS), BPH Impact Index (BII) score and patient perception of study treatment (PPST).

Safety assessments included adverse events (AE) and Serious Adverse Events (SAE)

UNIT 3: ETHICAL CONSIDERATIONS

3.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP) as defined by the International Conference of Harmonization (ICH) and in accordance with the ethical principles underlying European Union Directive. Furthermore, the study will be conducted in compliance with the protocol. The protocol, the amendments of protocol and the subject informed consent will receive IRB/IEC approval opinion prior to initiation of the study.

3.2 Informed Consent

Investigators must ensure that subjects , or, in those situations where consent cannot be given by subjects, their legally acceptable representatives, are clearly and fully informed about the purpose, potential risks, and other critical issues of the study in which they volunteer to participate. Freely given written informed

consent must be obtained from every subject or in those situations where consent cannot be given by subjects, their legally acceptable representatives.

Subjects unable to give their written consent may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with the subject's understanding and should they become capable, personally sign and date the consent form as soon as possible. The explicit wish of a subject unable to give his or her written consent, who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the study at any time should be considered by the investigator.

Subjects may withdraw consent from participation in the study at any time. In the event a subject withdraws consent to receive study drug, the site pay (with the subject's agreement) continue to contact the subject, general practitioner and any other physician or medical care provider for the collection of outcome and survival follow up data.

3.3 Subject Confidentiality

The Investigators and the Sponsor will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations. The Investigator must ensure that the subject's anonymity is maintained. On the eCRFs or other documents submitted to the Sponsor or the CRO, subjects should be identified by a unique subject identifier as designed by the Sponsor. Sponsor personnel whose responsibilities require access to personal data should agree to keep the identity of study subjects confidential.

UNIT 4: INVESTIGATION PLAN

4.1 Study Design and duration

This is a non-interventional observational study to evaluate the efficacy and safety of finasteride in men with BPH. The study will be event driven thus the number of subjects required and length of treatment are best estimates based on event rates in similar studies. The expected duration of the study, from first subject, first visit through the last follow up phone contact for the last subject is approximately 24 months.

Patients will visit the clinic 1 month after the first visit and then every 4 months until the end of the study period. Patient-reported symptoms, symptom impact, BPH-related QoL (Quality of Life), and treatment satisfaction were assessed using the IPSS, BPH Impact Index (BII) score, question 8 of the IPSS (IPSS-Q8; 'if you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?'), and patient perception of study treatment (PPST) at every visit.

The IPSS is a seven-item questionnaire that quantitatively measures the level of urinary symptoms reported as a total IPSS. The total IPSS can range from 0 to 35 and classifies BPH symptoms into mild (0–7), moderate (8–19), or severe (20–35).

An additional, independent eighth question (IPSS-Q8) was added to assess self-perceived QoL and BPH-related health status. The IPSS-Q8 score ranges from 0 to 6 where 0 means 'delighted' and 6 means 'terrible' life.

The BII is a four-item questionnaire that measures the impact of urinary problems on a subject's general sense of wellbeing in four domains of health: physical discomfort from urinary problems, worry about health because of urinary problems, bothersomeness of urinary symptoms and limitation of activities of daily living because of urinary problems. The total BII score ranges from 0 (no symptom impact) to 13 (significant symptom impact).

The PPST questionnaire consists of two questions that assess a subject's perception and satisfaction with the effect of study treatment on control of urinary symptoms. Question 1 was 'Overall, how satisfied are you with the treatment and

its effect on your urinary problems?', and question 2 was 'Would you ask your doctor for the treatment you received in this study?'. Question 1 was rated on a seven-point scale from 'very satisfied' to 'very dissatisfied'. Question 2 was rated on a three-point scale of 'yes', 'no' or 'not sure'.

At baseline and months 12 and 24, patients underwent DRE (Digital Rectal Exam), blood chemistry analysis, haematology and PSA tests, and urine analysis by dipstick. Data on AEs (Adverse Events) were collected from the time of administration of the first study treatment dose until discontinuation.

4.1.1 Independent Advisory Committee

An Idependent Advisory Committee will provide ongoing scientific and operational oversight to the study. The Committee will evaluate the ongoing study outcomes twice a year.

4.2 Study Population

4.2.1 *Inclusion criteria*

1. men aged >=50 years
2. confirmed clinical diagnosis of BPH and moderate LUTS (IPSS 8-19)
3. Prostate Volume >= 30ml by TRUS (at screening)
4. Serum prostate-specific antigen (PSA) level >=1.5 ng/ml

4.2.2 *Exclusion criteria*

1. Evidence or suggestion of prostate cancer
2. Neurogenic bladder dysfunction
3. History of acute urinary retention necessitating two or more catheterizations in the previous 2 years

4. History of prostate surgery or other invasive procedure (e.g. transurethral microwave thermotherapy, urethral stenting ,balloon urethroplasty)

5. History of condition predisposing patient to urethral strictures

6. Chronic bacterial prostatitis

7. Total serum PSA level of >10ng/ml

8. Use of drugs with antiandrogenic properties

9. Hematuria associated with untreated active urinary tract infection, prostatitis or bladder cancer

10. Current or prior treatment related to BPH

11. Any condition jeopardizing patient's ability to complete the study

4.2.3 Discontinuation of Subjects from treatment

Subjects should discontinue study treatment for any of the following reasons:

a) Withdrawal of informed consent (subject's decision to withraw for any reason)
b) Any clinical AE or intercurrent illness which in opinion of the Investigator, indicates that conyinued participation in the study is not in the best interest of the subject.

UNIT 5: STUDY ENDPOINTS & STATISTICAL ANALYSIS

5.1 Efficacy Assessments

5.1.1 Primary efficacy endpoint

The primary efficacy endpoint of the study will be the change in IPSS from baseline to month 24.

5.1.2 Secondary efficacy endpoints

The secondary efficacy endpoints will be the categorical improvements in IPSS (>=3 points or >=25%) and the time to, and proportion of, patients with clinical progression of BPH {rise in total IPSS of >=3 points compared with baseline, BPH-related AUR, recurrent UTI, overflow or urge incontinence or renal insufficiency (single >=50% rise from baseline serum creatinine and total value >=1.5mg/dl)}.

Health outcomes will be include change in BII score from baseline; rating of IPSS-Q8; and responses to two questions of the PPST questionnaire.

5.2 Safety Assessments

Safety assessments will include drug-related Adverse Events (AE) and Serious Adverse Events (SAE).

5.3 Statistical Analysis

5.3.1 Efficacy Analysis

Primary Efficacy Endpoint

The primary efficacy endpoint of the study will be the change in IPSS from baseline to month 24 (mean IPSS 24th month – mean IPSS baseline). The statistical test which is going to be used is t-test for dependent data (paired samples t-test) with P-value=0.05 (level of significance) in IBM SPSS Statistics 22. We are going to observe if there is statistically significant difference between mean IPSS in 24th month vs mean IPSS in baseline .

Secondary Efficacy Endpoint

Categorical changes in IPSS

Categorical improvements in IPSS (patients with improvement >=3 points in IPSS or >=25%) between 24th month and baseline are going to be observed with Descriptive Statistics using IBM SPSS Statistics 22. We are going to observe the percentage of the patients who will show improvement>=3 points in IPSS or >=25% between 24th month and baseline.

Clinical progression

Clinical progression of BPH (patients with symptom progression with rise in total IPSS >=3 between 24th month and baseline, BPH-related AUR, BPH- related UTI, BPH- related urinary incontinence, BPH- related renal insufficiency) is going to be observed with Descriptive Statistics using IBM SPSS Statistics 22. We are going to observe the percentage of the patients (and the cardinal number) who will develop clinical progression of BPH between 24th month and baseline.

Health outcomes (BII Score, IPSS Q-8 and PPST)

For BII Score and IPSS Q-8 we are going to observe the change between 24th month and baseline (mean BII Score 24th month – mean BII Score baseline and

mean IPSS Q8 24th month – mean IPSS Q8 baseline). The statistical test which is going to be used is t-test for dependent data (paired samples t-test) with P-value=0.05 (level of significance) in IBM SPSS Statistics 22. We are going to observe if there is statistically significant difference between mean BII Score 24th month vs BII Score baseline and between mean IPSS Q8 24th month vs IPSS Q8 baseline .

The PPST questionnaire consists of two questions that assess a subject's perception and satisfaction with the effect of study treatment on control of urinary symptoms. Question 1 was 'Overall, how satisfied are you with the treatment and its effect on your urinary problems?', and question 2 was 'Would you ask your doctor for the treatment you received in this study?'. Question 1 was rated on a seven-point scale from 'very satisfied' to 'very dissatisfied'. Question 2 was rated on a three-point scale of 'yes', 'no' or 'not sure'. We are going to exam the percentage of thepatients (and the cardinal number) in each category in the baseline and in the 24th month with Descriptive Statistics using IBM SPSS Statistics 22.

5.3.2 Safety Analysis

In this study we are going to record the occurrence of drug-related Adverse Events, serious Adverse Events, or Adverse Events leading to study/drug discontinuation with Descriptive Statistics using IBM SPSS Statistics 22 . We are going to observe the percentage of the patients (and the cardinal number) who will develop AE, SAE and Adverse Events leading to study/drug discontinuation using IBM SPSS Statistics 22.

In global bibliography the most commonly drug-related Adverse Events which have been reported are impotence/ retrograde ejaculation , decreased libido and gynaecomastia.

UNIT 6: ADVERSE EVENTS

6.1 Definitions

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administrated a pharmaceutical product and which does not necessarily have a casual relationship with this treatment.

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose :

- Results in death
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event

6.2 Severity of Adverse Event

- Mild (grade 1)- awareness of event but easily tolerated
- Moderate (grade 2)- discomfort enough to cause some interference with usual activity
- Severe (grade 3)- inability to carry out usual activity
- Very severe (grade 4)- life-threatening or disabling AE

6.3 Adverse Event Documentation-Reporting

Subjects must be carefully monitored for AE. All AE occurring after the subject has signed the informed consent form must be fully recorded in the subject's CRF. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product, action taken and outcome.

SAE must immediately (within 24 hours of the investigator's awareness) be reported and must be followed up until resolution or stabilization. If required and according to local law and regulations, SAE must be reported to the Ethics Committee and Regulatory Authorities.

6.4 Overdose

An overdose is defined as the accidental or intentional ingestion of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

UNIT 7: ADMINISTRATIVE SECTION

7.1 Compliance with the protocol

The study shall be conducted as described in this approved protocol. The Investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard to study subjects. Any significant deviation must be documented in the CRF.

7.2 Records Retention

The Investigator must retain investigational product disposition records, copies of CRFs (or electronic files) and source documents for the maximum period required by applicable regulations and guidelines or institution procedures, or for the period specified by the sponsor, whichever is longer. If the Investigator withdraws from the study (e.g. relocation, retirement) the records shall be transferred to a mutually agreed upon designee (e.g. another Investigator).

7.3 Case Report Forms

An Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated in the investigation. Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

The confidentiality of records that could identify subjects must be protected ,respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements.

The Investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF , including any paper SAE, must be promptly reviewed, signed and dated by a qualified physician who is an investigator or subinvestigator. The Investigator must retain a copy of the CRFs including records of the changes and corrections.

LIST OF ABBREVIATIONS

Term	*Definition*
5ARIs	5a-reductase inhibitors
AE	Adverse Event
AUR	Acute Urinary Retention
BPH	Benign prostatic hyperplasia
BII	BPH- Impact Index
CRF	Case Report Form
DHT	Dihydrotestosterone
DRE	Digital Rectal Exam
GCP	Good Clinical Practice
IA	Interim Analysis
ICH	International Conference of Harmonization
IEC	International Ethics Committee
IPSS	International Prostate Symptom Score
LUTS	Lower Urinary Tract Symptoms
PPST	Patient Perception of Study Treatment
PSA	Prostate Specific Antigen
QoL	Quality of Life
SAE	Serious Adverse Event
TRUS	Transrectal Ultrasound
TURP	Transurethral Prostatectomy
UTI	Urinary Tract Infection

REFERENCES

- L.Wilton, G.Pearce, E.Edet, S.Freemantle, M.D.B. Stephens and R.D.Mann. *The safety of finasteride used in benign prostatic hypertrophy: a non interventinal observational cohort study in 14.772 patients. British Journal of Urology (1996).78, 379-384*

- J. Curtis Nickel, MD, FRCSC; Yves Fradet, MD, FRCSC, Rex C. Boake, MD, FRCSC,
  Peter J. Pommerville, MD, FRCSC, Jean-Paul Perreault, MD, FRCSC, Salim K. Afridi, MD, FRCSC, Mostafa M. Elhilali, MD, FRCSC and the PROSPECT Study Group. *Efficacy and safety of finasteride therapyfor benign prostatic hyperplasia:results of a 2-year randomized controlled trial (the PROSPECT Study). Canadian Medical Association Journal (1996);155 (9)*

- Claus G. Roehrborn, Igor Oyarzabal Perez, Erik P.M. Roos, NicolaeCalomfirescu,
  Betsy Brotherton, Fang Wang, Juan Manuel Palacios, AveryanVasylyev and Michael J. Manyak*: (Duodart®) compared with watchful waiting withinitiation of tamsulosin therapy if symptoms donot improve, both provided with lifestyle advice,*
  in the management of treatment-naïve men withmoderately symptomatic benign prostatic
  hyperplasia: 2-year CONDUCT study results. BJU Int 2015;116:450-459

- J. Curtis Nickel, Peter Gilling, Teuvo L. Tammela, Betsy Morrill,Timothy H. Wilson and Roger S. Rittmaster :*Comparison of dutasteride and finasteride fortreating benign prostatic hyperplasia: theEnlarged Prostate International Comparator*
  Study (EPICS).BJU Int 2011;108:388-394

- S. A. Kaplan, D. E. Chung, R. K. Lee, S. Scofield, A. E. Te . *A 5-year retrospective analysis of 5a-reductase inhibitors in men with benign prostatic hyperplasia: finasteride has comparable urinary symptom efficacy and prostate volume reduction, but less sexual side effects and breast complications than dutasteride.Int J ClinPract, November 2012, 66, 11, 1052–1055*

- Glenn J. Gormley, M.D., Ph.D., Elizabeth Stoner, M.D., Reginald C. Bruskewitz, M.D., Julianne Imperato-McGinley, M.D., Patrick C. Walsh, M.D., John D. McConnell, M.D., Gerald L. Andriole, M.D., Jack Geller, M.D., Bruce R. Bracken, M.D., Joyce S. Tenover, M.D., Ph.D., E. Darracott Vaughan, M.D., Frances Pappas, M.S., Alice Taylor, M.S., Bruce Binkowitz, M.S., Jennifer Ng, S.D., and the Finasteride Study Group. *The Effect of Finasteride in Men with Benign Prostatic Hyperplasia.NEngl J Med 1992; 327:1185-1191*

- Tacklind J, Fink HA, MacDonald R, Rutks I, Wilt TJ. *Finasteride for Benign Prostatic Hyperplasia (Review).Cochrane Database of Systematic Reviews 2010, Issue 10. Art. No.: CD006015*.

- Jack W. McAninch, Tom F. Lue. *Smith and Tanagho's General Urology . 18th Edition, Lange Medical Book*