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# STUDY OF THE BIOEQUIVALENCE OF ANTI-BENIGN PROSTATIC HYPERPLASIA DRUG IN HEALTHY ADULT, MALE HUMAN SUBJECTS, UNDER FED CONDITION

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## ABSTRACT

Bioequivalence studies are the preliminary requirement for generic products to enter in the market. International regulatory authorities require that the final quality judgment of an oral dosage form be based on its in vitro dissolution profile and its *in vivo* bioavailability or bioequivalence evaluation. This is an open label, balanced, randomized, two treatments, two periods, two sequences, single dose, cross-over, and bioequivalence study in healthy, adult, subjects under fed conditions. Single oral dose of test formulation Tamsulosin HCl Capsules USP 0.4 mg (each hard gelatin capsule contains Tamsulosin HCl USP 0.4 mg) or reference formulation Flomax® (Tamsulosin hydrochloride) 0.4 mg was administered under lowlight with approximately 240 mL of drinking water at ambient temperature 30 min after initiation of a high fat calorie breakfast after an overnight fast of at least 10 hrs and not more than 12 hrs in period I. Similar procedure was followed in the II period of the study. All subjects finished the breakfast in 30 minutes or less. Subjects received alternate treatment in the subsequent period in such a way that each subject received both the treatments at the end of the study. Subjects received alternate treatments at the end of the study. The study was conducted according to the approved protocol, SOPs and ICH-GCP guidelines and applicable regulatory guidelines. A validated bio analytical method was adopted for conduct of analysis of the plasma samples of the study, which was selective, sensitive and cost effective. Based on geometric mean ratio of log transformed data and 90% confidence interval of test and reference product for $C_{max}$, $AUC_{0-t}$ and $AUC_{0-\infty}$, it is concluded that the ratio and extent of absorption of test and reference product are similar.

**Keywords:** Bioequivalence study of 2 products, Benign Prostatic Hyperplasia, Tamsulosin, Plasma concentration, Safety of volunteer's.

## INTRODUCTION

Tamsulosin (Flomax) is described as a selective alpha (α)1A-adrenergic antagonist (or blocker) that has been shown to improve lower urinary tract symptoms in patients with benign prostatic hyperplasia (BPH). Other (α)-blockers are also effective and available for treating patients with symptomatic BPH (e.g., terazosin, prazosin, doxazosin), 10-21 all of which are available by generic name, at lower cost. The effectiveness of tamsulosin and other α-blockers appear to be similar in the reduction of symptoms of BPH. Tamsulosin differs from the other α-blockers in selectively blocking the α receptors in the genitourinary area with a minimal effect on the smooth muscle vasculature. Hence, the effect of tamsulosin on blood pressure is negligible. The incidence of orthostatic hypotension has been reported to be approximately 1% with tamsulosin (Wikipedia, 2013). Tamsulosin is an oral drug for the treatment of men who are having difficulty

urinating because of benign prostatic hyperplasia (BPH). In men, the tube which carries urine from the bladder to the penis (called the urethra) travels through the prostate gland. As men get older, the prostate gland enlarges, and the muscle cells within the prostate gland and the neck of the bladder (which controls the flow of urine) tighten. The combination of enlargement and tightening of muscles compresses the urethra and obstructs the flow of urine. This results in difficulty urinating and retention of urine within the bladder. The tightening or contraction of the muscle cells is controlled by nerves. One type of nerve, the alpha adrenergic nerves, cause the muscle cells to tighten by releasing a chemical related to epinephrine (adrenalin). Tamsulosin blocks the effects of this chemical on the muscle cells and causes the muscles to relax. This results in a decrease in obstruction to the flow of urine. There are other drugs which block alpha adrenergic nerves throughout the body and which are used in treating diseases of the heart, blood vessels, and prostate for example, prazosin (Minipress), terazosin (Hytrin), doxazosin (Cardura), andalfuzosin (Uroxatral). Tamsulosin is more active against the alpha adrenergic nerves of the prostate and bladder neck than these other drugs and has a lesser effect on alpha adrenergic nerves elsewhere in the body. For this reason, tamsulosin causes fewer side effects, especially low blood pressure, than other alpha adrenergic blocking drugs. Moreover, tamsulosin therapy can be started at the optimum dose whereas other alpha adrenergic blocking drugs need to be started at low doses with the doses slowly increased over time in order to minimize the side effects. Tamsulosin was approved by the FDA in 1997 (MedicineNet, 2014).

- **Storage**

  Capsules should be stored at room temperature, 15-30 $^{o}$C (59-86 F).

- **Prescribed** for

  Tamsulosin is used to treat men who are having problems urinating because of BPH. Tamsulosin is not approved for the treatment of high blood pressure.

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**Drug Interactions**

The elimination of Tamsulosin from the body may be reduced by erythromycin, ketoconazole (Nizoral, Extina, Xolegel, Kuric), paroxetine (Paxil), cimetidine (Tagamet), ritonavir (Norvir), lopinavir, and other drugs that reduce the elimination of drugs by liver enzymes. Reduced elimination may lead to increased side effects of tamsulosin. PDE-5 inhibitors (for example, vardenafil [Levitra, Staxyn], Adcirca, sildenafil [Viagra], Revatio], tadalafil [Cialis] add to the blood pressure lowering effects of tamsulosin and may result in severe blood pressure reduction.

- **Pregnancy**

  Tamsulosin is not prescribed for women.

- **Nursing Mothers**

  This medication is used only in men. It is not known if tamsulosin is secreted into breast milk.

- **Side Effects**

  The most common adverse effects of tamsulosin areanemia (decreased red blood cells), decreased white blood cells, nausea, vomiting, abnormal taste, increased triglycerides, and weakness. Low blood pressure, dizziness or fainting, headache, abdominal pain, weight loss,muscle pain, abnormal ejaculation, upper respiratory tract infections, andrash also may occur. Orthostatic hypotension (low blood pressure when rising from sitting or lying down position), priapism (prolonged erection), and an eye problem called intraoperative floppy iris syndrome (IFIS) have been observed during tamsulosin treatment (Wikipeidia, 2013).

- **Uses**

  This medication is used to treat the symptoms of a prostate gland condition called BPH (benign prostatic hyperplasia, also known as enlarged

prostate). Tamsulosin is an alpha-blocker that works by relaxing the muscles in the bladder neck and prostate. Relaxing these muscles leads to relief of symptoms of BPH such as the feeling of needing to urinate frequently or urgently, weak stream, difficulty in beginning the flow of urine, and the need to urinate during the middle of the night. This medication should not be used to treat high blood pressure (Chute, 1993).

- **Storage**

  Store at room temperature at 77 degrees F (25 degrees C) away from light and moisture. Brief storage between 59-86 degrees F (15-30 degrees C) is permitted. Do not store in the bathroom. Keep all medicines away from children and pets. Do not flush medications down the toilet or pour them into a drain unless instructed to do so (Kaplan, 1995).

## Causes of Benign Prostatic Hyperplasia

- Testosterone is produced by the Leydig cells of the testes and is converted by 5α-reductase to dihydrotestosterone (DHT). Testosterone and DHT promote prostatic epithelial and stromal cell proliferation, apoptosis inhibition, and prostatic angiogenesis. Balance between cellular proliferation and apoptosis exists in patients with normal intraprostatic levels of androgen and estrogen, but DHT imbalance occurs with advancing age, favoring prostatic epithelial and stromal cell proliferation

*Obstructive lower urinary tract symptoms are produced via two mechanisms:*

- The enlarged prostate can obstruct the prostatic urethra and impede continuous urinary flow.
- The prostatic stromal smooth muscle cells, which are controlled by α-adrenergic stimulation, can become hyperactive and constrict the prostatic urethra. Hyperactivity may be secondary to certain medications, including tricyclic antidepressants (imipramine, amitriptyline, nortriptyline, doxepin), anticholinergic agents (propantheline, tolterodine, oxybutynin), diuretics (furosemide, thiazides), narcotics (morphine, codeine), first-generation antihistamines (fexofenadine, diphenhydramine, chlorpheniramine), and decongestants (phenylpropanolamine).
- Irritative (storage) urinary symptoms result from bladder instability. The obstructing prostate increases the intravesicular pressure, and the bladder's smooth muscles adapt by increasing in size. When the bladder muscles become hypertrophic, the bladder becomes hypersensitive and unstable, causing irritative (storage) urinary symptoms (AUA Foundation, 2005)

## Treatment Choices

Currently, the main ways of dealing with BPH are:

- Watchful waiting (no treatment)
- Medical treatments (drugs)
- Minimally-invasive treatments
- Surgical treatments

## Inclusion Criteria as per the Approved Protocol

- Literate male subjects in the age range of 18-45 years (both inclusive).
- BMI range within 18.50-24.99 Kg/m2 (both inclusive) and weight not less than 50 Kg.
- Had voluntarily given written informed consent to participate in this study.
- Were of normal health as determined by medical history, physical examination and laboratory investigations of the subjects performed within 21 days prior to the commencement of the study.

## Exclusion Criteria as per the Approved Protocol

- Hypersensitivity and/or intolerance to Tamsulosin or any of its excipients or related group of drugs.

- History of pancreatitis or hepatitis or gastritis or gastrointestinal ulcer/bleeding.
- History of drug induced rash, anaphylaxis and photosensitivity reaction.
- History of seizures.
- History of any psychiatric illness which may impair the ability to provide written informed consent.
- History of serious gastrointestinal, hepatic, renal, cardiovascular, pulmonary, neurological or hematological disease, diabetes or glaucoma.
- Any evidence of organ dysfunction or any clinically significant deviation from normal, in physical or clinical determinations.
- Presence of disease markers of HIV 1 and 2, Hepatitis B and C viruses or syphilis infection.
- Laboratory values that are significantly different from the normal reference range and/or are deemed to be of clinical significance by the investigator.
- Clinically abnormal ECG or chest X-ray.
- Systolic blood pressure less than 100mm Hg or more than equal to 140 mm Hg.
- Diastolic blood pressure less than 60 mm Hg or more than or equal to 90 mm Hg.
- Pulse rate less than 60 beats/minute or more than or equal to 100 beats/minute.
- Difficulty with donating blood.
- History of smoking (positive history of smoking from last one year).
- History of drug dependence or alcoholics (positive history of alcohol consumption from last one year).
- Use of any enzyme modifying drugs, MAOIs and other prescription drugs within 30 days prior to Day 1 of this study or use of any other the counter medications (OTC drug) during the 2 weeks period prior to the onset of study.
- Participation in any clinical trial within 12 weeks preceding Day 1 of the screening.
- Subjects who, through completion of this study, would have donated and/or lost more than 500 mL of blood in the past 3 months.
- There was no deviation in this regard.

## Sample Size

A sample size of twenty two (22) healthy adult human subjects fulfilling the inclusion criteria. Plasma samples of all evaluated subjects completing both the periods of the study will be analyzed.

## Randomization

Randomization schedule for all 22 volunteer was generated before the start of study by using SAS software. Volunteers were administered each treatment (Test or Reference). During the two period of the study according to the randomization schedule. The randomization was balanced and code was kept under controlled access. The drug accountability was maintained by pharmacist throughout study under supervision of chief investigator. All the study drugs (i.e. dispensed but un-dosed) returned from bio study was sent back to pharmacy and recorded.

## TREATMENTS

- **Reference (R)**
  Flomax® (tamsulosin hydrochloride) 0.4 mg.
- **Test (T)**
  Tamsulosin Hydrochloride Capsules USP 0.4 mg (each hard gelatin capsule contains Tamsulosin HCl USP 0.4 mg).
  The orders of receiving the test and reference products for each subject during the each period of the study were determined according to a SAS version 9.2 generated randomization schedule.

## SAFETY EVALUATION

The study formulations [test (T) or reference (R)] were evaluated in 12 subjects. Eleven (11) subjects were exposed to both test and reference formulations. Both the test (T) and reference (R) formulations were administered as a single oral doses of test formulation Tamsulosin Hydrochloride Capsules USP 0.4 mg (each hard gelatin capsule contains Tamsulosin HCl USP 0.4 mg) or reference formulation [Flomax® (tamsulosin hydrochloride) 0.4 mg] under

lowlight with approximately 240 mL of drinking water at ambient temperature 30 min after initiation of a high calorie breakfast after an overnight fast of atleast 10 hrs and not more than 12 hrs. similar procedure was followed in period II. Subjects received alternate treatment in the subsequent period in such a way that each completed subject received both the treatments at the end of the study.

## DRUG ANALYSIS

### Chemicals Used

*Buffer Solution*

Dissolved 154.16 mg ammonium acetate in 1000ml HPLC grade water.

*Mobile Phase*

Prepared a mixture of methanol and 2mM ammonium acetate buffer solution in ratio 90:10, V/V.

*Rinsing Solution*

Prepared a mixture of methanol and HPLC grade water in ratio 90:10, V/V.

5mM Sodium Carbonate buffer solution:

Dissolved 530 mg of sodium carbonate in 1000 ml of HPLC grade water.

*Diluent Solution*

Prepared a mixture of methanol and 5mM sodium carbonate buffer solution in ratio 50 : 50, V/V.

## RESULT

In order to investigate the relative bioavailability of the test drug against the reference drug, 90% confidence intervals were calculated for the intrasubject ratio (test/reference) of the geometric least square means of primary pharmacokinetic parameters ($C_{max,}$ $AUC_{0-t,}$ $AUC_{0-\infty}$ ). The pharmacokinetic parameters of test drug are summarized in Table 5.1.1 and pharmacokinetic parameters of reference drug are summarized in Table 5.1.2. the mean (SD) $C_{max}$ test and reference drugs are 1145.35 (457.66) ng/ml and 1162.58 (444.11) ng/ml, respectively, were attained at $T_{max}$ of 3.042 and 1.958 hours respectively. All subjects presented an $AUC_{0-t}/AUC_{0-\infty}$ ratio was greater than 80%. The mean elimination half life was 1.406 and 1.370 hours for test and reference drugs respectively. The study was completed. All parameters were determined in a model-independent way. The $T_{1/2}$ was determined by means of linear regression. The planned sampling time points were included for all pharmacokinetic measurements and calculations.

## DISCUSSIONS

To exclude any clinically important difference in the rate and extent at which the active entity of the drugs becomes available at the site of action, assessment of bioequivalence to test product to reference product is necessary. The current study had some limitations that should be considered. This was an open label study, so it might not address objectively the efficacy and safety profiles of the formulations tested. The study was also limited by inclusion of healthy male subjects who were administered single dose in fed conditions. This was a fed study in which the subjects were given healthy breakfast before the administration of the drug. This was also done to check the effect of the food on the absorption of drug.

## CONCLUSION

11 subjects completed the study with 6 adverse events. Subject No. 007 was withdrawn due to post dose adverse event emesis (vomiting). No clinically significant abnormalities on physical examination including vital signs measurement and ECG recording and laboratory results were observed. Both the drugs were well tolerated. All subjects presented an $AUC_{0-t}/AUC_{0-\infty}$ ratio was greater than 80%. The mean elimination half life was 1.406 and 1.370 hours for test and reference drugs respectively. The pharmacokinetic parameters were tested by paired t-test at 5% level of significance. It can be observed that all the p-values are greater than 0.05 indicating no significant difference among the parameters obtained for test and reference drugs. In order to investigate the relative bioavailability of the test drug against the reference drug, 90% confidence intervals were calculated for the intra subject ratio (test/reference) of the geometric least square means of primary pharmacokinetic parameters ($C_{max,}$ $AUC_{0-t,}$ $AUC_{0-\infty}$ ). The study may help in the preliminary requirement for generic products

to enter in the market, development of new formulations of the existing drugs, control of quality of a drug product during the early stages of marketing in order to determine the influence of processing factors, storage and stability on drug absorption and determination of influence, patient related factors and possible interaction with other drugs on the efficiency of absorption.

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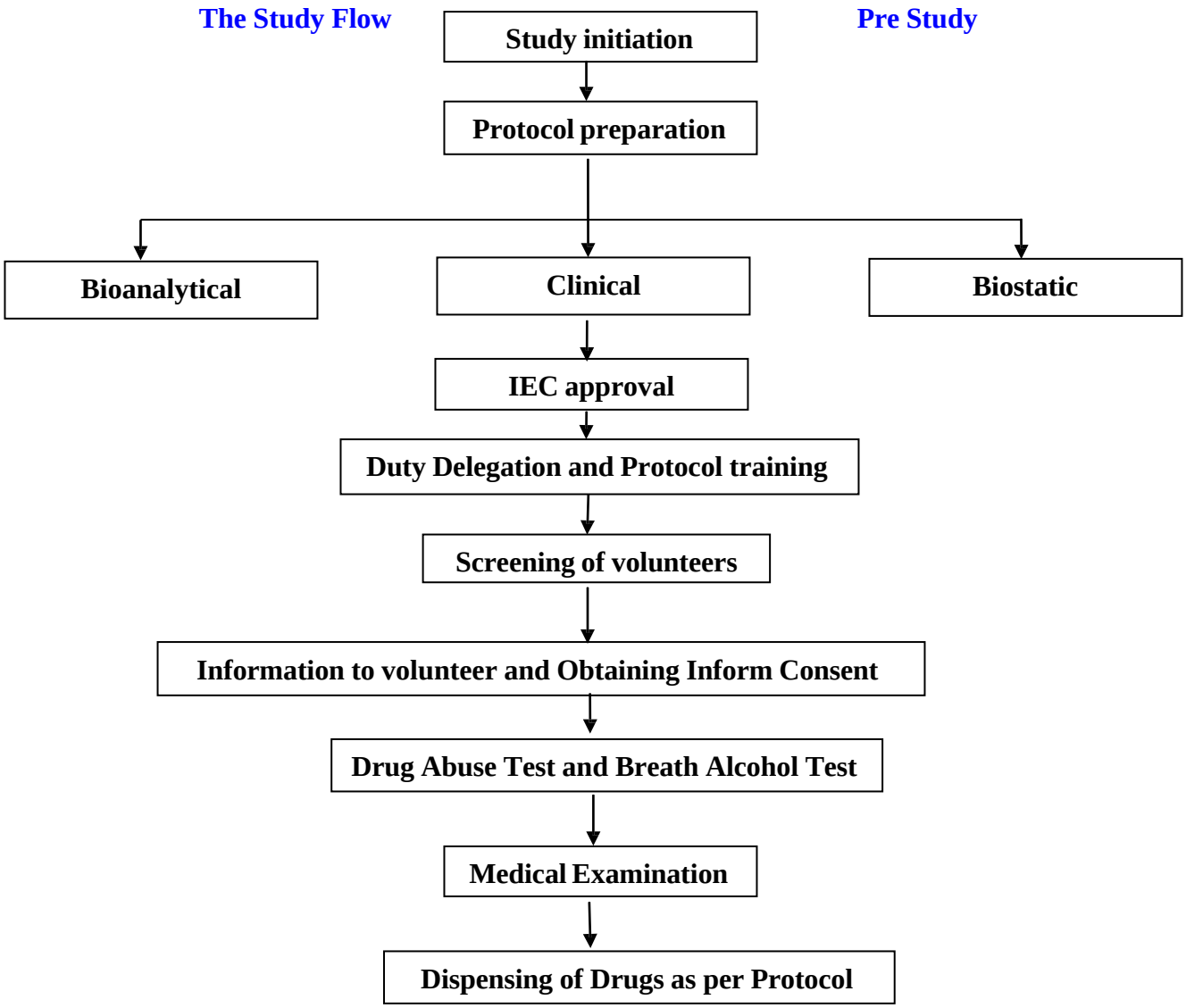
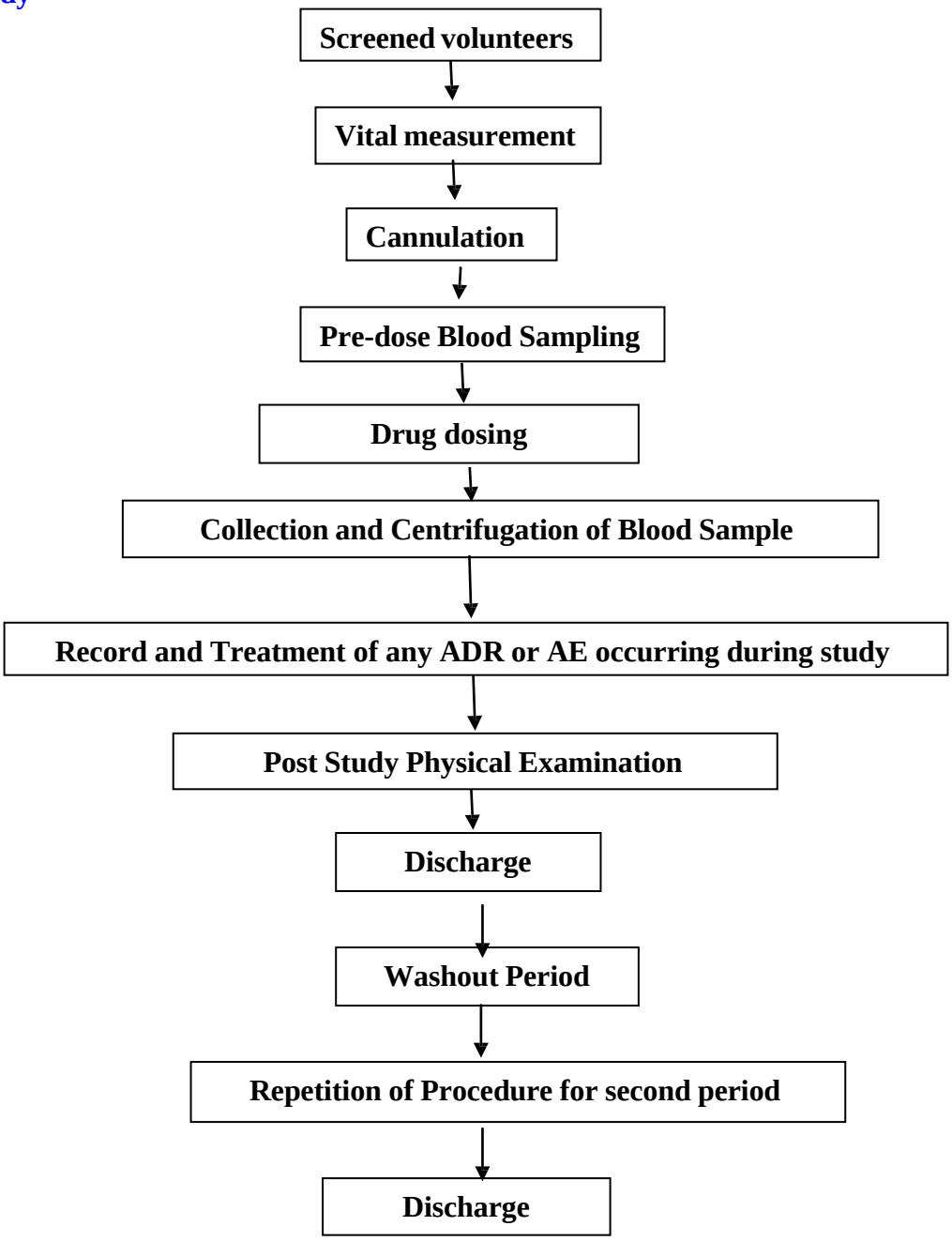
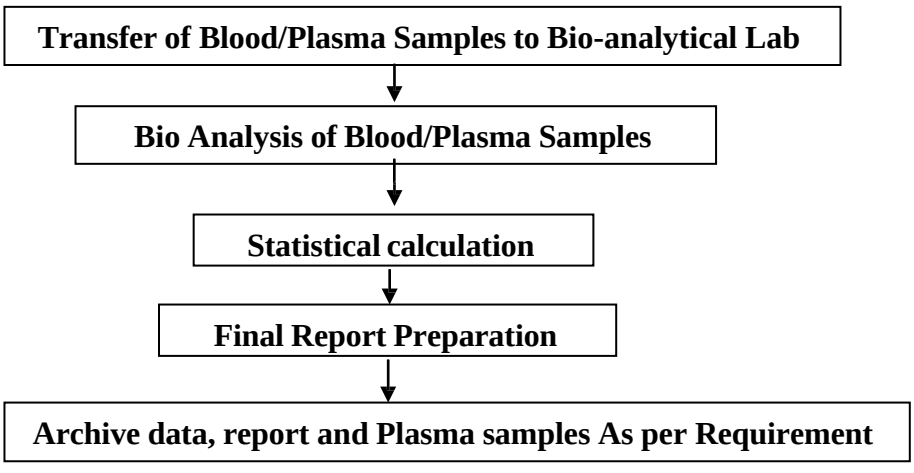
**Flow Chart Showing the Steps of Conduction of Study Material & Methods**

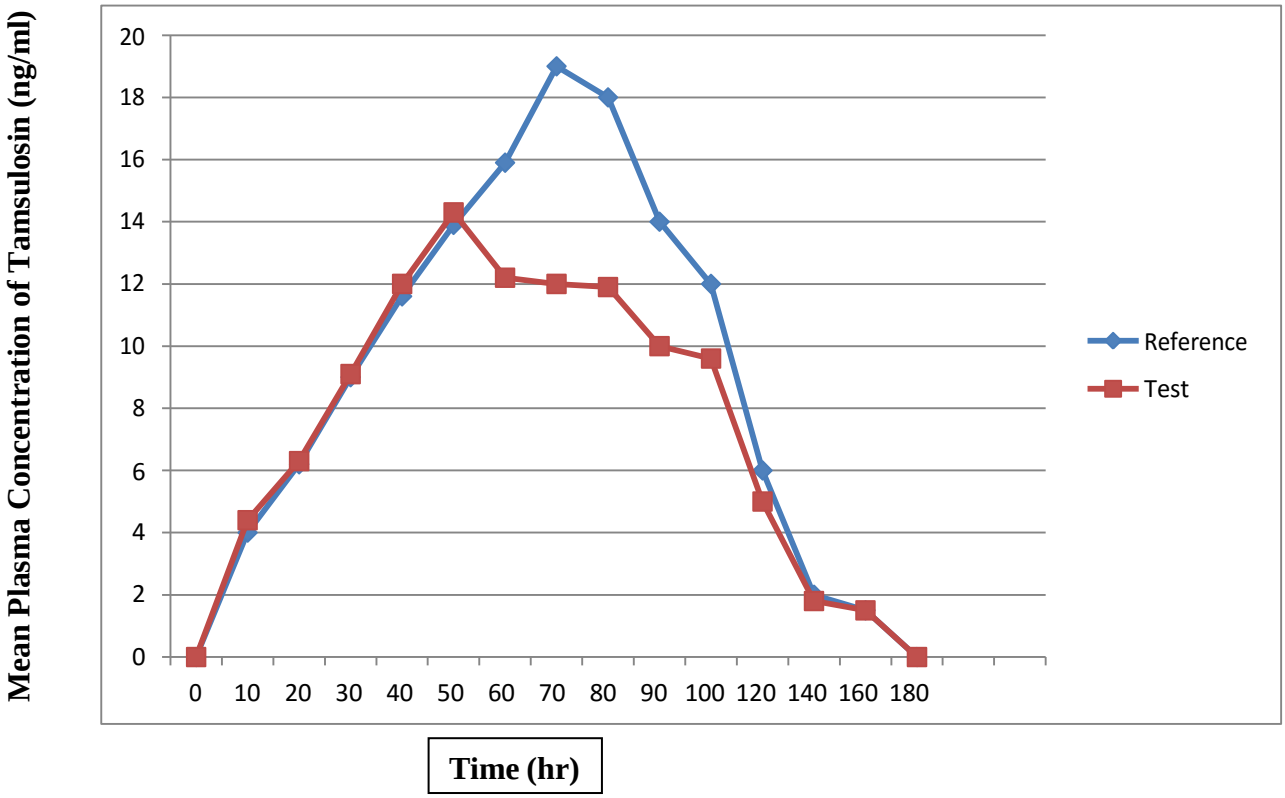


## During Study




## Post Study






Linear plot of mean plasma concentration of Tamsulosin versuses time curve after administration of Test (T) and Reference (R) formulations in healthy,adult, male human subjects, under fasting conditions.

| | T | R |
|---|---|---|
| Cmin (ng/mL)=4.0 ± 2.6 | | 3.8 ± 2.5 |
| Cmax (ng/mL)10.1 ± 4.8 | | 17.1 ± 17.1 |
| Cmax/Cmin Ratio3.1 ± 1.0 | | 5.3 ± 2.2 |
| Tmax (hours)6.0 | | 4.0 |
| AUCτ (ng•hr/mL)151 ± 81.5 | | 199 ± 94.1 |

Cmin = observed minimum concentration

Cmax = observed maximum tamsulosin hydrochloride plasma concentration

Tmax = median time-to-maximum concentration

AUCτ = Area under the tamsulosin hydrochloride and Flomax plasma time curve over the dosing interval

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