# STUDY TITLE

An open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover, oral bioequivalence study of Solifenacin Succinate Tablets 10 mg of airis PHARMA Private Limited., India with VESICARE® (Solifenacin Succinate) Tablets 10 mg of Astellas Pharma US, Inc., Northbrook, IL 60062 in healthy, adult, human subjects under fasting conditions.

**Country of Submission**: USA

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| **CONTRACT RESEARCH ORGANIZATION** |
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| **SPONSOR** |
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# Declaration by the KEY STUDY PERSONNEL

## Principal Investigator

I, the undersigned, have read and understood this protocol and hereby agree to conduct the study in accordance with the protocol, comply with all requirements regarding the obligations of Investigator, the Declaration of Helsinki (WMA General Assembly, Fortaleza, Brazil, October 2013), USFDA guidelines and guidelines of ICH for Good Clinical Practice set forth by applicable regulatory authorities.

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**Dr. A. Sumanlata, MBBS, DLO, Dip. Hosp. Admn.** Date

Principal Investigator

dr.sumanlata@qpsbioserve.com

Tel: +91-40-4377 0873 / 1875

## Bioanalytical Investigator

I, the undersigned, have read and understood this protocol, and this study will be performed in compliance with the final protocol, applicable principles of Good Laboratory Practices (GLP), relevant SOP’s and applicable regulatory guidelines.

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**Mr. L. Ramalingam** Date

GM - Bioanalytical

ramalingam@qpsbioserve.com

Tel: +91-40-4377 0873 / 1875

## Biostatistician

I, the undersigned, have read and understood this final protocol, and this study will be performed in accordance with the relevant SOP’s and applicable regulatory guidelines.

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**Mr. M. Raghavendra** Date

Lead Statistician

raghavendra.mamidi@qpsbioserve.com

Tel: +91-40-4377 0873 / 1875

## Sponsor’s Declaration

I, on behalf of airis PHARMA Private Limited., India, have read, understood and approve this protocol. I agree to comply with all the obligations of sponsor and all other pertinent requirements of the current version of the ICH ‘Guidelines for Good Clinical Practices’, ‘USFDA guidelines’, “Ethical Guidelines for Biomedical Research on Human Subjects” published by Indian Council of Medical Research (ICMR), New Delhi and ‘GCP’ guidelines issued by CDSCO and the Principles enunciated in the Declaration of Helsinki (WMA General Assembly, Fortaleza, Brazil, October 2013).

|  |  |  |
| --- | --- | --- |
|  | **Signature** | **Date** |
| **Dr. Ramesh Kannuri, M.Pharm, PhD**  airis PHARMA Private Limited  Plot No 64 and 65, Survey No.342,  ALEAP Industrial Estate, Opp. JNTU,  Pragathi Nagar  Hyderabad-500090, India  Tel:91-7661993111 |  |  |

# Synopsis

| **SYNOPSIS** | | | | |
| --- | --- | --- | --- | --- |
| **Study Title** | An open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover, oral bioequivalence study of Solifenacin Succinate Tablets 10 mg of airis PHARMA Private Limited., India with VESICARE® (Solifenacin Succinate) Tablets 10 mg of Astellas Pharma US, Inc., Northbrook, IL 60062 in healthy, adult, human subjects under fasting conditions. | | | |
| **Study Design** | An open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover, oral bioequivalence study in healthy, adult, human subjects under fasting conditions. | | | |
| **Study Objective(s)** | To assess the bioequivalence of Solifenacin Succinate Tablets 10 mg of airis PHARMA Private Limited., India with VESICARE® (Solifenacin Succinate) Tablets 10 mg of Astellas Pharma US, Inc., Northbrook, IL 60062 in healthy, adult, human subjects under fasting conditions | | | |
| To monitor adverse events and ensure the safety of subjects | | | |
| Sample Size | 48 healthy, adult, human subjects will be recruited in the study | | | |
| **Washout Period** | At least 21 days between each drug administration. | | | |
| **Investigational Drug Products** | Test (T) | Solifenacin Succinate Tablets 10 mg  *Manufactured by* : Kemwell Biopharma Pvt Ltd, India  *Manufactured for :* airis PHARMA Private Limited., India | | |
| Reference  (R) | VESICARE ® (Solifenacin Succinate) Tablets 10 mg  *Manufactured by:* Astellas Pharma Technologies, Inc.  Norman, Oklahoma 73072  *Marketed and Distributed by:* Astellas Pharma US, Inc.,Northbrook, IL 60062 | | |
| Subject Eligibility Criteria | Volunteers willing to participate in the study have to be healthy, adult, humans between 18 and 45 years of age (both inclusive) and body mass index between 18.5 and 29.9 Kg/height in m2 (both inclusive).  Demographic data, medical history, general and physical examination, ECG, Hematology, Biochemistry, Serology, Urine analysis, Urine Pregnancy test (for females), Urine drug screening and alcohol test will be performed.  The volunteers who meet the inclusion and exclusion criteria will be enrolled into the study. | | | |
| Subject  Housing | In each period, the subjects will be housed from at least 11 hours before drug administration to at least 24 hours after drug administration. Subjects will report to study site for 48.00 and 72.00 hours post-dose return visits. | | | |
| Study Duration | The total duration of the study from enrollment to end of the study is approximately 26 days. | | | |
| **Drug Administration Procedure** | In each period, after an overnight fast of at least 10 hours, subjects will receive single dose of Test (T) or Reference (R) product while in sitting posture with about240 ± 2ml of drinking water according to a randomization schedule in the presence of investigator.  Oral cavity check will be carried out by the trained study personnel immediately after drug administration.  In total, there will be 2 study periods, after the last period each subject will have received the study products, Test (T) once and Reference (R) once. | | | |
| **Study Restrictions** | Water | | | 1.00 hr pre-dose to 1.00 hr post dose. |
| Physical Activity | | | Remain seated or semi recumbent position for the first 4.00 hrs after investigational product administration and avoid severe physical exertion. |
| **Safety Monitoring/ Period** | * Blood pressure and Pulse rate will be examined at the time of admission to clinical unit, prior to drug administration (0.00 hr), 2.00 and 8.00 hours post dose (within ± 40 minutes from the scheduled time) and at the time of check out. * Oral temperature will be examined at the time of admission to clinical unit, prior to drug administration (0.00 hr) and at the time of check out. * Subject’s wellbeing will be questioned at 0.00, 2.00 and 8.00 hours (within ± 40 minutes from the scheduled time) along with vitals and at the time of check out. * An ECG will be performed within 60 minutes prior to check-out. | | | |
| PK Sampling/ Period | Blood samples (4 ml) will be collected at Pre-dose (0.00) and at 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 6.50, 7.00, 7.50, 8.00, 8.50, 9.00, 10.00, 12.00, 24.00, 48.00 and 72.00 hours post dose.  A total of twenty-three samples will be collected from each subject during each period. The total blood loss for each subject is about 244 mL and not exceeding 244 + 10 mL for the study.  The blood samples will be collected in K2EDTA tubes. After collection, the plasma will be separated by centrifuging the samples at 3000 RPM at 4ºC for 10 minutes.  The plasma will be transferred into two pre-labeled sample tubes. 0.8 mL of plasma will be transferred into each aliquot and will be stored at -20ºC ± 10ºC till analysis. | | | |
| **Analytical Methods** | Plasma concentrations of Solifenacin will be assayed by a validated LC-MS/MS analytical method. | | | |
| **Pharmacokinetic Parameters** | Primary: | | Cmax and AUC0-72 | |
| Secondary: | | Tmax | |
| Bioequivalence Criteria | The test (T) product is considered as bioequivalent to the reference (R) if the 90% two one sided confidence interval for the difference of the least square means of the logarithmic transformed values of Cmax and AUC0-72 at 5 % level of significance is between 80.00% and 125.00% for Solifenacin. | | | |

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# FACILITIES

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| --- | --- |
| Clinical Laboratory Facility | QPS Bioserve India Pvt. Limited,  #6-56/6/1A, Opp: IDPL Factory,  Balanagar, Hyderabad-500 037,  Telangana, India.  Tel: +91-40-4377 0873 / 1875  Fax: +91-40-4377 0877 |
| Clinical, Bioanalytical, Pharmacokinetic & Statistical Analysis and Reporting Facility | QPS Bioserve India Pvt. Limited,  #6-56/6/1A, Opp: IDPL Factory,  Balanagar, Hyderabad-500 037,  Telangana, India.  Tel: +91-40-4377 0873 / 1875  Fax: +91-40-4377 0877 |
| Ethics Committee | Dr. A. S. Kanagasabapathy,  Chairperson,  QPS Bioserve Ethics Committee  #6-56/6/1A, Opp: IDPL Factory,  Balanagar, Hyderabad-500 037,  Telangana, India.  Tel: +91-40-4377 0873 / 1875  Fax: +91-40-4377 0877 |
| Drug Controller General of India (DCGI) | The Drugs Controller General (India)  Directorate General of Health Services  Ministry of Health & Family Welfare  FDA Bhawan,  Near Mata Sundari Women’s College  Kotla Road, New Delhi-110 002  E-mail:- [dci@nb.nic.in](mailto:dci@nb.nic.in) |
| Head of Institution | Dr. V.V.S. Shiva Prasad  Chief Operating Officer,  QPS Bioserve India Pvt. Limited  #6-56/6/1A, Opp: IDPL Factory,  Balanagar, Hyderabad-500 037,  Telangana, India.  Tel: +91-40-4377 0873 / 1875  Fax: +91-40-4377 0877 |

# Ethical considerations

## Basic Principles

The study will be carried out in accordance with the provisions of the current version of the ICH ‘Guidelines for Good Clinical Practices’, ICMR ‘Guidelines for Biomedical Research on Human subjects’, USFDA guidelines, and the principles enunciated in the Declaration of Helsinki (WMA General Assembly, Fortaleza, Brazil, October 2013).

## Institutional Ethics Committee

The protocol and informed consent form will be submitted to the Institutional Ethics Committee for review. Upon approval, the study will be conducted as per the approved protocol.

## Informed Consent

Volunteers will be given enough time to understand the study procedures. The potential hazards, benefits and the rights of the subject(s) during the course of the study will be explained in English or vernacular language and the volunteer(s) are encouraged to seek clarifications. For volunteers who have difficulty in reading and/or understanding, written consent will be obtained by a legally acceptable representative or impartial witness. Audio- video recording of Informed consent will be performed. A written informed consent signed and dated by the subject and the investigator will be obtained for each subject in the study and a photocopy of the same will be provided to the subject.

## Termination of the Study

1. The sponsor reserves the right to discontinue the study at any time. Reasons for the termination will be provided to the subjects, IEC and Regulatory authorities as applicable.
2. The investigator reserves the right to discontinue the study at any time for the reasons of subject’s safety and welfare.
3. The IEC may terminate the study, if there are major violations of ethics or due to any serious adverse event(s).

## Subject Compensation

The subjects will be paid an adequate compensation approved by the IEC, on account of their time, participation in the trial and for any inconvenience caused.

## Insurance Policy

The study will be covered by an insurance contract, where in all subjects participating in the study are covered for indemnity.

## Confidentiality

The personal and medical information of the study participants will be kept confidential. The study data is only accessible for study personnel, monitors, quality assurance auditors, IEC, sponsor representative(s) and regulatory authorities.

# BRIEF PHARMACOLOGY

## Description

VESIcare® (solifenacin succinate) is a muscarinic receptor [antagonist](http://www.rxlist.com/script/main/art.asp?articlekey=7836). Chemically, solifenacin succinate is butanedioic acid, compounded with (1S)-(3R)-1-azabicyclo[2.2.2]oct-3-yl 3,4-dihydro-1-phenyl-2(1H)iso-quinolinecarboxylate (1:1) having an empirical formula of C23H26N2O2•C4H6O4, and a molecular weight of 480.55. The structural formula of solifenacin succinate is:

|  |
| --- |
| VESIcare (solifenacin succinate) Structural Formula Illustration |

Solifenacin succinate is a white to pale-yellowish-white crystal or crystalline powder. It is freely soluble at room temperature in water, glacial [acetic acid](http://www.rxlist.com/script/main/art.asp?articlekey=32085), dimethyl sulfoxide, and methanol. Each VESIcare tablet contains 5 or 10 mg of solifenacin succinate and is formulated for oral administration. In addition to the active ingredient solifenacin succinate, each VESIcare tablet also contains the following inert ingredients: lactose monohydrate, corn starch, hypromellose 2910, magnesium stearate, talc, polyethylene glycol 8000 and titanium dioxide with yellow ferric oxide (5 mg VESIcare tablet) or red ferric oxide (10 mg VESIcare tablet).

## Mechanism of Action

Solifenacin is a competitive muscarinic receptor [antagonist](http://www.rxlist.com/script/main/art.asp?articlekey=7836). Muscarinic receptors play an important role in several major cholinergically mediated functions, including contractions of urinary bladder [smooth muscle](http://www.rxlist.com/script/main/art.asp?articlekey=5514) and stimulation of salivary secretion.

## Pharmacokinetics

**Absorption**

After oral administration of VESIcare to healthy volunteers, peak plasma levels (Cmax) of solifenacin are reached within 3 to 8 hours after administration, and at steady state ranged from 32.3 to 62.9 ng/mL for the 5 and 10 mg VESIcare tablets, respectively. The absolute bioavailability of solifenacin is approximately 90%, and plasma concentrations of solifenacin are proportional to the dose administered.

**Food Effect**

VESIcare may be administered without regard to meals. A single 10 mg dose administration of VESIcare with food increased Cmax and AUC by 4% and 3%, respectively.

**Distribution**

Solifenacin is approximately 98% (in vivo) bound to human plasma proteins, principally to ∞1-acid [glycoprotein](http://www.rxlist.com/script/main/art.asp?articlekey=16842). Solifenacin is highly distributed to non-CNS tissues, having a mean steady-state volume of distribution of 600L.

**Metabolism**

Solifenacin is extensively metabolized in the liver. The primary pathway for elimination is by way of CYP3A4; however, alternate metabolic pathways exist. The primary metabolic routes of solifenacin are through N-oxidation of the quinuclidin ring and 4R-hydroxylation of tetrahydroisoquinoline ring. One pharmacologically active metabolite (4R-hydroxy solifenacin), occurring at low concentrations and unlikely to contribute significantly to clinical activity, and three pharmacologically inactive metabolites (N-glucuronide and the N-oxide and 4R-hydroxy-N-oxide of solifenacin) have been found in human plasma after oral dosing.

**Elimination**

Following the administration of 10 mg of 14C-solifenacin succinate to healthy volunteers, 69.2% of the radioactivity was recovered in the urine and 22.5% in the feces over 26 days. Less than 15% (as mean value) of the dose was recovered in the urine as intact solifenacin. The major metabolites identified in urine were N-oxide of solifenacin, 4R-hydroxy solifenacin and 4R-hydroxy-N-oxide of solifenacin and in feces 4R-hydroxy solifenacin. The elimination half-life of solifenacin following chronic dosing is approximately 45-68 hours.

## Adverse Effects

**Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, [adverse reaction](http://www.rxlist.com/script/main/art.asp?articlekey=26227) rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

VESIcare has been evaluated for safety in 1811 patients in randomized, placebo-controlled trials. Expected adverse reactions of antimuscarinic agents are [dry mouth](http://www.rxlist.com/script/main/art.asp?articlekey=24997), constipation, blurred vision ([accommodation](http://www.rxlist.com/script/main/art.asp?articlekey=10528) abnormalities), urinary retention, and dry eyes. The incidence of dry mouth and constipation in patients treated with VESIcare was higher in the 10 mg compared to the 5 mg dose group.

In the four 12-week double-blind clinical trials, severe fecal impaction, [colonic](http://www.rxlist.com/script/main/art.asp?articlekey=19645) obstruction, and [intestinal obstruction](http://www.rxlist.com/script/main/art.asp?articlekey=4003) were reported in one patient each, all in the VESIcare 10 mg group. Angioneurotic [edema](http://www.rxlist.com/script/main/art.asp?articlekey=3192) has been reported in one patient taking VESIcare 5 mg. Compared to 12 weeks of treatment with VESIcare, the incidence and severity of adverse reactions were similar in patients who remained on drug for up to 12 months.

The most frequent adverse reaction leading to study discontinuation was dry mouth (1.5%). Table 1 lists the rates of identified adverse reactions, derived from all reported adverse events, in randomized, placebo-controlled trials at an incidence greater than placebo and in 1% or more of patients treated with VESIcare 5 or 10 mg once daily for up to 12 weeks.

**Table 1: Percentages of Patients with Identified Adverse Reactions, Derived from All Adverse Events Exceeding Placebo Rate and Reported by 1% or More Patients for Combined Pivotal Studies**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Placebo (%)** | **VESIcare 5 mg (%)** | **VESIcare 10 mg (%)** |
| Number of Patients | 1216 | 578 | 1233 |
| **GASTROINTESTINAL DISORDERS** | | | |
| Dry Mouth | 4.2 | 10.9 | 27.6 |
| Constipation | 2.9 | 5.4 | 13.4 |
| Nausea | 2 | 1.7 | 3.3 |
| Dyspepsia | 1 | 1.4 | 3.9 |
| Abdominal Pain Upper | 1 | 1.9 | 1.2 |
| Vomiting NOS | 0.9 | 0.2 | 1.1 |
| **INFECTIONS AND INFESTATIONS** | | | |
| [Urinary Tract Infection](http://www.rxlist.com/urine_infection/article.htm) NOS | 2.8 | 2.8 | 4.8 |
| Influenza | 1.3 | 2.2 | 0.9 |
| Pharyngitis NOS | 1 | 0.3 | 1.1 |

|  |  |  |  |
| --- | --- | --- | --- |
| **NERVOUS SYSTEM DISORDERS** | | | |
| Dizziness | 1.8 | 1.9 | 1.8 |
| **EYE DISORDERS** | | | |
| Vision Blurred | 1.8 | 3.8 | 4.8 |
| Dry Eyes NOS | 0.6 | 0.3 | 1.6 |
| **RENAL AND URINARY DISORDERS** | | | |
| Urinary Retention | 0.6 | 0 | 1.4 |
| **GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** | | | |
| Edema Lower Limb | 0.7 | 0.3 | 1.1 |
| Fatigue | 1.1 | 1 | 2.1 |
| **PSYCHIATRIC DISORDERS** | | | |
| Depression NOS | 0.8 | 1.2 | 0.8 |
| **RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** | | | |
| Cough | 0.2 | 0.2 | 1.1 |
| **VASCULAR DISORDERS** | | | |
| Hypertension NOS | 0.6 | 1.4 | 0.5 |

**Post-Marketing Experience**

Because these spontaneously reported events are from the worldwide postmarketing experience, the frequency of events and the role of solifenacin in their causation cannot be reliably determined.

The following events have been reported in association with solifenacin use in worldwide postmarketing experience:

**General:** peripheral edema, hypersensitivity reactions, including [angioedema](http://www.rxlist.com/script/main/art.asp?articlekey=2253) with [airway obstruction](http://www.rxlist.com/script/main/art.asp?articlekey=8541), rash, [pruritus](http://www.rxlist.com/script/main/art.asp?articlekey=5095), [urticaria](http://www.rxlist.com/script/main/art.asp?articlekey=5919), and anaphylactic reaction;

**Central Nervous:** headache, confusion, hallucinations, [delirium](http://www.rxlist.com/script/main/art.asp?articlekey=23364) and [somnolence](http://www.rxlist.com/script/main/art.asp?articlekey=13097);

**Cardiovascular:** QT prolongation; Torsade de Pointes, [atrial fibrillation](http://www.rxlist.com/script/main/art.asp?articlekey=2384), [tachycardia](http://www.rxlist.com/script/main/art.asp?articlekey=5698), [palpitations](http://www.rxlist.com/script/main/art.asp?articlekey=4741);

**Hepatic:** liver disorders mostly characterized by abnormal liver function tests, AST ([aspartate aminotransferase](http://www.rxlist.com/script/main/art.asp?articlekey=6610)), ALT ([alanine](http://www.rxlist.com/script/main/art.asp?articlekey=15589) [aminotransferase](http://www.rxlist.com/script/main/art.asp?articlekey=6591)), GGT (gamma-glutamyl transferase);

**Renal:** renal impairment;

**Metabolism and nutrition disorders:** decreased appetite, [hyperkalemia](http://www.rxlist.com/script/main/art.asp?articlekey=3837);

**Dermatologic:** exfoliative [dermatitis](http://www.rxlist.com/script/main/art.asp?articlekey=2951) and [erythema multiforme](http://www.rxlist.com/script/main/art.asp?articlekey=14094);

**Eye disorders:** [glaucoma](http://www.rxlist.com/script/main/art.asp?articlekey=3596);

**Gastrointestinal disorders:** [gastroesophageal reflux](http://www.rxlist.com/script/main/art.asp?articlekey=3554) disease and [ileus](http://www.rxlist.com/script/main/art.asp?articlekey=3896);

**Respiratory, thoracic and mediastinal disorders:** [dysphonia](http://www.rxlist.com/script/main/art.asp?articlekey=24137);

**Musculoskeletal and connective tissue disorders:** muscular weakness;

## Indications

VESIcare is a muscarinic [antagonist](http://www.rxlist.com/script/main/art.asp?articlekey=7836) indicated for the treatment of [overactive bladder](http://www.rxlist.com/script/main/art.asp?articlekey=18373) with symptoms of urge [urinary incontinence](http://www.rxlist.com/script/main/art.asp?articlekey=18377), urgency, and urinary frequency.

## Contraindications

VESIcare is contraindicated in patients with:

* urinary retention
* gastric retention
* uncontrolled narrow-angle [glaucoma](http://www.rxlist.com/script/main/art.asp?articlekey=3596)
* in patients who have demonstrated hypersensitivity to the drug

## Warnings and Precautions

**Angioedema and Anaphylactic Reactions**

[Angioedema](http://www.rxlist.com/script/main/art.asp?articlekey=2253) of the face, lips, tongue, and/or [larynx](http://www.rxlist.com/script/main/art.asp?articlekey=6224) have been reported with solifenacin. In some cases angioedema occurred after the first dose. Cases of angioedema have been reported to occur hours after the first dose or after multiple doses. Angioedema associated with upper [airway](http://www.rxlist.com/script/main/art.asp?articlekey=10665) swelling may be life threatening. If involvement of the tongue, hypopharynx, or larynx occurs, solifenacin should be promptly discontinued and appropriate therapy and/or measures necessary to ensure a patent airway should be promptly provided. Anaphylactic reactions have been reported rarely in patients treated with solifenacin succinate. Solifenacin succinate should not be used in patients with a known or suspected hypersensitivity to solifenacin succinate. In patients who develop anaphylactic reactions, solifenacin succinate should be discontinued and appropriate therapy and/or measures should be taken.

**Urinary Retention**

VESIcare, like other [anticholinergic](http://www.rxlist.com/script/main/art.asp?articlekey=2281) drugs, should be administered with caution to patients with clinically significant bladder outflow obstruction because of the risk of urinary retention.

**Gastrointestinal Disorders**

VESIcare, like other anticholinergics, should be used with caution in patients with decreased [gastrointestinal](http://www.rxlist.com/script/main/art.asp?articlekey=3555) motility.

**Central Nervous System Effects**

VESIcare is associated with anticholinergic central nervous system (CNS) effects. A variety of CNS anticholinergic effects have been reported, including headache, confusion, hallucinations and [somnolence](http://www.rxlist.com/script/main/art.asp?articlekey=13097). Patients should be monitored for signs of anticholinergic CNS effects, particularly after beginning treatment or increasing the dose. Advise patients not to drive or operate heavy machinery until they know how VESIcare affects them. If a patient experiences anticholinergic CNS effects, dose reduction or drug discontinuation should be considered.

**Controlled Narrow-Angle Glaucoma**

VESIcare should be used with caution in patients being treated for narrow-angle [glaucoma](http://www.rxlist.com/script/main/art.asp?articlekey=3596).

**Hepatic Impairment**

VESIcare should be used with caution in patients with [hepatic](http://www.rxlist.com/script/main/art.asp?articlekey=3704) impairment. Doses of VESIcare greater than 5 mg are not recommended in patients with moderate hepatic impairment (Child-Pugh B). VESIcare is not recommended for patients with severe hepatic impairment (Child-Pugh C).

**Renal Impairment**

VESIcare should be used with caution in patients with renal impairment. Doses of VESIcare greater than 5 mg are not recommended in patients with severe renal impairment (CLcr < 30 mL/min).

## Drug Interactions

**Potent CYP3A4 Inhibitors**

Following the administration of 10 mg of VESIcare in the presence of 400 mg of ketoconazole, a potent inhibitor of CYP3A4, the mean Cmax and AUC of solifenacin increased by 1.5 and 2.7-fold, respectively. Therefore, it is recommended not to exceed a 5 mg daily dose of VESIcare when administered with therapeutic doses of ketoconazole or other potent CYP3A4 inhibitors. The effects of weak or moderate CYP3A4 inhibitors were not examined.

**CYP3A4 Inducers**

There were no in vivo studies conducted to evaluate the effect of CYP3A4 inducers on VESIcare. In vitro drug [metabolism](http://www.rxlist.com/script/main/art.asp?articlekey=4359) studies have shown that solifenacin is a substrate of CYP3A4. Therefore, inducers of CYP3A4 may decrease the concentration of solifenacin.

**Drugs Metabolized by Cytochrome P450**

At therapeutic concentrations, solifenacin does not inhibit CYP1A1/2, 2C9, 2C19, 2D6, or 3A4 derived from human liver microsomes.

**Warfarin**

Solifenacin has no significant effect on the pharmacokinetics of R-warfarin or S-warfarin.

**Oral Contraceptives**

In the presence of solifenacin there are no significant changes in the plasma concentrations of combined oral contraceptives (ethinyl estradiol/[levonorgestrel](http://www.rxlist.com/script/main/art.asp?articlekey=30735)).

**Digoxin**

Solifenacin had no significant effect on the pharmacokinetics of digoxin (0.125 mg/day) in healthy subjects.

# INVESTIGATIONAL PLAN

## Rationale

This study is being conducted to compare the bioavailability and characterize the pharmacokinetic profile of the test formulation with respect to the reference formulation in healthy, adult, human subjects under fasting conditions.

## Study Objectives

The following are the study objectives

1. Primary Objective: To assess the bioequivalence of Solifenacin Succinate Tablets 10 mg of airis PHARMA Private Limited., India with VESICARE® (Solifenacin Succinate) Tablets 10 mg of Astellas Pharma US, Inc., Northbrook, IL 60062 in healthy, adult, human subjects under fasting conditions.
2. Secondary Objectives:

* To monitor adverse events and ensure the safety of subjects.

## Study Design

An open label, balanced, randomized, two-treatment, two-period, two-sequence, single dose, crossover, oral bioequivalence study in healthy, adult, human subjects under fasting conditions.

## Sample Size

48 healthy, adult, human subjects will be recruited into the study.

## Sample Size Justification

Based on the available literature data, the Intra-subject variability observed was found to be ~ 20 % for Cmax for Solifenacin succinate. Sample size computation was determined by considering the following assumptions:

T/R ratio ~ 89% to 112.4%

Intra- subject CV (%) ~ 20% for Cmax

Significance Level = 5%

Power = 80%

BE limit = 80% -125%

Based on the above estimates, a sample size of 45 subjects are required. However, considering dropouts and withdrawals, 48 subjects will be sufficient to establish bioequivalence between test and reference formulations with adequate power.

## Randomization

The randomization schedule will be generated using Proc Plan Procedure in SAS® Software (Version 9.4 or higher).

The following sequence would be followed:

|  |  |  |
| --- | --- | --- |
|  | **Period 1** | **Period 2** |
| Sequence 1 (24 subjects) | T | R |
| Sequence 2 (24 subjects) | R | T |

## Un Blinding

The bioanalytical division will be kept blinded to the randomization schedule until Pharmacokinetic and Statistical Analysis.

This is an open label study; hence this is not applicable.

## Washout Period

The half-life of Solifenacin is approximately 45-68 hours and hence 21 days washout period will be sufficient to avoid drug carryover effect.

# investigational DRUG PRODUCTS

## Test Product

Solifenacin Succinate Tablets 10 mg

*Manufctured by:* Kemwell Biopharm Pvt. Ltd., India

*Manufactured for:* airis PHARMA Private Limited., India.

## Reference Product

VESICARE ® (Solifenacin Succinate) Tablets 10 mg

*Manufactured by:* Astellas Pharma Technologies, Inc. Norman, Oklahoma 73072

*Marketed and Distributed by:* Astellas Pharma US, Inc.,Northbrook, IL 60062

## Drug Product Receipt and Storage

The sponsor will supply sufficient quantities of the test and reference products to allow the completion of the study and for retention. The study medication will be stored at recommended storage conditions in pharmacy

## Investigational Drug Product Dispensing and Accountability

Investigational drug product(s) will be dispensed in a suitable pack(s) as appropriate according to the randomization schedule. Standby investigational drug products will be dispensed in order to handle any unexpected loss or damage of the investigational drug product during administration. The unadministered/standby investigational drug product(s) will be accounted.

A specimen label of the pack is below:

|  |  |
| --- | --- |
| **FOR CLINICAL RESEARCH USE ONLY** | |
| Study No. |  |
| Period |  |
| Product Name |  |
| Subject No. |  |
| Batch / Lot No. |  |
| Randomization Code |  |

## 

## Retention Samples

The retention samples consist of a maximum of 300 units or sufficient quantity to perform five times all of the release tests required in the application or supplemental application. Each reserved sample will be retained and stored as per regulatory requirement at QPS Bioserve India Pvt. Limited.

## Unused Investigational Drug Products

The investigational drug products that have not been dispensed will be retained in their original containers. Any product that had been dispensed but not used including standby will be returned to the pharmacy.

# clinical phase

## Subject Screening

The following must be assessed by the Investigator or a physician within 21 days prior to the enrollment.

### Demographics

Medical history and demographic data, including name, sex, age, body weight (Kg), height (cm), BMI (Kg/m2) will be recorded.

### Physical Examination

Each volunteer will undergo a complete physical examination, including vital sign measurements, 12 lead-ECG.

### Pre-Study Laboratory Tests

#### Hematology

Total Leukocyte Count, total Erythrocyte Count, hemoglobin, HCT (PCV), Lymphocytes, monocytes, mixed cells/granulocytes (neutrophils, basophils, eosinophils) and platelet count.

#### Clinical Chemistry

Random blood glucose, BUN, serum creatinine, total bilirubin, ALT, AST, serum cholesterol, total proteins and electrolytes (Na and K).

#### Serology

HIV-1, HIV-2, HbsAg and HCV will be evaluated.

#### Urinalysis

* **Physical Examination**: Colour, appearance and specific gravity.
* **Chemical Examination**: pH, protein/albumin, glucose, ketones, bilirubin, blood and urobilinogen.

#### Drugs of Abuse

Subjects will be tested for drugs of abuse in urine. The drugs of abuse screen will include benzodiazepines, cocaine, amphetamines, cannabinoids, barbiturates and morphine.

#### Alcohol

Subjects will be tested for alcohol using a breath analyzer.

#### Pregnancy Test

For female subjects, a urine pregnancy test will be performed at screening and at each check-in in each period.

The pre-study laboratory test results will be examined by qualified personnel and eligible volunteers will be enrolled into the study. The clinical decision limits for pre-study are provided in appendix-I.

## Inclusion Criteria

A willing study participant to become eligible for the study must fulfill all of the following criteria:

1. Must be healthy, adult, human beings within 18 and 45 years of age (both inclusive) weighing at least 50 kg, having a body mass index between 18.5 and 29.9 (both inclusive), calculated as weight in Kg/height in m2.

Ability to understand and willingness to sign statements of informed consent.

1. Acceptable medical history, physical examination, laboratory investigations including Hematology, Clinical chemistry, Serology, Urine analysis, ECG results performed within 21 days prior to enrollment (Laboratory values must be within clinical decision limits or considered by the physician / investigator to be of no clinical significance).
2. Female Subjects

* of child bearing potential practicing an acceptable method of birth control for the duration of the study as judged by the investigator(s), such as condoms, foams, jellies, diaphragm, intrauterine device (IUD), or abstinence.
* surgically sterile (bilateral tubal ligation, bilateral oophorectomy, or hysterectomy has been performed on the subject).
* is clinically considered infertile or is in a menopausal state (at least one year without menses).

## Exclusion Criteria

A willing study participant will be excluded from the study, if any of the following criteria is noted:

1. Systolic blood pressure less than 90 mm of Hg or more than 140 mm of Hg and Diastolic blood pressure less than 60 mm of Hg or more than 90 mm of Hg.
2. Oral temperature below 95.0°F or above 98.6°F and pulse rate below 60/min or above 100/min.
3. History of hypersensitivity or idiosyncratic reaction to investigational drug product or any tricyclic compounds drugs such as amitriptyline, desipramine, imipramine, protriptyline and nortriptyline etc.,
4. Known history of cardiovascular, pulmonary, hepatic, renal, gastrointestinal, endocrine, immunological, dermatological, neurological, psychiatric disease or disorder.
5. History of gastrointestinal ulcer, GI bleeding or gastrointestinal surgery.
6. Presence of any significant organ abnormalities.
7. History of clinically significant allergies including drug allergies or allergic bronchial asthma.
8. Regular smoker who has a habit of smoking more than nine cigarettes per day and has difficulty in abstaining from smoking during sample collection period.
9. Habit of alcoholism and difficulty in abstaining from alcohol during the sample collection period.
10. Difficulty in abstaining from xanthine containing food or beverages (like tea, coffee, chocolates and cola drinks) and tobacco products at least 48 hours prior to check-in.
11. Difficulty in abstaining from xanthine containing food or beverages (like tea, coffee, chocolates and cola drinks) and tobacco products during in-house stay in the clinic.
12. Difficulty in abstaining from grapefruit/grape fruit juice/ flavonoid containing liquids for at least 48 hours prior to check-in.
13. Difficulty in abstaining from grapefruit/grape fruit juice/ flavonoid containing liquids during in-house stay in the clinic.
14. Intake of over the counter (OTC) or prescribed medications and enzyme modifying medication or systemic medication for the last 30 days before dosing.
15. Habit of tobacco chewing.
16. Confirmed positive in alcohol screening (breath alcohol test).
17. Confirmed positive in selected drug of abuse (for benzodiazepines, cannabinoids, amphetamine, cocaine, barbiturates, morphine) on the day of study check-in of both the periods.
18. Confirmed positive in hepatitis screening (HbsAg/HCV) or for HIV antibody.
19. Participated in any other clinical investigation using experimental drug/donated blood in past 90 days before the date of start of study.
20. Difficulty in swallowing Tablets.
21. Confirmed positive in urine pregnancy test (for females).
22. Female detected to be pregnant, breast feeding or who is likely to become pregnant during the study.

## Subject Housing

In each period, the subjects will be housed from at least 11 hours before drug administration to at least 24 hours after drug administration. Subjects will report to study site for 48.00 and 72.00 hours post-dose return visits.

## Drug Administration

In each period, after an overnight fast of at least 10 hours, subjects will receive single dose of Test (T) or Reference (R) product while in sitting posture with about240 ± 2ml of drinking water according to a randomization schedule in the presence of investigator.

Oral cavity check will be carried out by the trained study personnel immediately after drug administration.

In total, there will be 2 study periods, after the last period each subject will have received the study products, Test (T) once and Reference (R) once.

## Study Restrictions

1. Drinking water will be restricted from 1 hour pre-dose until 1-hour post dose except during administration of the drug. Drinking water will be allowed *ad libitum* at all other times.
2. The subject will be instructed to remain seated or semi recumbent position for the first four hours after dosing and avoid severe physical exertion throughout the in house period after dosing except when clinically indicated to change the posture or in case of any natural exigency.

## Distribution of Meal

All the subjects need to fast for at least 10 hours prior to dosing and for at least   
4.0 hours post-dose. A standardized meal will be given at appropriate times post dose during the in-house stay. All meal contents will be similar for all the subjects throughout the study.

**Note:**

* The subjects will not be given any grapefruit/grape fruit juice/ flavonoid containing liquids during the in-house stay in the clinic.
* The subjects will not be given any xanthine containing food or beverages (like tea, coffee, chocolates and cola drinks) during the in-house stay in the clinic.
* The subject will not be allowed to smoke during the in-house stay in the clinic.

The Investigator or designee can alter the subject’s diet based on the medical or physiological conditions and the details will be documented. In case the meal and PK sampling time coincides, meal will be served after collection of the PK sample.

## Blood Sampling

In each period, the PK samples (about 4 ml) will be collected at Pre-dose (0.00) and at 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 6.50, 7.00, 7.50, 8.00, 8.50, 9.00, 10.00, 12.00, 24.00, 48.00 and 72.00 hours post dose.

A heparin-lock technique will be used to prevent coagulation of the blood in the cannula. In order to reduce the fluctuation of the plasma concentration-time profiles due to the residual blood sample from the previous collection, the first 0.5 ml of blood will be discarded prior to each blood sample collection.

A total of twenty-three samples will be collected from each subject during each period. The total blood loss for each subject is about 244 mL (including 12 mL for the screening, 08 mL for post study evaluation, 20 mL for study analysis which will be used for generating pool of blank plasma for bio analytical purpose which will be collected at the time of pre-dose in period-I only and 20 mL discarded heparinized blood prior to sample collection through the cannula).

The total volume of blood loss for the study will be as follows

|  |  |
| --- | --- |
| Screening | About 12 mL |
| Post study | About 8 mL |
| Study Analysis | About 20 mL at the time of pre-dose in period-I only. |
| PK Sampling: | About 204 mL (23 X 2 X 4 mL + 20 mL discarded heparinized blood prior to sample collection through cannula). |
| Total: | About 244 mL |

The total blood loss for each subject is about 244 mL and not exceeding   
244 + 10 mL for the study.

In each period, blood samples will be collected by means of intravenous cannulation / veni-puncture and transferred into pre-labeled sample tube (mentioning Study number, Subject number, Period and Sampling time point) containing K2 EDTA as the anticoagulant. The sample tube will be inverted gently to and fro for each sample point**.**

The pre-dose sample will be collected within 1 hour prior to dosing and the post dose samples will be collected within 2 minutes of the schedule time for in house samples and ± 60 minutes of the schedule time for return visits. Any blood samples drawn beyond the specified window period will be recorded.

Actual time of sample collection will be considered for pharmacokinetic & statistical analysis.

After collection, the plasma will be separated by centrifuging the samples at   
3000 RPM at 4ºC for 10 minutes.

The plasma will be transferred into two pre-labeled sample tubes. 0.8 mL of plasma will be transferred into each aliquot and will be stored at -20ºC ± 10ºC till analysis.

## Safety Monitoring

### Vitals and Wellbeing

The following will be measured in both the periods:

* Blood pressure and Pulse rate will be examined at the time of admission to clinical unit, prior to drug administration (0.00 hr), 2.00, and 8.00 hours post dose (within ± 40 minutes from the scheduled time) and at the time of check out.
* Oral temperature will be examined at the time of admission to clinical unit, prior to drug administration (0.00 hr) and at the time of check out.
* Subject’s wellbeing will be questioned at prior to drug administration (0.00 hr), 2.00 and 8.00 hours post-dose (within ± 40 minutes from the scheduled time) along with vitals and at the time of check out.
* An ECG will be performed within 60 minutes prior to check-out.

### Handling of Adverse Event / Serious Adverse Event

Any Adverse event will be managed by qualified physician and if required subject will be shifted to the hospital for treatment.

The relationship of the adverse event to the study medication will be judged. All adverse events encountered during the study will be recorded. Subjects experiencing adverse events will be followed up until the adverse event is resolved or lost to follow-up.

The severity of the adverse events will be graded as follows:

| **SEVERITY RELATIONSHIP** | |
| --- | --- |
| Mild | Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient. |
| Moderate | Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning. |
| Severe | Events interrupt the participant’s normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating. |

| **CAUSALITY RELATIONSHIP** | |
| --- | --- |
| **Relationship** | **Description** |
| Certain | * Event or laboratory test abnormality, with plausible time relationship to drug intake. * Cannot be explained by disease or other drugs. * Response to withdrawal plausible (pharmacologically, pathologically) * Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) * Rechallenge satisfactory, if necessary. |
| Probable  (Likely) | * Event or laboratory test abnormality, with reasonable time relationship to drug intake * Unlikely to be attributed to disease or other drugs * Response to withdrawal clinically reasonable * Rechallenge not required. |
| Possible | * Event or laboratory test abnormality, with reasonable time relationship to drug intake. * Could also be explained by disease or other drugs. * Information on drug withdrawal may be lacking or unclear |
| Unlikely | * Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) * Disease or other drugs provide plausible explanations |
| Conditional  (Unclassified) | * Event or laboratory test abnormality * More data for proper assessment needed, or * Additional data under examination |
| Unassessable  (Unclassifiable) | * Report suggesting an adverse reaction * Cannot be judged because information is insufficient or contradictory * Data cannot be supplemented or verified |

|  |  |
| --- | --- |
| **EXPECTEDNESS RELATIONSHIP** | |
| Expectedness | Event is known to be associated with the intervention or condition under study. |
| Unexpectedness | Nature or severity of the event is not consistent with information about the condition under study or intervention in the protocol /consent form/ product brochure/ investigator brochure. |

### Concomitant medication

If drug therapy (concomitant medication) is required prior to or during the study or washout period, decisions will be taken by the investigator to continue or discontinue the subject based on the following:

1. The pharmacology and pharmacokinetics of the non-study medication.
2. The likelihood of drug-drug interactions, thereby affecting pharmacokinetic comparison of the study medications.
3. The time and duration of administration of the non-study medication.

All such instances will be recorded and reported in the final report.

### Serious Adverse Events Reporting

If any serious adverse event(s) occurred during the study, QPS Bioserve India Pvt. Limited will provide all necessary treatment. All SAE(s) will be reported to the Sponsor, DCGI and Ethics Committee verbally or E-mail within twenty four hours and a written report to Sponsor, DCGI and Ethics Committee within fourteen calendar days.

The Sponsor or his representative will report the serious adverse event(s) to the Chairman of Ethics Committee, Chairman of Independent Expert Committee constituted by DCGI (in case of death) and Head of the CRO within 14 calendar days. The Sponsor representative will pay the DCGI recommended compensation to the subject / nominee(s) within 30 calendar days after notification.

## Subject withdrawal/dropout

The investigator can withdraw any subject from the study due to one or more following reasons:

1. If the subject chooses to dropout from the study with or without stating any reason.
2. Since it is not in subject’s best interest to continue in the study, as per the opinion of investigator.
3. If the subject is found to be violating the inclusion and exclusion criteria.
4. When the subject requires the use of an unacceptable concomitant medication.
5. If the subject suffers from significant inter-current illness or has to undergo surgery during the study.
6. Subjects who experience emesis (vomiting) within two times median tmax of Solifenacin.
7. If subject experience serious adverse event, he/she will be discontinued from the study unconditionally.

The date and reason for withdrawal will be recorded in the subject withdrawal record. All the safety data normally required at the end of the study will be obtained, if possible.

## Post-study Laboratory Examination

The post-study laboratory tests will be carried out at the end of the clinical study /early withdrawal.

Each volunteer will undergo a 12 lead-ECG within 60 minutes prior to time of check-out.

### Hematology

Total leukocyte count, total erythrocyte count, hemoglobin, HCT (PCV), lymphocytes, monocytes, mixed cells/granulocytes (neutrophils, basophils, eosinophils) and platelet count.

### Clinical Chemistry

BUN, serum creatinine, total bilirubin, ALT, AST, serum cholesterol, total proteins and electrolytes (Na and K).

### Pregnancy Test

For female subjects, a urine pregnancy test will be performed at the End of Study or Early Termination procedures.

The post-study laboratory results will be examined by qualified personnel. The clinical decision limits for the post-study are provided in appendix-II. Clinically significant results will be considered as adverse events and necessary treatment and follow-up will be made.

## Rest Period

Rest period for this study is 90 days and subject should not participate in any other clinical investigation using experimental drug/donation of blood until the completion of rest period.

# BIOAnalytical procedures

Plasma concentrations of Solifenacin will be assayed by a validated   
LC-MS/MS analytical method.

The bioanalysis will be conducted using a validated method in accordance with the applicable principle of Good Laboratory Practices (GLP).

The subjects who have completed all the periods will be considered for the analysis. Samples of withdrawn or dropout subjects due to adverse events will also be analyzed, and only plasma concentration vs. time data of that subject will be tabulated separately and reported in the bioanalytical report and will not be included in pharmacokinetic and statistical analysis. Subjects who are withdrawn or dropout due to personal reasons or tested positive in urine drugs of abuse or breath alcohol test will not be considered for analysis.

Subject samples will be quantified using a calibration curve and analytical variations during sample analysis will be evaluated using at least 5% of Quality Control samples in each run.  Samples will be reanalyzed for analytical reasons and non-analytical reasons as per SOP (SOP No: BAU010) of QPS Bioserve India Pvt. Limited.

**Incurred Sample Reanalysis (ISR**): Incurred Sample Reanalysis will be performed for Solifenacin as per In house SOP of QPS Bioserve India Pvt Ltd.

# PHARMACOKINETIC AND STATISTICAL ANALYSIS

## Pharmacokinetic Analysis

Pharmacokinetic analysis will be conducted using Phoenix® WinNonlin® version 6.4 or higher. Pharmacokinetic analysis will include all the subjects who have completed the study. The data from the subject’s withdrawn/dropout will not be used for pharmacokinetic and statistical analysis, however, these concentration data will be tabulated in a separate table.

The missing samples (M) and Non Reportable Values (NRV) will be considered as missing and the concentration values below the limit of quantification (BLQ) will be designated as zero for pharmacokinetic analysis.

The following subjects will be excluded from the pharmacokinetic analysis:

* Subjects with pre-dose concentration more than 5% of the Cmax in any period.
* Subjects with first point Cmax.
* Subjects with four or more consecutive missing samples in any period.
* Subjects with less than three quantifiable post dose concentrations in any period.

The following pharmacokinetic parameters will be computed using non-compartmental model.

|  |  |
| --- | --- |
| Cmax | Maximum measured plasma concentration over the time span specified. |
| AUC0-72 | The area under the plasma concentration versus time curve, from time 0 to the 72 hour concentration, as calculated by the linear trapezoidal method. |
| tmax | Time of the maximum measured plasma concentration. If the maximum value occurs at more than one time point, tmax is defined as the first time point with this value. |

## Statistical Analysis

Statistical analysis will be performed using SAS® software version 9.4 or higher (SAS® Institute Inc., USA).

* 1. **Summary Statistics**

The descriptive statistics (such as count (N), mean, median, minimum, maximum, standard deviation (SD) and coefficient of variation (CV)) for the relevant pharmacokinetic parameters will be estimated for both Test and Reference formulations.

The geometric mean and coefficient of variation will be estimated for Cmax and AUC0-72.

* 1. **Analysis of variance**

The ANOVA will be estimated at alpha 0.05 on the log-transformed data for Cmax and AUC0-72. The ANOVA model will include sequence, treatment and period as fixed effects and subject (sequence) as random effect. The significance of the sequence effect at alpha 0.10 will be calculated using the subject nested within the sequence as the error term.

* 1. **Ratio analysis**

The ratio of least-square means (LSMs) of Test and Reference formulations will be calculated using the least square means for log-transformed pharmacokinetic parameters of Cmax and AUC0-72. The geometric mean will be reported for the log-transformed pharmacokinetic parameters of Cmax and AUC0-72 of the Test and Reference formulations.

* 1. **Intra-Subject Variability**

The Intra-Subject variability will be calculated using log transformed pharmacokinetic parameters of Cmax and AUC0-72.

* 1. **Power**

The power (i.e. probability of detection a 20% difference relative to the least square means of reference treatment at the 5% significance level under the null hypothesis) will be calculated for log-transformed Cmax and AUC0-72.

* 1. **Confidence Interval**

90% two one-sided confidence intervals for the difference between treatments least-square means will be calculated for the log-transformed Cmax and AUC0-72. The confidence interval will be expressed as percentages relative to the Least-square means of the reference treatment.

* 1. **Graphical Presentation of Data**

Individual and Mean plasma concentration vs. time plots will be generated on both Linear and Semi-log axis for Solifenacin.

## Bioequivalence Criteria

The test (T) product is considered as bioequivalent to the reference (R) if the 90% two one sided confidence interval for the difference of the least square means of the logarithmic transformed values of Cmax and AUC0-72 at 5 % level of significance is between 80.00% and 125.00% for Solifenacin.

## Outlier

Outliers in a data set are defined as observations that appear to be inconsistent in T/R ratios with the rest of the data for any primary PK parameter. They can be identified as the values, which completely distort descriptive statistics. Subjects who exhibit extremely high or low T/R ratios are detected using statistical method namely Studentized residual test (using SAS® software version 9.4 or higher). A valid clinical or physiological reason will be explored for such an outlier, if found, and will be reported if identified by the Investigator of the study.

However, to avoid the biasedness in the results, the statistical analysis will be performed on both the data sets i.e. including as well as excluding the outliers for the particular primary PK parameters.

The final study report will present the data including the outliers and the data excluding the outliers will be presented as a supportive data.

# PROTOCOL REVISIONS / AMENDMENTs

Any significant change in the study procedure or study design will only be effected upon agreement with the sponsor and after obtaining a favorable opinion from the IEC.

# deviations

All deviations from this protocol will be recorded, handled and reported as per the procedures.

# QUALITY ASSURANCE

Quality assurance conducts independent study audits during the study conduction. Quality assurance has access to all the study documents, related to this study.

# ARCHIVAL

All the electronic copy of the study data will be retained by QPS Bioserve India Private Limited for a period of 15 years after completion of the study and the paper study data will be archived for 5 years from the completion of the study.

# Study report

The final report will be prepared according to the eCTD (electronic Common Technical Document) format.

The study report will include reports on the clinical phase, bioanalytical phase and data analysis phase of the study. The report will contain data regarding the analytical methodology and the chromatography (including at least 20% of the serially selected subject chromatograms), the pharmacokinetic calculations, the statistical analysis of the data, and a clinical report along with raw data. The deviations from the protocol will be documented as protocol deviations and presented in the final report.

# REVISION SUMMARY

The revised protocol (version 01) will include the changes listed in appendix VI

# References

# 

* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm090334.pdf
* http://www.accessdata.fda.gov/drugsatfda\_docs/label/2013/021518s016lbl.pdf
* ICH (International Council for Harmonisation) E6 ‘Guideline for Good Clinical Practice’
* ICH (International Council for Harmonisation) E3 ‘Structure And Content of Clinical Study Reports’ (1995)
* Ethical Principles for Medical Research Involving Human Subjects, Declaration of Helsinki (Brazil 2013).
* The common technical document for the registration of pharmaceuticals for human use efficacy – M4E (R1) Clinical overview and clinical summary of module 2 module 5 : clinical study reports (2002)
* Schedule Y (amended version 2013) of CDSCO (Central Drugs Standard Control Organization).
* Ethical guidance for biomedical research on human participants, ICMR (Indian Council of Medical Research, 2006).

# GLOSSARY OF TERMS

1. **Adverse Event (AE):** An Adverse Event is any untoward medical occurrence in a subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.
2. **Actual Sampling Time:** The exact sampling time at which the sample was collected.
3. **Audit:** A systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately, reported according to the protocol, good clinical practice (GCP), and the applicable regulatory requirements.
4. **Bioavailability:** is a measurement of the rate and extent (amount) of drug that reaches the systemic circulation from the site of administration.
5. **Bioequivalence:** Pharmaceutical equivalents whose rate and extent of absorption are not statistically different when administered to patients or subjects at the same molar dose under similar experimental conditions.
6. **Case Report Form (CRF):** A printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor or on each trial subject.
7. **Check-in:** The process of admitting a volunteer to a study. Normally this is done on the day before dosing.
8. **Checkout**: The process of discharging a subject on completion of housing.
9. **Compliance:** Adherence to all the study requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
10. **Essential Documents:** Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.
11. **Good Clinical Practice (GCP):** A standard for design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trial that provides assurance that the data and reported results are credible and accurate, and that the rights integrity, and confidentiality of trial subjects are protected.
12. **Housing:** The time during which the subject is lodged in the clinical ward, from “check-in” to “check-out” after the last in-house sample is collected.
13. **Impartial Witness:** A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends and present during the entire informed consent process if the subject or the subject’s legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.
14. **Informed Consent:** A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject’s decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
15. **Investigational Product:** A pharmaceutical form of an active ingredient being tested or used as a reference in a clinical study.
16. **Investigator:** A person responsible for the conduct of the clinical trial at a trial site.
17. **Legally Acceptable Representative:** An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure[s] involved in the research.
18. **Monitoring:** The act of overseeing the progress of a clinical study, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), GCP, and the applicable regulatory requirement(s).
19. **Randomization:** The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.
20. **Return visits:** Blood samples collected outside the housing period, for which the subject makes scheduled visits.
21. **Sampling Time:** Time of blood collection after drug administration (in hours)
22. **Schedule Sampling Time:** The predetermined sampling time at which the same should be collected.
23. **Serious Adverse Event:** An adverse event is any undesirable experience associated with the use of a drug product in a subject. The event is serious and should be reported when the patient outcome is:

* **Death:** If the subject’s death is suspected as being a direct outcome of the adverse event.
* **Life-Threatening:** If the subject was at substantial risk of dying at the time of the adverse event or it is suspected that the use or continued use of the product would result in the subject’s death.
* **Hospitalization (initial or prolonged):** If admission to the hospital or prolongation of a hospital stay results because of the adverse event.
* **Disability:** If the adverse event resulted in a significant, persistent, or permanent change, impairment, damage or disruption in the subject’s body function / structure, physical activities or quality of life.
* **Congenital Anomaly:** If there are suspicions that exposure to a drug product prior to conception or during pregnancy resulted in an adverse outcome in the child.
* **Requires Intervention to Prevent Permanent Impairment or Damage:** If you suspect that the use of a drug product may result in a condition which required medical or surgical intervention to preclude permanent impairment or damage to a patient.

1. **Sponsor:** An individual, company, institution, or organization that takes responsibility for the initiation, management, and/or financing of a clinical trial.
2. **Standard Operating Procedures (SOPs):** Detailed, written instructions to achieve uniformity of the performance of a specific function.
3. **Study duration:** The period between start of study specific screening till the last compensation payment is made to the subject.
4. **Subject:** An individual who has been admitted into a given study.
5. **Volunteer:** A human who has shown interest in participating in a study
6. **Wellbeing (of the trial subjects):** The physical and mental integrity of subjects participating in a clinical trial.

# Abbreviations

|  |  |
| --- | --- |
| AE | Adverse Event |
| ALT | Alanine transaminase |
| ANOVA | Analysis of variance |
| AST | Aspartate transaminase |
| AUC | Area under the plasma concentration versus time curve |
| AUCt | Area under the plasma concentration versus time curve to the last measurable concentration (t) |
| AUCinf (AUCi) | Area under the plasma concentration versus time curve to infinity |
| BA | Bioavailability |
| BE | Bioequivalence |
| BLQ | Below Limit of Quantification |
| BP | Blood Pressure |
| BUN | Blood Urea Nitrogen |
| cm | Centimeter |
| Cmax | Maximum measured analyte concentration in the biological fluid |
| CV | Coefficient of Variation |
| ECG | Electrocardiogram |
| EU/dL | Ehrlich unit per deciliter |
| GCP | Good Clinical Practice |
| g/dL | gram per deciliter |
| HbsAg | Hepatitis B surface antigen |
| HCV | Hepatitis C virus |
| HIV | Human immunodeficiency virus |
| hr | Hour |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonisation. |
| ICMR | Indian Council of Medical Research. |
| IEC | Institutional Ethics Committee |
| IV | Intravenous |
| K | Potassium |
| K2EDTA | Dipotassium Ethylene diamine tetra acetic acid |
| kel | Elimination rate constant |
| Kg | Kilogram |
| LSM | Least-square means |
| mg | Milligram |
| mg/dL | Milligram per deciliter |
| ml | Milliliter |
| mm of Hg | Millimeter of Mercury |
| mm3 | Cubic millimeter |
| mmol/L | Milimol per litre |
| Na | Sodium |
| OTC | Over the Counter |
| PA (view) | Postero-Anterior view |
| PCV | Packed Cell Volume |
| PK | Pharmacokinetic |
| RBC | Red Blood Cells |
| SAS | Statistical Analysis System |
| SGOT | Serum Glutamic Oxaloacetic Transaminase |
| SGPT | Serum Glutamic Pyruvic Transaminase |
| SOP | Standard Operating Procedure |
| t1/2 | Elimination half-life |
| tmax | Time of the maximum measured plasma concentration |
| U/L | Units per liter |
| WBC | White Blood Cells |
| WMA | World Medical Association |
| % | Percentage |

APPENDIX – I   
PRE-STUDY LABORATORY ASSESSMENT

|  |  |  |  |
| --- | --- | --- | --- |
| **HAEMATOLOGY** | | | |
| **Parameter** | **Units** | **Clinical Decision Limits** | |
| **Male** | **Female** |
| Total Leukocyte Count (WBC Count) | 103/mm3 | 3.57 to 12.25 | 3.40 to 13.00 |
| Total Erythrocyte Count (RBC Count) | 106/mm3 | 3.83 to 6.88 | 2.98 to 6.50 |
| Hemoglobin | g/dL | ≥11.1 | ≥9.0 |
| HCT (PCV) | % | 33.3 to 56.1 | 27 to 47.3 |
| Lymphocytes | % | 14.4 to 49.5 | 14.4 to 49.5 |
| Monocytes | % | 2 to 11.5 | 2 to 10.4 |
| Mixed Cells/Granulocytes (Neutrophils, Basophils, Eosinophil’s) | % | 40.5 to 91.3 | 38.7 to 90.2 |
| Platelet Count | 103/mm3 | 131 to 508 | 130 to 456 |

|  |  |  |  |
| --- | --- | --- | --- |
| **CLINICAL CHEMISTRY / BIOCHEMISTRY** | | | |
| **Parameter** | **Units** | **Clinical Decision Limits** | |
| **Male** | **Female** |
| Random Blood Glucose | mg/dL | 61.2 to 163.2 | 63.9 to 163.2 |
| Blood Urea Nitrogen (BUN) | mg/dL | 6 to 26 | 6 to 26 |
| Serum Creatinine | mg/dL | 0.5 to 1.8 | 0.45 to 1.35 |
| Total Bilirubin | mg/dL | 0.39 to 1.5 | 0.3 to 1.25 |
| SGPT (ALT) | U/L | Less than 112.5 | Less than 85 |
| SGOT (AST) | U/L | 14 to 84 | 12 to 74 |
| Serum Cholesterol | mg/dL | 115 to 279 | 117 to 277 |
| Total Proteins | g/dL | 5.78 to 9.78 | 5.70 to 9.78 |
| Sodium | mmol/L | 122.4 to 159.5 | 122.4 to 159.5 |
| Potassium | mmol/L | 3.15 to 5.40 | 3.06 to 5.28 |

|  |  |
| --- | --- |
| **SEROLOGY** | |
| **Description** | **Clinical Decision Limits** |
| HIV – 1 | Negative |
| HIV – 2 | Negative |
| HbsAg | Negative |
| HCV | Negative |

|  |  |
| --- | --- |
| **DRUGS OF ABUSE** | |
| **Description** | **Clinical Decision Limits** |
| Benzodiazepines | Negative |
| Cannabinoids | Negative |
| Amphetamine | Negative |
| Cocaine | Negative |
| Barbiturates | Negative |
| Morphine | Negative |

|  |  |
| --- | --- |
| **URINE ANALYSIS** | |
| **Manual Examination** | |
| **Description** | **Clinical Decision Limits** |
| Colour | Colourless / Yellow |
| Appearance | Clear |
| **Instrumental Analysis** | |
| **Description** | **Clinical Decision Limits** |
| Glucose | Negative |
| Bilirubin | Negative |
| Ketones | Negative |
| Blood | Negative |
| pH | 5.0 – 8.0 |
| Protein / Albumin | Negative |
| Specific Gravity | 1.000 to 1.030 |
| Urobilinogen | 0.2 – 1.0 (EU/dL) |

|  |  |
| --- | --- |
| **Others** | 12 lead – ECG |
| Breath alcohol screening |
| Urine pregnancy test (for females) |

# APPENDIX – II POST-STUDY LABORATORY SAFETY ASSESSMENT

|  |  |  |  |
| --- | --- | --- | --- |
| **HAEMATOLOGY** | | | |
| **Parameter** | **Units** | **Clinical Decision Limits** | |
| **Male** | **Female** |
| Total Leukocyte Count (WBC Count) | 103/mm3 | 3.57 to 12.25 | 3.40 to 13.00 |
| Total Erythrocyte Count (RBC Count) | 106/mm3 | 3.83 to 6.88 | 2.98 to 6.50 |
| Hemoglobin | g/dL | ≥11.1 | ≥9.0 |
| HCT (PCV) | % | 33.3 to 56.1 | 27 to 47.3 |
| Lymphocytes | % | 14.4 to 49.5 | 14.4 to 49.5 |
| Monocytes | % | 2 to 11.5 | 2 to 10.4 |
| Mixed Cells/Granulocytes (Neutrophils, Basophils, Eosinophil’s) | % | 40.5 to 91.3 | 38.7 to 90.2 |
| Platelet Count | 103/mm3 | 131 to 508 | 130 to 456 |

|  |  |  |  |
| --- | --- | --- | --- |
| **CLINICAL CHEMISTRY / BIOCHEMISTRY** | | | |
| **Parameter** | **Units** | **Clinical Decision Limits** | |
| **Male** | **Female** |
| Blood Urea Nitrogen (BUN) | mg/dL | 6 to 26 | 6 to 26 |
| Serum Creatinine | mg/dL | 0.5 to 1.8 | 0.45 to 1.35 |
| Total Bilirubin | mg/dL | 0.39 to 1.5 | 0.3 to 1.25 |
| SGPT (ALT) | U/L | Less than 112.5 | Less than 85 |
| SGOT (AST) | U/L | 14 to 84 | 12 to 74 |
| Serum Cholesterol | mg/dL | 115 to 279 | 117 to 277 |
| Total Proteins | g/dL | 5.78 to 9.78 | 5.70 to 9.78 |
| Sodium | mmol/L | 122.4 to 159.5 | 122.4 to 159.5 |
| Potassium | mmol/L | 3.15 to 5.40 | 3.06 to 5.28 |

|  |  |
| --- | --- |
| **Others** | Urine pregnancy test (for females) |

# Appendix - III SCHEDULE OF EVENTS

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Activity** | **Screening**  **Within 21 days prior to enrollment** | **Study Period** | | | **Study completion/**  **Early Termination** |
| **Enrollment** | **Dosing** | **Check out** |
| Informed Consent# | X | X |  |  |  |
| Medical History and Demographic Data | X |  |  |  |  |
| Physical Examination | X |  |  |  |  |
| 12-lead ECG | X |  |  | X |  |
| Vital Signs Measurement | X | X | X | X |  |
| Hematology | X |  |  |  | X |
| Urine analysis | X |  |  |  |  |
| Clinical Chemistry | X |  |  |  | X |
| Serology (HIV-I & II, HbsAg & HCV) | X |  |  |  |  |
| Drugs of Abuse |  | X |  |  |  |
| Record of Concomitant Medication | X | X | X | X | X |
| Inclusion / Exclusion criteria |  | X |  |  |  |
| Breath alcohol Screening |  | X |  |  |  |
| Housing in Study Unit |  | X | X |  |  |
| Drug Dosing |  |  | X |  |  |
| PK Sampling\*\* |  |  | X | X |  |
| Adverse Events Monitoring |  | X | X | X | X |
| Urine pregnancy test (for females) | X | X |  |  | X |

\* # At the time of P-I check-in only

\*\* Including return visit samples at 48.00 and 72.00 hr post-dose

# Appendix IV (TIMETABLE OF EVENTS)

| **Time Relative to Dose Administration (h)** | **Clock Time in h (Days)** # | **Check-in / check-out** | **Vitals** | **Blood Sampling** | **Drug dosing** |
| --- | --- | --- | --- | --- | --- |
| Upto -11.00 | Upto 2100 (D 1) | **X** | **X** |  |  |
| Pre dose Sample (0.00 hr) | Prior to dosing  (D 2) |  | **X** | **X** |  |
| 0.00 | 0800 (D 2) |  |  |  | Solifenacin T/R |
| 1.00 | 0900 (D 2) |  |  | **X** |  |
| 1.50 | 0930 (D 2) |  |  | **X** |  |
| 2.00 | 1000 (D 2) |  | **X** | **X** |  |
| 2.50 | 1030 (D 2) |  |  | **X** |  |
| 3.00 | 1100 (D 2) |  |  | **X** |  |
| 3.50 | 1030 (D 2) |  |  | **X** |  |
| 4.00 | 1200 (D 2) |  |  | **X** |  |
| 4.50 | 1230 (D 2) |  |  | **X** |  |
| 5.00 | 1300 (D 2) |  |  | **X** |  |
| 5.50 | 1330 (D 2) |  |  | **X** |  |
| 6.00 | 1400 (D 2) |  |  | **X** |  |
| 6.50 | 1430 (D 2) |  |  | **X** |  |
| 7.00 | 1500 (D 2) |  |  | **X** |  |
| 7.50 | 1430 (D 2) |  |  | **X** |  |
| 8.00 | 1600 (D 2) |  | **X** | **X** |  |
| 8.50 | 1630 (D 2) |  |  | **X** |  |
| 9.00 | 1700 (D 2) |  |  | **X** |  |
| 10.00 | 1800 (D 2) |  |  | **X** |  |
| 12.00 | 2000 (D 2) |  |  | **X** |  |
| 24.00 | 0800 (D 3) | **X** | **X** | **X** |  |
| 48.00 | 0800 (D 4) |  |  | **X** |  |
| 72.00 | 0800 (D 5) |  |  | **X** |  |

Note: # The above table is indicative. This schedule may change based on actual dosing time.

Blood for post study safety assessment will also be collected after the last sample (72.00 hr post-dose) of period II.

# Appendix - v STUDY FLOWCHART

Randomization

Screening

Eligibility Criteria

Subject Selection (N = 48)

Period I

Treatment T (24) Treatment R (24)

Washout

(At least 21 Days)

Crossover

Period II

Treatment R (24) Treatment T (24)

PK and Statistical Analysis

Bioanalysis of samples

Final Study Report

N – Number of subjects

R – Reference Product

T – Test product

# Appendix - VI REVISION SUMMARY

| **Change Description** | **Section Affected** | **Justification** |
| --- | --- | --- |
| **Version 00 to Version 01** | | |
| Updated Principal Investigator details | Section 3.1 | Updated as per Administrative changes |
| Updated Bioanalytical Investigator designation | Section 3.2 | Updated as per Administrative changes |
| Updated Sample Size | Section 4.0 and 8.4 | Updated due to sponsor request |
| Updated the subject housing and return visits | Section 4.0 and 10.4 | Updated as per PI suggestion |
| Updated the safety monitoring for vitals and wellbeing time points | Section 4.0 and 10.9.1 | Updated based on subject housing |
| Updated PK Sampling/ Period for total blood volume collected from each subject and aliquot volume | Section 4.0 and 10.8 | Updated due to subject housing as the 48.00 and 72.00 are updated to post-dose return visits and Bioanalytical method |
| Updated Sample Size Justification | Section 8.5 | Updated due to change in Sample size. |
| Updated Randomization | Section 8.6 | Updated due to change in sample size |
| Deleted Statistical Analysis for multiple groups | Section 12.4 | Updated due to performing the study in single group |
| Updated Revision Summary | Section 18.0 | In-line with current practice |
| Updated Clinical Decision limits | Appendix I and II | In-line with current practice |
| Updated about return visit samples | Appendix III | Updated based on return visit samples |
| Updated the time table of events | Appendix IV | Updated based on subject housing |
| Updated Sample size | Appendix V | Updated due to change in Sample Size |