CLINICAL STUDY REPORT

1.0 TITLE PAGE

A study to evaluate the impact of different controlled ovarian stimulation protocols on physical and psychological burden in patients undergoing In-Vitro Fertilization/In-Vitro Cytoplasmic Sperm Injection

Test Drug/Investigational Product	Not Applicable
Development Phase of Study	Not Applicable (observational study)
Protocol Identification Number	P 08388
Indication Studied	In-Vitro Fertilization/In-Vitro Cytoplasmic Sperm Injection
Study Design	Two-arm, multi-center, prospective, non-interventional, observational, comparative study
Patient Population	18-45 years old females undergoing Controlled Ovarian Stimulation (COS) as a part of first cycle IVF/ICSI treatment
Study Duration	Approximately 15 months
Sponsor	Organon (India) Private Limited, a subsidiary of Merck & Co. Inc., Whitehouse Station, NJ, USA. 8th Floor, Platina, Plot No. C 59, G- Block, Bandra Kurla Complex, Bandra (E), Mumbai 400098, Maharashtra (INDIA) Tel: +91 22 67898888 Fax: +91 22 67898889
Study Initiation Date	14/Jun/2012 (first subject enrolled)
Study Completion Date	18/Sep/2013 (last subject last visit)
Principal or Coordinating Investigator(s)	Dr. Manish R Banker Dr. Firuza Parikh Dr. Hrishikesh Pai Dr. Pratap Kumar Dr. Monu Patnaik Dr. Mamata Deenadayal Dr. Nayana Patel Dr Jatin Shah Dr. B. Sarat Dr. Madhuri Patil Dr. K. Jayakrishnan Dr. Jayashree Bhattacharya
Sponsor's Responsible Medical Officer	Dr. Ashish Birla Project Manager – MSD Tel-+91 22 67892304 M-+91 9967622006 **email- ashish.birla2@merck.com**

Version No.: 1
Date: 06/May/2014

2.0 SYNOPSIS

Name of Sponsor/ Company: Organon (India) Private Limited, a subsidiary of Merck & Co. Inc.,	Individual Study Table Referring to part of the dossier:	(For National Authority Use only)
Name of Finished Product: Not applicable	Volume:	
Name of Active Ingredient: Not applicable	Page:	

Title of Study: A study to evaluate the impact of different controlled ovarian stimulation protocols on physical and psychological burden in patients undergoing In-Vitro Fertilization/In-vitro Cytoplasmic Sperm Injection (Protocol number P 08388)

Investigators: 12

Study Center(s): 12

Publication (reference): None

Study period (years): Approximately 15 months **(Date of first enrollment):** 14/Jun/2012 **(date of last completed):** 18/Sep/2013	**Phase of Development:** Not applicable

Objectives:

Primary Trial Objective: To document and compare psychological, physical burden, impact on patient's well-being and impact of medication associated with controlled ovarian stimulation among women undergoing first cycle IVF/ICSI between those receiving standard of care gonadotropin with daily administration of GnRH agonist versus recombinant gonadotropin in pen formulation with daily administration of GnRH antagonist.

Secondary Trial Objective: To compare safety of controlled ovarian stimulation among women undergoing first cycle IVF/ICSI between those receiving standard of care gonadotropin with daily administration of GnRH agonist versus recombinant gonadotropin in pen formulation with daily administration of GnRH antagonist.

Methodology: This was a two-arm, multi-centric, prospective, non-interventional, observational, comparative study. The study was carried out for a period of 15 months at 12 centres across India. This study was conducted among female subjects of 18-45 years of age undergoing Controlled Ovarian Stimulation (COS) as a part of first cycle IVF/ICSI.

The number of subjects who were screened for the study was 712. After screening, only those subjects, found eligible as per the inclusion/exclusion criteria were enrolled for the study. A total of 692 female subjects were enrolled in the study.

Subjects were enrolled in the ratio of 1**:** 2 (Group A, GnRH Antagonist**:** Group B, GnRH Agonist). A block of six subjects were recruited to ensure that the balance between the two groups was maintained at any point of time. Two subjects of Group A (GnRH antagonist) and 4 patients of Group B (GnRH agonist) (1: 2 ratio) were completed before proceeding with enrolment of the next patient in either of the group. Subsequent enrolment in either of the groups was continued in the similar manner. The first subject was recruited from either treatment group (GnRH antagonist regimen or conventional GnRH agonist regimen).

For subjects treated with GnRH antagonist protocol, protocol Visit 1 was the last clinical visit prior to start of ovarian stimulation with gonadotropin. For subjects treated with GnRH agonist protocol, protocol Visit 1 was the last clinical visit prior to start of pituitary down-regulation with a GnRH agonist. All eligible subjects were asked to fill out baseline questionnaires: Hospital Anxiety and Depression Scale (HADS)/Hopkins Symptom Check List (HSCL) questionnaires at their respective sites.

Visit 2 was the day of administration of hCG injection or the last day of ovarian stimulation, if the treatment cycle was cancelled prior because of premature LH surge or premature ovulation. On this visit, the subjects were asked to fill the HADS, HSCL and COSI questionnaires.

A telephone call was made by the Investigator to each subject who did not visit the clinic by the 16^{th} day, on the 17^{th} day after hCG injection to enquire about OHSS or any adverse events. On receiving positive feedback, relevant medical history and AE details were collected and the

subject was called to the clinic. For all subjects, diagnosed with OHSS, an OHSS questionnaire was filled by the Investigator/ designee for those subjects.

Number of Patients (planned and analyzed):
It was planned to enroll 669 subjects in this study. However, to have evaluable 671 subjects (as per protocol population) 692 subjects were enrolled in the study.

Main criteria for inclusion:

1. Each subject was a female who underwent Controlled Ovarian Stimulation (COS) as a part of first cycle IVF/ICSI using recombinant Follicle Stimulating Hormone (rFSH; using pen delivery system) with GnRH antagonist (e.g. ganirelix or cetrorelix) protocol, or a female using Human Menopausal Gonadotropin (hMG) with conventional long GnRH agonist, or mixed protocol with hMG/rLH and Urinary Follicle Stimulating Hormone (uFSH) /rFSH with conventional long GnRH agonist (e.g. leuprolide, etc)
2. Subjects were ≥18 to ≤45 years of age
3. Use of drugs (gonadotropin, GnRH agonist/antagonist, Human Chorionic Gonadotropin [hCG], hMG, uFSH, rFSH, rLH) was consistent with approved label
4. Each subject willingly provided written informed consent for the study
5. Each subject filled the study specific questionnaires

Test product, dose and mode of administration, batch number: Not applicable

Duration of treatment: Not applicable. It was a non-interventional observational study.

Reference therapy, dose and mode of administration, batch number: Not Applicable

Criteria for evaluation:

Primary Endpoints:

1. Change in psychological burden (anxiety, depression) compared between two groups using HAD scale
2. Change in physical burden by comparison of score using HSCL scale, between the two groups
3. Psychological burden and wellbeing and impact of medication by comparison of scores using COSI questionnaire between the two groups at the end of GnRH agonist or antagonist administration

Secondary Endpoints:

1. Number of patients with at least one adverse event, serious adverse event will be compared between the two groups
2. Incidence of OHSS will be compared between the two groups

Statistical Methods:

Statistical analysis of the Primary Endpoint

- **Psychological burden using Hospital Anxiety and Depression Scale (HADS)**

Psychological burden (Normal, Borderline abnormal and Abnormal) was summarized using number (n) and percentage (%) by treatment group and change from visit 1. The HADS scores was summarized using number of subjects (N), Mean, Median, Q1, Q3, Minimum and Maximum.

- **Physical burden using Hopkins Symptom Check List (HSCL) scale**

The change in physical burden between two groups will be compared statistically using Wilcoxon test. The HSCL scores were summarized using number of subjects (N), Mean, Median, Q1, Q3, Minimum and Maximum. The difference in physical burden using Hopkins Symptom Check List (HSCL) scale between treatment groups was summarized for each question by number (n) and percentage (%).

- **Psychological burden, wellbeing using Controlled Ovarian Stimulation Impact (COSI) Questionnaire**

Psychological burden, wellbeing and impact of medication by comparison of total scores using COSI questionnaire between the two treatment groups at the end of GnRH agonist or antagonist administration was analyzed using Mann- Whitney U test. The endpoints were summarized using number of subjects (N), Mean, Median, Q1, Q3, Minimum and Maximum.

Assessment of Safety Endpoint

- **Adverse Event**

The number and percentage of patients with at least one adverse event, serious adverse event was presented for the two groups.

- **Ovarian Hyper-Stimulation Syndrome (OHSS)**

The incidence of OHSS was presented using number and percentage of subjects with OHSS for the two groups.

Data Set(s) Analyzed:

The analysis was done on all subjects (Safety Population) allocated to any treatment arm in the study.

Handling of Missing Data

The missing data was not imputed. Change was calculated only for subjects with non-missing data at both the time points.

Summary-Conclusions:

Primary Endpoint Results:

The mean (SD) anxiety score in group A and Group B on Visit 1 was 6.2 (4.34) and 6.2 (4.18) respectively and on Visit 2, it was 5.7 (4.16) and 5.9 (4.20) respectively. On Visit 1 and Visit 2, the mean (SD) depression score in Group A and Group B was 5.5 (4.03), 5.2 (3.98) and 5.5 (4.25), 5.4 (4.09) respectively. The mean change in anxiety and depression (HADS) score in Group A and Group B was -0.5 (3.67), -0.1 (3.57) and -0.4 (3.68), 0.1 (3.67) respectively.

The average physical burden (HSCL) in both the treatment groups was in the range of 17.9-19.1. The change from Visit 1 was statistically significant in both the treatment groups. Using COSI questionnaire, there was no significant difference in psychological burden in Group A: 19.8 (6.35) vs Group B 19.2 (6.12); well-being 25 (9.64) vs 23.8 (8.98) and impact using medication 14.8 (5.37) vs 14.4 (5.62).

Safety results:

In this study, one AE was reported in Group B. The reported AE was due to OHSS; therefore, it was regarded as SAE in this study by the investigators. There was no report of any life threatening AE or SAE throughout the study.

Conclusion:

The psychological and physical burden of subjects undergoing IVF/ ICSI treatment; and safety of the two treatment protocols in the Indian context was observed in this study. There was significant impact in both treatment protocols with respect to physical burden however not with psychological burden. Although there was no significant difference between both the treatment protocols on physical burden. There was one case of serious adverse event in subjects GnRH agonist protocol. The measures should be taken to reduce the treatment burden and thus improve the quality of life of patients as well as treatment outcome. It is concluded that factors related to physical burden and safety of the IVF/ ICSI treatment should be taken into consideration during patient counseling.

Date of Report: 06/MAY/2014

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4.0 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
AE	Adverse Event
ART	Assisted Reproductive Technology
COS	Controlled Ovarian Stimulation
COSI	Controlled Ovarian Stimulation Impact (Questionnaire)
CRF	Case Record Form
CRO	Clinical Research Organization
CSR	Clinical Study Report
ESHRE	European Society of Human Reproduction & Embryology
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GIFT	Gamete Intrafallopian Transfer
GnRH	Gonadotropin Releasing Hormone
HADS	Hospital Anxiety and Depression Scale
hCG	Human Chorionic Gonadotropin
hMG	Human Menopausal Gonadotropin
HSCL	Hopkins Symptom Check List
ICD	Informed Consent Document
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICSI	In-vitro Cytoplasmic Sperm Injection
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IVF	In-Vitro Fertilization
LAR	Legally Acceptable Representative
LH	Luteinizing Hormone
rLH	Recombinant Luteinizing Hormone
OHSS	Ovarian Hyper-Stimulation Syndrome
PI	Prescribing Information
rFSH	Recombinant Follicle Stimulating Hormone
uFSH	Urinary Follicle Stimulating Hormone
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SCL	Symptom Checklist
SCL-SOM	Symptom Distress Checklist-Somatization
SD	Standard Deviation
SOC	Standard Of Care
SOP	Standard Operating Procedure
WHO	World Health Organization
ZIFT	Zygote intrafallopian transfer

5.0 ETHICS

5.1 INDEPENDENT ETHICS COMMITTEE (IEC) OR INSTITUTIONAL REVIEW BOARD (IRB)

The study protocol (and its amendment), Informed Consent Document (ICD) (and its amendment) were reviewed and approved by IRBs/IECs responsible for the respective investigating sites, prior to study initiation.

The study was initiated only after IRB/IEC provided written approval to conduct the study, and approval documents were obtained by the Investigator and Sponsor (designee). No deviations from the protocol were initiated without prior written IRB/IEC approvals of an appropriate amendment. Investigator provided to the Sponsor a statement from the IRB/IEC confirming the IRB/IEC was organized and operated according to Good Clinical Practices (GCP) and applicable laws and regulations. Details of IECs/IRBs are presented in Appendix 16.1.3**.**

5.2 ETHICAL CONDUCT OF THE STUDY

Ethical principles that have their origin in the Declaration of Helsinki, all applicable local laws, rules and regulations relating to the conduct of the study were followed. All information collected during the course of the study was kept confidential. The study was registered with Clinical Trials Registry-India (CTRI) CTRI/2012/07/002770.

5.3 PATIENT INFORMATION AND CONSENT

The Investigator/study team member informed all the study procedures to potential participants (or their Legally Acceptable Representative [LAR], if applicable), in language understandable to them and answered all their study related queries. Each potential participant was provided sufficient time and opportunity to decide whether or not to participate in the study. Written informed consent was obtained from all the participants before performing any study-related procedure. The process of obtaining informed consent was in accordance with Declaration of Helsinki and all applicable regulatory requirements.

The ICD was revised once (version 2, dated 30/May/2012) prior to initiation of the study. Informed consent was obtained from all the subjects on the version 2 of the ICD.

The ICD was signed and dated by the Investigator (designee) and the subject. The signed and dated consent form was retained by the Investigator as part of the trial records. A copy of the signed and dated consent form was provided to the subject. Samples of both versions of informed consent document are presented in Appendix 16.1.3 of this report.

6.0 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This was a prospective observational study conducted at 12 study sites in India. **Table 6-1** lists the names and addresses of Investigators and the study sites. **Table 6-2** lists the details of ethics committees of study sites, and **Table 6-3** lists primary study administrative activities and the names and addresses of vendors, laboratories, and Contract Research Organization (CRO) used by the SPONSOR during the conduct of this study.

This study was sponsored by Organon (India) Private Limited, a subsidiary of Merck & Co. Inc., Whitehouse Station, NJ, USA and the SPONSOR'S medical expert responsible for the content of this clinical study report is Dr. Subrat Ray.

Table 6-1 Investigational Sites

Site No.	Investigator	Site Name and Address
1	Dr. Manish R Banker	Pulse Women Hospital Pvt. Ltd, 108, Swastik Society, B/h St. Xavier Hostel, Navarangpura, Ahmedabad-380009
2	Dr. Firuza Parikh	Dept. of Neuropsychiatry, 5th Floor, Jaslok Hospital & Research Centre, 15, Dr. G. Deshmukh Marg, Mumbai-400026
3	Dr. Hrishikesh Pai	Dr. D. Y. Patil Fertility Center, 4th floor, D-wing, Sector–5, Nerul, Navi Mumbai-400406
4	Dr. Pratap Kumar	Department of Obstetrics & Gynaecology, Kasturba Medical College & Hospital, Manipal University, Manipal-576104 , Mangalore
5	Dr. Monu Patnaik	Shanti Memorial Hospital, Uditnagar, Rourkela-769012
6	Dr. Mamata Deenadayal	Infertility Institute and Research Center 91-1-192, St. Mary's Road, Opp. Prashant Theatre, Secunderabad-500003, Andhra Pradesh, India.
7	Dr. Nayana Patel	Akanksha IVF Centre, Kaival Hospital, Naya Padakar Lane, Station Road, Anand,

Site No.	Investigator	Site Name and Address
		Gujarat-388001
8	Dr Jatin Shah	Mumbai Fertility Clinic And IVF Center Kamala Polyclinic & Nursing Home, 66-C, Motiwala Building, 1st Floor, Gowalia Tank, A.K Marg, Mumbai - 400026.
9	Dr. B. Sarat	Apollo Hospitals, 21, Greams Lane, Off Greams Road, Chennai - 600006, Tamil Nadu, India
10	Dr. Madhuri Patil	#1, Uma Admirality, First Floor, Bannerghatta Road, Bangalore-560029
11	Dr. K. Jayakrishnan	K J K Hospital, Shawallace Lane, Nalanchira, Trivandrum-695015, Kerala
12	Dr. Jayashree Bhattacharya	A.H IVF & Infertility Research Centre Pvt. Ltd, 853, Opposite Kalikapur State Bank of India, Kalikapur Road, Kolkata- 700078

Table 6-2 Details of Ethics Committees

Site No.	Investigator	Ethics Committee	EC Address
1	Dr. Manish R Banker	Clinicom	"SUSHRUTA", #1/1, 1st Temple Road, 15th Cross, Malleswaram, Bangalore 560003 Tel: 91-80-23313377, 23567777 E-mail: clinicom@gmail.com
2	Dr. Firuza Parikh	The Ethics Committee, Jaslok Hospital & Research Centre	15, Dr. G Deshmukh Marg Mumbai – 400026
3	Dr. Hrishikesh Pai	Institutional ethics Committee, Padamshree Dr. D.Y. Patil Medical College & Hospital and	Plot #2, Sector – 5, Nerul, Navi Mumbai – 400706 Tel : 022-27702218, Fax: 022-27709576

		Research Centre	
4	Dr. Pratap Kumar	Manipal University Ethics Committee	Manipal university, Post box # 7, Manipal–Karnataka , Tel: 0820-2571201; Fax: 0820-2571934
5	Dr. Monu Patnaik	Clinicom	"SUSHRUTA", #1/1, 1st Temple Road, 15th Cross, Malleswaram, Bangalore 560003 Tel: 91-80-23313377, 23567777 E-mail: clinicom@gmail.com
6	Dr. Mamata Deenadayal	Clinicom	"SUSHRUTA", #1/1, 1st Temple Road, 15th Cross, Malleswaram, Bangalore 560003 Tel: 91-80-23313377, 23567777 E-mail: clinicom@gmail.com
7	Dr. Nayana Patel	Clinicom	"SUSHRUTA", #1/1, 1st Temple Road, 15th Cross, Malleswaram, Bangalore 560003 Tel: 91-80-23313377, 23567777 E-mail: clinicom@gmail.com
8	Dr Jatin Shah	Clinicom	"SUSHRUTA", #1/1, 1st Temple Road, 15th Cross, Malleswaram, Bangalore 560003 Tel: 91-80-23313377, 23567777 E-mail: clinicom@gmail.com
9	Dr. B. Sarat	Apollo Independent Ethics Committee	Apollo Hospitals Enterprise limited, 21, Greams lane,

			Apollo hospitals- Chennai 600006
10	Dr. Madhuri Patil	Clinicom	"SUSHRUTA", #1/1, 1st Temple Road, 15th Cross, Malleswaram, Bangalore 560003 Tel: 91-80-23313377, 23567777 E-mail: clinicom@gmail.com
11	Dr. K. Jayakrishnan	Clinicom	"SUSHRUTA", #1/1, 1st Temple Road, 15th Cross, Malleswaram, Bangalore 560003 Tel: 91-80-23313377, 23567777 E-mail: clinicom@gmail.com
12	Dr. Jayashree Bhattacharya	Clinicom	"SUSHRUTA", #1/1, 1st Temple Road, 15th Cross, Malleswaram, Bangalore 560003 Tel: 91-80-23313377, 23567777 E-mail: clinicom@gmail.com

Table 6-3 Study Administrative Structure

Function	Name of Responsible Company/Organization
Sponsor	Organon (India) Private Limited, a subsidiary of Merck & Co. Inc. 8th Floor, Platina, Plot No. C 59, G- Block, Bandra Kurla Complex, Bandra (E), Mumbai 400098, Maharashtra (India)
Sponsor's Representative	Dr Ashish Birla, Project Manager – MSD Tel-+91 22 67892304 M-+91 9967622006 email- ashish.birla2@merck.com
Clinical Trial Management, Data Management, Biostatistics, Study Report	GVK biosciences Private Limited #307-309. BPTP Park Centra, Sector-30, Gurgaon, Haryana-122001 (India) Tel.: +91-124-4324000; Fax No.: +91-124-4324001

7.0 INTRODUCTION

Infertility is defined as “A disease of the reproductive system characterized by the failure to achieve pregnancy after 12 months or more of regular unprotected sexual intercourse” (WHO-ICMART glossary). It is a critical component of reproductive health, and affects men and women across the globe leading to distress and depression.

World Health Organization (WHO) estimated that approximately 50 to 80 million couples worldwide suffer from infertility (WHO, Assisted Reproductive Technologies). In developing countries, it has been estimated that one in every four couples is affected by infertility, primarily aged between 18-45 years. In a large survey conducted in India by WHO, the overall prevalence of infertility has been estimated to be between 3.9 (age-standardized to 25-49 years) and 16.8 (age-standardized to 15-49 years) per cent (WHO, DHS Comparative Reports No. 9, 2004).

Infertility is classified into two types, primary and secondary infertility. A woman would be classified as having primary infertility, when she is unable to ever bear a child, either due to the inability to become pregnant or the inability to carry a pregnancy to a live birth. Similarly, a woman would be classified as having secondary infertility, when she is unable to bear a child, either due to the inability to become pregnant or the inability to carry a pregnancy to a live birth, although previously carried a pregnancy to a live birth (WHO, Sexual and reproductive health).

Couples experiencing reproductive health problems experience considerable psychological stress, including feelings of low self-esteem, isolation, loss of control, sexual inadequacy and depression. Clinical depression rates of women trying to conceive are often similar to women who have heart disease or cancer (WHO, Assisted Reproductive Technologies).

Treatment for infertility depends on its cause, and may include counseling, fertility treatments like in vitro fertilization. Medical treatment of infertility generally involves the use of fertility medication, medical device, surgery, or a combination of all these treatments. If conservative medical treatments fail to achieve a full term pregnancy, the patients are suggested by their physician to undergo in vitro fertilization (IVF). *In vitro* fertilization (IVF) has been widely used to treat most causes of subfertility; however, pregnancy rate following IVF remains around 20-30% per started cycle. Therefore, some adjuvant therapies are used to achieve better outcomes. Administration of high doses of exogenous gonadotropins stimulates ovaries, and improves IVF success rate. In order to prevent the premature surge of luteinizing hormone (LH), Gonadotropin-releasing hormone (GnRH) agonists were introduced in ovarian stimulation for IVF. Treatment with GnRH antagonists is considered as an alternative for prevention of premature LH surge during ovarian stimulation. In contrast with GnRH agonists which down regulate pituitary GnRH receptors, and

desensitize gonadotropic cells, GnRH antagonists bind pituitary GnRH receptors competitively, and inhibit gonadotropin release directly. Lower incidence of OHSS has been reported in recent studies after using GnRH antagonists.

For couples trying to conceive; IVF offers a hopeful solution to many infertile couples. However, IVF involves a considerable amount of physical, emotional and financial burden on couples.

It is observed IVF treatment is often discontinued by the couples before achieving a successful outcome due to psychological stress (Olivius, 2004, Rajkhowa, 2006). The physical and psychological burdens of treatment are the most frequent cause of dropout by women and their partners enrolled in IVF programs, therefore, reduction of treatment burden may reduce the discontinuation that occurs after an initial failed cycle. (Rajkhowa, 2006). Some studies suggest that elevated anxiety and depression may actually lower pregnancy rates (Klonoff-Cohen, 2001).

Pen formulation with rFSH over conventional syringe has an advantage being easy to use, prepare, deliver, and dispose. The other advantage of pen formulation is, it offers convenience of self-administration and self-sufficiency for women who require fewer clinic visits.

This was the first study to understand the physical and psychological burden in patients comparing an antagonist protocol with the conventional protocol in IVF. This study included only patients undergoing 1st cycle of IVF treatment. The previous studies on IVF have shown that in the women of less than 35 years of age, the success rate was 21% after 1st cycle and it was increased by 40% by the 5th cycle (Macaldowie, 2012).

8.0 STUDY OBJECTIVE(S)

8.1 PRIMARY OBJECTIVE

To document and compare psychological, physical burden, impact on patient's well-being and impact of medication associated with controlled ovarian stimulation among women undergoing first cycle IVF/ICSI between those receiving standard of care gonadotropin with daily administration of GnRH agonist versus recombinant gonadotropin in pen formulation with daily administration of GnRH antagonist.

8.2 SECONDARY OBJECTIVE

To compare safety of controlled ovarian stimulation among women undergoing first cycle IVF/ICSI between those receiving standard of care gonadotropin with daily administration of GnRH agonist versus recombinant gonadotropin in pen formulation with daily administration of GnRH antagonist.

9.0 INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN - DESCRIPTION

This was a prospective, non-interventional, observational, two-arm, comparative study designed to compare psychological and physical burden associated with COS among Indian women undergoing first cycle IVF/ICSI between those using either GnRH antagonist or agonist protocol.

The study was planned to be carried out for a period of 10 months at 12 sites across India. The target was to enrol a total of 669 women aged 18-45 years undergoing COS for first cycle IVF/ICSI using either GnRH antagonist or agonist protocol. The total duration of each subject's participation in the study was approximately 3 weeks to 6 weeks (after enrolment) based on the treatment protocol subject was receiving.

On Visit 1 (screening and enrollment visit), the investigator explained the study to each subject, answered all of her questions, and obtained written informed consent before performing any study-related procedure. After screening, only those subjects, found eligible as per the inclusion/exclusion criteria were enrolled for the study. A total of 692 female subjects were enrolled in the study.

Subjects were enrolled in the ratio 1: 2 in Group A (GnRH antagonist) and Group B (GnRH agonist). Subjects were enrolled only after the treatment decision (for Group A or B) had already been made by the Investigator. These treatments were a part of routine medical procedures and/or medications prescribed to the subjects and not as a part of this study.

- Group A: Recombinant FSH (using pen delivery system) with GnRH antagonist (e.g. ganirelix or cetrorelix) protocol

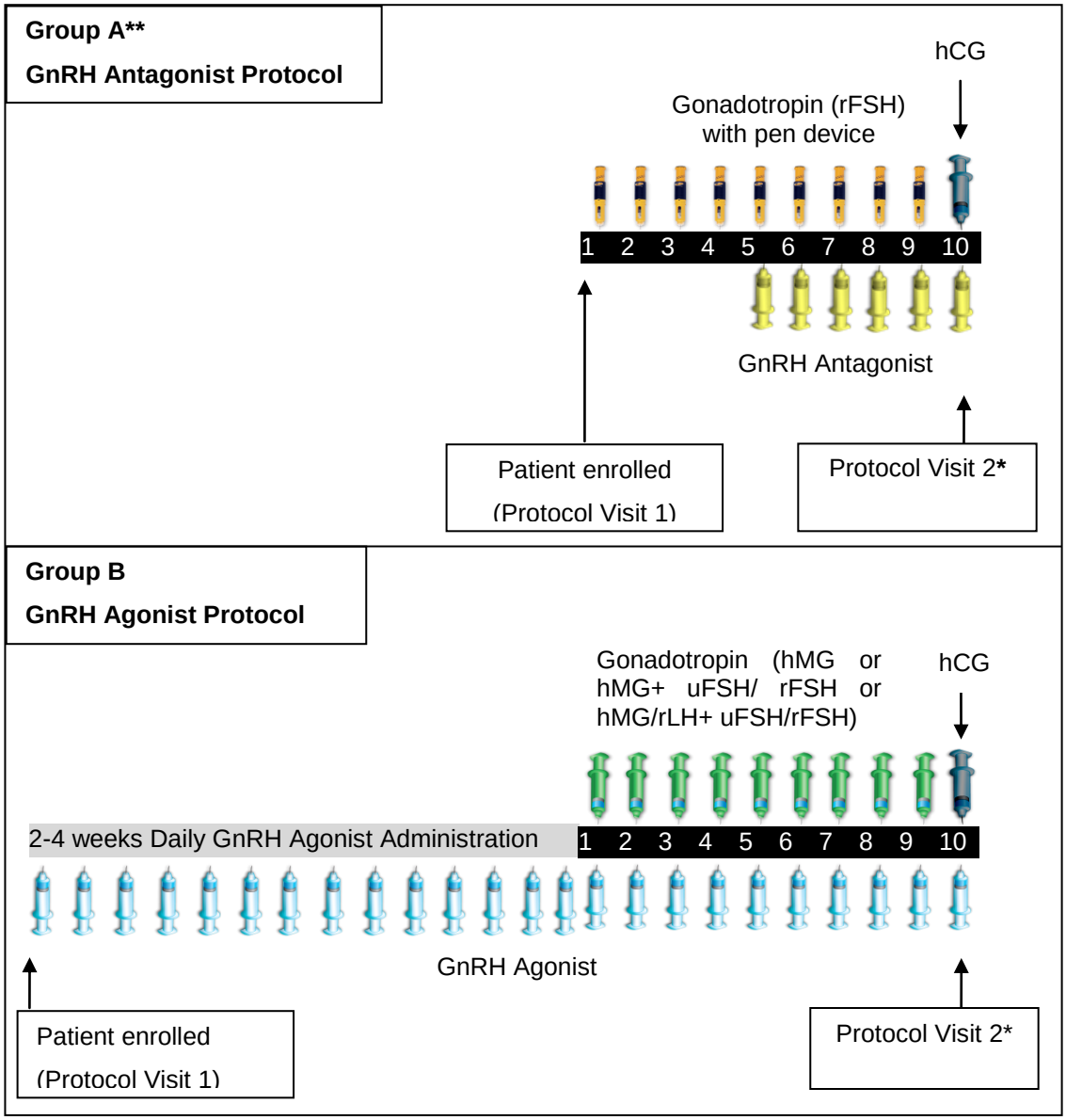
- Group B: Human Menopausal Gonadotropin (hMG) or mixed protocol with hMG/rLH and uFSH/rFSH with conventional long GnRH agonist (e.g. leuprolide, etc)

The treatments were being administered according to the standard of care at each site and in compliance with the approved prescribing information of the respective drug product being administered.

Subjects were recruited in a block of six to ensure that the balance between the two groups was maintained at any point of time. Two subjects for Group A (GnRH antagonist) and 4 for Group B (GnRH agonist) (1: 2 ratio) were completed before proceeding with enrolment of the next subject in either of the group. Subsequent enrolment in either of the groups was continued in the similar manner.

Schematic presentation of the study activities and flow chart is provided in **Figure 9-1**.

Figure 9-1 Trial design schematic diagram



*As a part of standard clinic practice for IVF programme, in case of successful embryo transfer, a routine follow up visit is generally done on the 16th day after hCG injection (protocol Visit 2, (consider hCG injection day as Day 0). If the patient visits the clinic between 14th to 16th after hCG injection, the patient will be assessed for OHSS and other AEs. In case the patient does not visit the clinic by 16th day, a telephone call will be made by the Investigator/ designee to her on the 17th day after hCG injection to enquire about OHSS or any adverse events. If positive feedback is obtained, then patient will be called to the clinic, to assess OHSS or other AE. For all patients, diagnosed with OHSS with Sponsor's product, an OHSS questionnaire will be filled by the Investigator/ designee.

**During the course of the treatment rLH can be supplemented by the treating physicians if there is a necessity in the GnRH Antagonist Protocol regimen (Group A).

Table 9-1 Trial Flow Chart

Assessments	Visit 1 † (Screening and enrolment)	Visit 2 (hCG injection day or early discontinuation or treatment)
Informed consent	X	
Inclusion/exclusion for subject eligibility	X	
Baseline demography	X	
Personal medical history, menstrual history, family history	X	
Medications related documentation	X	X
SOC therapy (Group A or Group B)	X	
Hospital Anxiety and Depression Scale (HADS) questionnaire	X	X
Hopkins Symptom Check List (HSCL) questionnaire	X	X
Controlled Ovarian Stimulation Impact (COSI) questionnaire		X
Concomitant medications	X	X
Monitoring of adverse events and OHSS*	X	X

Abbreviations: SOC: Standard of Care, OHSS: Ovarian Hyper Stimulation Syndrome

*As a part of standard clinic practice for IVF programme, in case of successful embryo transfer, a routine follow up visit is generally done on the 16th day after hCG injection (consider hCG injection day as Day 0) (protocol Visit 2). If the patient visits the clinic between 14th to 16th day after hCG injection, the patient were assessed for OHSS and other AEs. In case the patient does not visit the clinic by the 16th day, a telephone call will be made by the Investigator/ designee to her on the 17th day to enquire about OHSS or any adverse events. If positive feedback is obtained, then patient will be called to the clinic, to assess OHSS or other AE**.** For all patients, diagnosed with OHSS with Sponsor's product, an OHSS questionnaire will be filled by the Investigator/ designee and sent to the Sponsor.

†For patients treated with GnRH antagonist protocol, protocol visit 1 will be the last clinical visit prior to start of ovarian stimulation with gonadotropin. For patients treated with GnRH agonist protocol, protocol visit 1 will be the last clinical visit prior to start of pituitary down-regulation with a GnRH agonist.

For subjects treated with a GnRH antagonist protocol, protocol Visit 1 was the last clinical visit prior to start of ovarian stimulation with gonadotropin. For subjects treated with a GnRH agonist protocol, protocol Visit 1 was the last clinical visit prior to start of pituitary down-regulation with a GnRH agonist. No stratification based on age, or other characteristics was performed. All eligible

subjects were asked to fill out baseline questionnaires: Hospital Anxiety and Depression Scale (HADS)/ Hopkins Symptom Check List (HSCL) questionnaires (Appendix 16.1.8) at their respective sites.

Visit 2 was the day of administration of hCG injection or the last day of ovarian stimulation, if the treatment cycle was cancelled prior because of premature LH surge or premature ovulation. On this visit, the subjects were asked to fill the HADS, HSCL and COSI questionnaires (Appendix 16.1.8).

Generally, as a part of standard clinical practice for IVF programme, in case of successful embryo transfer, a routine follow up visit was done on the 16th day after hCG injection (consider hCG injection day as Day 0). Between 14th to 16th day after hCG injection, the subjects were assessed for OHSS and other AEs. A telephone call was made by the Investigator/ designee to each subject who did not visit the clinic by the 16th day, on the 17th day after hCG injection to enquire about OHSS or any adverse events. On receiving positive feedback, relevant medical history and AE details were collected and subject was called to the clinic. For all subjects, diagnosed with OHSS, an OHSS questionnaire (Appendix 16.1.8) was filled by the Investigator/ designee for subjects under treatment.

9.2 DISCUSSION OF STUDY DESIGN

This was a multi-center, prospective, non-interventional, comparative study among Indian women undergoing first cycle IVF or ICSI with GnRH antagonist or GnRH agonist protocol. The study was carried out in India and no aspect of this study did interfere with or influence the routine medical procedures and/or medications administered. The study primarily aimed to document and compare psychological, physical burden, impact on patient's well-being and impact of medication associated with controlled ovarian stimulation among women undergoing first cycle IVF/ICSI between those receiving standard of care gonadotropin with daily administration of GnRH agonist versus recombinant gonadotropin in pen formulation with daily administration of GnRH antagonist. The study was carried out at various IVF centres in India. Questionnaires were used as study instrument to collect the data for accessing study objectives. On protocol Visit 1 subjects filled HADS and HSCL questionnaires (Appendix 16.1.8). At protocol Visit 2, subjects filled COSI questionnaire (Appendix 16.1.8), along with the HADS and HSCL questionnaires. After 14-15 days of hCG injection administration, subjects were enquired about OHSS or any adverse events. An OHSS questionnaire (Appendix 16.1.8) was filled by the Investigator/ designee for all subjects who were diagnosed with OHSS.

It was an observational study. Physical and psychological impact and burden of different COS protocols, in subjects undergoing IVF/ICSI is documented in previous studies (Olivius., 2004; Rajkhowa, 2006; Klonoff-Cohen, 2001; Heijnen, 2007; Klerk, 2007). The rationale behind this study was to assess the physical and psychological burden and impact on well-being of different stimulation protocols in the Indian context. This study included only patients undergoing 1st cycle of IVF treatment. The previous studies on IVF have shown that in the women of less than 35 years of age, the success rate was 21% after 1st cycle and it increased to 40% by the 5th cycle (Macaldowie, 2012).

9.3 SELECTION OF STUDY POPULATION

Study population comprised of women ≥18 to ≤ 45 years of age who were undergoing COS for first cycle IVF/ICSI using either GnRH antagonist or agonist protocol. Subjects were required to meet the inclusion criteria and not the exclusion criteria to be eligible for participating in this study.

9.3.1 Inclusion Criteria

A subject must meet all the criteria listed below to participate in the study.

- Each subject must be female who will be undergoing Controlled Ovarian Stimulation (COS) as a part of first cycle IVF/ICSI using recombinant Follicle Stimulating Hormone (rFSH; using pen delivery system) with GnRH antagonist (e.g. ganirelix or cetrorelix) protocol, or a female using Human Menopausal Gonadotropin (hMG) with conventional long GnRH agonist, or mixed protocol with hMG/rLH and Urinary Follicle Stimulating Hormone (uFSH) / rFSH with conventional long GnRH agonist (e.g. leuprolide, etc)

- Each subject was ≥18 to ≤45 years of age

- Use of drugs (gonadotropin, GnRH agonist/antagonist, hCG, hMG, uFSH, rFSH, rLH) was consistent with approved label

- Each subject was willing and able to provide written informed consent for the study

- Each subject was able to fill the study specific questionnaires

9.3.2 Exclusion Criteria

A subject meeting any of the exclusion criteria listed below was excluded from participating in the study:

- Subject with prior history of OHSS
- Subject using depot formulation of GnRH agonist
- Subject already receiving GnRH agonist or antagonist stimulation protocol
- Subject was enrolled in another observational study or clinical trial
- Subject was suffering from any neurological or psychiatric illness
- Subject had any clinically significant condition or situation, other than the condition being studied that, in the opinion of the Investigator, would interfere with the study evaluations or optimal participation in the study

9.3.3 Removal of Patients from Therapy

A subject could discontinue from the study at any time for any reason. In this study, subjects were allowed to discontinue from the treatment, but continue to participate in the scheduled activities as long as the subject does not withdraw consent. It was the right and the duty of the investigator to stop treatment in any case in which emerging effects were of unacceptable risk to the individual subject. The Investigator could also stop the treatment of any subject with unmanageable factors that interfered significantly with the study procedures and/or the interpretation of results.

Following information were collected when a subject was discontinued:

1. The reason the subject discontinued
2. Final assessment

Every effort was made to ensure that all procedures and evaluations scheduled for the study Visit 2 were performed (**Table 9-2: Trial Flow Chart**).

9.4 TREATMENTS

9.4.1 Treatments Administered

No aspect of this study did interfere with or influence the routine medical procedures and/or medications prescribed to the subjects. This was a non-interventional, observational study among Indian women undergoing first cycle IVF or ICSI using GnRH antagonist (e.g. ganirelix or cetrorelix) or GnRH agonist (e.g. leuprolide, etc) protocol.

Each of the treatment protocol was administered according to the standard of care at each site and in compliance with the current approved prescribing information of the respective drug product being administered.

9.4.2 Identity of Investigational Product(s)

Not applicable

9.4.3 Method of Assigning Patients to Treatment Groups

No randomization of the subjects was performed. Treatment was administered to each subject based on decision made according to standard of care by the Investigator.

Patients were enrolled in the ratio of 1: 2 (Group A, GnRH Antagonist: Group B, GnRH Agonist). Subject recruitment was done in a block of 6 patients to ensure that the balance between the two groups is maintained at any point of time. 2 patients of Group A (GnRH antagonist) and 4 patients of Group B (GnRH agonist) was completed before proceeding with enrolment of the next patient in either of the group. Subsequent enrolment in either of the groups was continued in the above stated manner.

The first patient was recruited from either treatment group (GnRH antagonist regimen or conventional GnRH agonist regimen). No stratification based on age, or other characteristics was performed.

9.4.4 Selection of Doses

Subjects prescribed by investigators to receive GnRH agonist or antagonist regimen, within the approved indication for IVF/ICSI was invited to participate in the study. Subjects were enrolled only after the treatment decision (for either of the GnRH agonist or antagonist protocol) was made by the investigator.

9.4.5 Selection and Timing of Dose for Each Patient

Drug treatment (product, dose, duration) was prescribed by the investigator as per the standard of care in compliance with the current approved Prescribing Information (PI) of the respective product.

9.4.6 Blinding

Not applicable.

9.4.7 Prior and Concomitant Medications

Use of prior and concomitant medications was restricted according to the PI of the drug products being used for controlled ovarian stimulation.

9.4.8 Treatment Compliance

At the second protocol-specified visit, the Investigator or qualified designee recorded whether treatment had been taken as per prescription in the preceding interval. If not, the date(s) and reason for each dose, non-compliance was recorded.

9.5 STUDY VARIABLES

Primary Endpoints:

1. Change in psychological burden (anxiety, depression) compared between two groups using HAD scale

2. Change in physical burden by comparison of score using HSCL scale, between the two groups

3. Psychological burden and wellbeing and impact of medication by comparison of scores using COSI questionnaire between the two groups at the end of GnRH agonist or antagonist administration

Secondary Endpoints:

1. Number of patients with at least one adverse event, serious adverse event will be compared between the two groups

2. Incidence of OHSS will be compared between the two groups

9.5.1 Efficacy and Safety Measurements Assessed and Flow Chart

The study visit schedule is given in **Table 9-1**.

9.5.2 Appropriateness of Measurements

The tools and techniques used for efficacy and safety assessments in this study were well documented and are generally regarded as reliable, accurate, and relevant. These have been used previously in similar studies.

Instruments Used for Measuring Primary Endpoints in the Study

Hospital Anxiety and Depression Scale (HADS)

The HADS is a 14-item scale, designed to evaluate patient's anxiety (HADS-A, 7 items) and depression (HADS-D, 7 items). Each item is answered by the patient on a four-point (0–3) response category so the possible scores range from 0–21 for anxiety and 0–21 for depression. The scoring is done by adding the response marks against all questions marked as "A" to give out the anxiety score and against the questions marked as "D" to give the depression score. The score of 0–7 for either subscale could be regarded as being in the normal range, a score of 11 or higher indicating the probable presence of mood disorder, and a score of 8–10 being suggestive of the presence of the respective state (Chern, 2011; Snaith, 2003; Zigmond, 1983).

Hopkins Symptoms Checklist (HSCL) (12-items)

The Hopkins symptoms checklist (HSCL) is a well-known and widely used screening instrument which is used from 1950s. It was originally developed by a group of researchers named Parloff, Kelman and Frank at the John Hopkins University. Several refinements and additions of items were made by different researchers to yield the HSCL, which was the first form of the questionnaire to be used as a criterion measure in psychotropic drug trials (Derogatis, 1974).

The HSCL had numerous minor variations, but the 58-question version was a major landmark in the scale's evolution (Derogatis, 1974). This scale, termed the Symptom Distress Checklist (SCL) (Derogatis, 1973), comprised mainly conventional neurotic symptoms and had a four-point scale of distress. In the SCL-90, for example, the distress of symptoms is rated from 0 = not at all, to 4 = extremely (Derogatis, 1973). The present version of HSCL, which is being used in this study is 12-item somatization scale derived from the Hopkins Symptom Checklist (SCL-90) (Derogatis, 1974 and Holi, 1998). Symptom Distress Checklist–Somatization (SCL-SOM) intends to measure self-reported intensity of somatic symptoms. The questions will be rated on the four scale ranging from 1 to 4 (1 - Not at all, 2 - a little bit, 3 - quite a bit, 4 - Extremely). The total and mean scores of the questionnaire responses from the subjects will be analyzed using the statistical methods.

Controlled Ovarian Stimulation Impact (COSI) Questionnaire

Based on study (presented in poster session by Brod et al., at European Society of Human Reproduction & Embryology [ESHRE], 2011) conducted on 267 women undergoing fertility treatment, COSI can be considered conceptually and psychometrically sound as a measure of the impact of COS on women's functioning and well-being.

To evaluate impact of IVF/ICSI on various aspects of patients' daily life and well-being, domain and total scores from the COSI questionnaire will be calculated. The COSI questionnaire consists of six questions (Q1-Q6) with one or more item(s) per question. The answers are combined into a single total score per question that ranges from 9-45 (Q1), 4-20 (Q2), 1-5 (Q3), 5-25 (Q4), 5-25 (Q5), 4-20 (Q6), with a higher score reflecting a lower treatment impact on patients' daily life and well-being. Three domains of the impact of ovarian stimulation will be assessed using this questionnaire. Psychological burden, interference with daily life, and handling of medication will be assessed using the total calculated score of Q1 (range 9 to 45), Q4+Q5+Q6 (range 10 to 50), and Q2+Q3 (range 5 to 25), respectively.

Instruments Used for Measuring Secondary Endpoints in the Study

Clinical Classification of OHSS

The World Health Organization criteria (WHO, 1973), has provided a comprehensive classification of the degrees of hyperstimulation (detailed in **Table 9-2)**. For this protocol the following, slightly modified classification will be used:

OHSS of any grade will be considered a SAE and reported in the same manner as described for SAE reporting.

Table 9-2 Clinical Classification of OHSS

Grade I	mild	Is characterized by excessive steroid secretion and ovarian enlargement (5-7 cm). Abdominal discomfort, including abdominal pain, is present.
Grade II	moderate	Is characterized by distinct ovarian cysts (ovary size 8-10 cm), accompanied by abdominal pain and tension, nausea, vomiting, diarrhoea.
Grade III	severe	Is characterized by enlarged cystic ovaries (ovary size >10 cm), accompanied by ascites and occasionally hydrothorax. Abdominal tension and pain may be severe. Pronounced hydrothorax together with an abdominal cavity filled with cysts and fluid elevating the diaphragm may cause severe breathing difficulties. Large quantities of fluid inside the cysts and in the peritoneal and pleural cavities cause haemoconcentration and increased blood viscosity. In rare cases, the syndrome may further be complicated by the occurrence of thromboembolic phenomena.

Assessment of Adverse Events

Assessment of Severity

The determination of adverse events rested on the medical judgment of the investigator. The determination of adverse event severity was also made by the investigator.

The severity of AEs (except for OHSS which was graded as described in **Table 9-2**) was graded according to the following definitions:

Mild: awareness of sign, symptom, or event, but easily tolerated;

Moderate: discomfort enough to cause interference with usual activity and may warrant intervention;

Severe: incapacitating with inability to do normal daily living activities or significantly affects clinical status, and warrants intervention;

Assessment of Causality

The investigator assessed the relationship of any AE (including SAEs) to the use of the drug, as unlikely related, possibly related, or probably related, based on available information, using the guidelines listed below:

Yes, there is reasonable possibility of drug relationship. There is evidence of exposure to suspect drug. The temporal sequence of the AE onset relative to the administration of the suspect drug is reasonable. The AE is more likely explained by the suspect drug than by another cause.

No, there is not a reasonable possibility of drug relationship. Subject did not receive the suspect drug or temporal sequence of the AE onset relative to administration of the suspect drug is not reasonable or there is another obvious cause of the AE. (Also, entered for a subject with overdose without an associated AE).

Primary Efficacy Variable(s)

The primary objective of this study was to document and compare psychological, physical burden, impact on patient's well-being and impact of medication associated with controlled ovarian stimulation among women undergoing first cycle IVF/ICSI between those receiving standard of care gonadotropin with daily administration of GnRH agonist versus recombinant gonadotropin in pen formulation with daily administration of GnRH antagonist.

9.5.3 Drug Concentration Measurement

Not applicable

9.6 DATA QUALITY ASSURANCE

In this study, quality assurance and quality control systems were maintained in accordance with written SOPs to assure that study was conducted and data was generated, recorded, and reported in compliance with the protocol, good clinical practice (GCP) standards and the applicable regulatory requirements. All tables, listings and figures (TLFs) underwent program validation and spot data validation.

9.7 STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

9.7.1 Statistical and Analytical plans

The analysis was done on all the subjects allocated to any treatment arm in the study. Detailed methodology for the statistical analyses of the data collected in this study was documented in the approved Statistical Analysis Plan (SAP; Appendix 16.1.7). The latest version of SAP was used for the analysis of data.

Statistical Considerations

- Statistical Significance: All hypothesis testing for this study was done using two-sided, 0.05 level tests.
- Handling Dropouts and Missing Data: The missing data was not imputed. Change was calculated only for subjects with non-missing data at both the time points.
- Statistical Software: The statistical analysis for the safety data was done using the software SAS version 9.1.3 (SAS Institute, Cary, NC, USA).

Study Populations

The analysis was done on all subjects allocated to any treatment arm in the study and was considered as safety population.

Table 9-3 Population sets used for endpoints/analysis

Endpoints/Analysis	Population/ Analysis sets
Subject disposition	All subjects
Demographic and baseline characteristics	Safety population
Efficacy analysis	Safety population
Safety analysis	Safety population
All listings	Safety population

Statistical Analysis of the Primary Endpoints

Psychological burden using HAD scale

Psychological burden (Normal, Borderline abnormal and Abnormal) was summarized using number of subjects (n) and percentage (%) by treatment group. Change from Visit 1 was calculated using Bhapkar's Test.

Psychological burden (anxiety, depression) was analyzed using Hospital Anxiety and Depression Scale (HADS). Chi-square test / Fisher's exact test was used to compare the HADS response between treatment groups in each visit. HADS score between the two treatment groups was compared and analyzed using Mann-Whitney U test by visit and for the change from Visit 1. The HADS scores was summarized using number of subjects (N), Mean, Median, Q1, Q3, Minimum and Maximum.

Wilcoxon Signed Rank test was used to calculate the significant change from Visit 1 in HADS score for each treatment group.

Physical burden using HSCL scale

Physical burden was analyzed using Hopkins Symptom Check List (HSCL) scale. HSCL score between the two treatment groups was compared and analyzed using Mann-Whitney U test by visit and for change from Visit 1. The HSCL scores were summarized using number of subjects (N), Mean, Median, Q1, Q3, Minimum and Maximum.

Wilcoxon Signed Rank test was used to calculate the significant Change from Visit 1 in physical burden using HSCL score in each treatment group. The difference in physical burden using HSCL scale between treatment groups was summarized for each question by number (n) and percentage (%) and was compared using Chi square Test/Fisher's exact test.

Psychological burden, wellbeing and impact of medication using COSI questionnaire

Psychological burden, wellbeing and impact of medication by comparison of total scores using Controlled Ovarian Stimulation Impact (COSI) questionnaire between the two treatment groups at the end of GnRH agonist or antagonist administration was analyzed using Mann-Whitney U test. The endpoints were summarized using number of subjects (N), Mean, Median, Q1, Q3, Minimum and Maximum.

Statistical Analysis of the Secondary Endpoint

Adverse Event

The specific Adverse events were summarized by Adverse events by (MedDRA) system organ class and preferred term; Serious adverse events by system organ class and preferred term; Adverse Events by system organ class, preferred term and severity; Serious Adverse Events by system organ class, preferred term and severity; Adverse Events by system organ class, preferred term and outcome ;Serious Adverse Events by system organ class, preferred term and outcome; Adverse Events by system organ class, preferred term and Relationship with study drug ;Serious Adverse Events by system organ class, preferred term and Relationship with study drug; Adverse Events by system organ class, preferred term and action taken with study medication and Serious Adverse Events by system organ class, preferred term and action taken with study medication. The summary included the number and percentage (%) of adverse events in each treatment group. The number (n) and percentage (%) of subjects with at least one adverse event or serious adverse event was presented for the two groups. Number of subjects with at least one adverse event or serious adverse event were compared between the two groups using Chi-square test/Fisher's Exact Test.

Physical Examination

Physical examinations at screening were summarized by treatment group. Number (n) and percentage (%) was summarized for Normal and Abnormal categories.

Ovarian Hyper-Stimulation Syndrome (OHSS)

The incidence of Ovarian Hyper-Stimulation Syndrome (OHSS) was presented using number (n) and percentage (%) of subjects with OHSS for the two groups. Incidence of OHSS was compared between the two groups using Chi-square test/Fisher's Exact Test. Besides, Ovarian Hyper-Stimulation Syndrome (OHSS) data will be listed by treatment group.

Treatment Exposure and Compliance

Descriptive statistics such as n, mean, standard deviation (SD), median, Q1, Q3, Min and Max were provided for the duration (days) of study medication by treatment group.

Concomitant Medications

Concomitant medications within each therapeutic category were summarized by treatment group using number (n) and percentage (%).

9.7.2 Determination of sample size

It was planned to enroll a total of 669 (including dropout rate) subjects in the study. Assuming 10% of difference in scale of anxiety, depression and physical discomfort would be of clinical significance, for 80% power with 5% significance and with 20% additional for incomplete data, the total subjects planned to be enrolled in Group A was 222 and Group B was 447. However, a total of 692 subjects were actually enrolled in the study (in Group A 232 and in Group B 460 subjects were enrolled) to yield approximately 671 evaluable subjects (Group A 230 and in Group B 441) in the per protocol population.

9.8 CHANGES IN CONDUCT OF THE STUDY OR PLANNED ANALYSES:

Changes to the conduct of the study were made once. Changes to the protocol were considered to effect how the data would be analyzed. For a comprehensive list of changes to the protocol, see Appendix 16.1.1. Below is a brief summary of changes:

Protocol Amendment 1, dated May 30, 2012: Recombinant luteinizing hormone (rLH) treatment was added in the GnRH agonist protocol (Group B), and it was further amended that during the course of the treatment, rLH can be supplemented by the treating physicians, if there was a necessity in the GnRH antagonist Protocol regime (Group A). The number of study centers was increased to 10-12.

The following sections were updated in the protocol to include addition of rLH treatment in the study groups:

- Section 2.1 Trial design diagram
- Section 7.1 Overall trial design
- Section 7.3.1 Subject inclusion criteria

- Section 7.4.1.1 Treatments Administered

10.0 STUDY PATIENTS

10.1 DISPOSITION OF PATIENTS

The investigators screened 712 potential participants and enrolled 692 subjects who met the inclusion criteria in this study. In Group A (GnRH antagonist protocol with rFSH pen) 232 and in Group B (GnRH agonist protocol with rFSH or hMG/ rLH or uFSH or mixed rFSH / uFSH and hMG/rLH and other protocols) 460 subjects were enrolled. All enrolled subjects allocated to any treatment arm in the study were considered as safety population. In Group A 230 and in Group B 441 subjects completed the study as per protocol. The disposition of subjects in this study is summarized in flow chart in **Figure 10-1** and subjects assigned to treatment protocols is described in in **Figure 10-2.**

Listing of subjects enrolled is presented in Appendix 16.2.1.

Figure 10-1: Subject Disposition

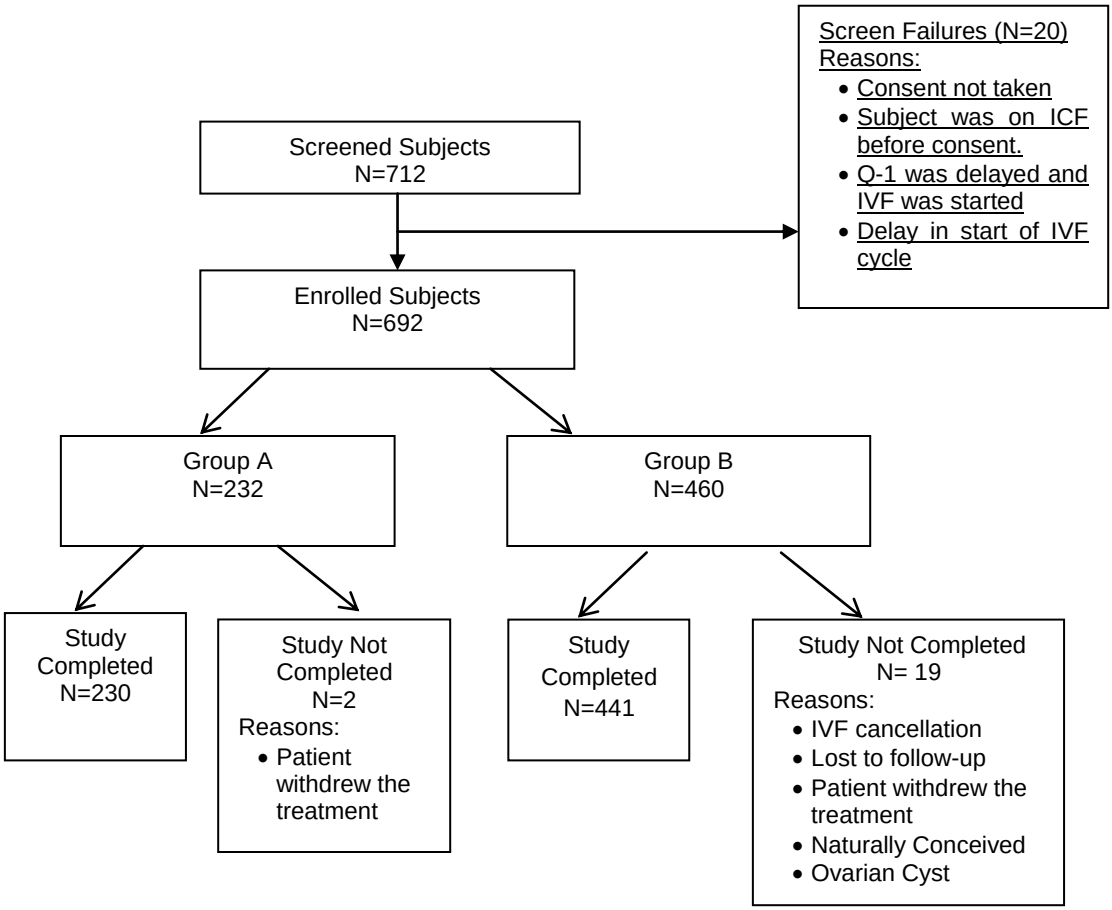
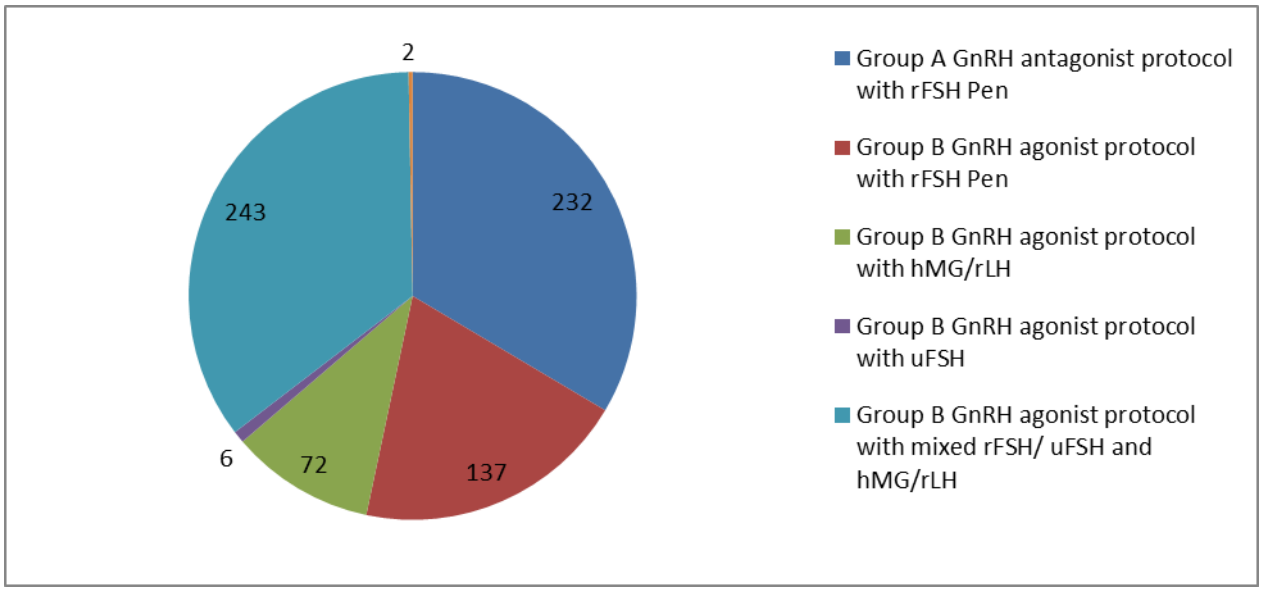


Figure 10-2 Subject enrollment According to Treatment Assigned



Source Statistical table 14.1.1

10.2 PROTOCOL DEVIATIONS

In the study 62 screen failures were recorded due to protocol deviations (62/503). However, to have evaluable 671 subjects (as per protocol population) 16 screen failures were replaced in the study.

There were 441 (441/503) protocol deviations reported in this study; and none of the subject was discontinued due to protocol deviation. The most common deviations were visits performed outside of the window specified in the protocol. Protocol deviations did not create any impact on the analyses of study and safety of subjects. A listing of all protocol deviations is presented in Appendix 16.2.2.

11.0 STUDY RESULTS

11.1 DATA SETS ANALYZED

The analysis was done on all subjects enrolled and allocated to any treatment group in the study and were considered as safety population. The safety population was the primary population used for analysis of data. Listing of subjects who discontinued the study as per protocol is given in Appendix 16.2.1. The baseline change analysis between or within group A and B (for various scales used in the study) was done for only those subjects for whom visit 2 data were available.

11.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

The baseline demographic characters between groups were comparable. In Group A 232 and in Group B 460 subjects were enrolled with mean (±SD) age of 30.6 (3.83) and 30.7 (4.21) years, in each group respectively. In Group A 55.6 % and in Group B 55.2% subjects belonged to the city where the study center was situated. A summary of demographic and baseline characteristics is presented in **Table 11-1**.

Listings of subject's demographic and baseline data are provided in Appendix 16.2.1.

Table 11-1 Summary of Demographic and Baseline characteristics

Characteristics	Statistics	Group A (N=232)	Group B (N=460)
Age (years)	N	232	460
	Mean (SD)	30.6 (3.83)	30.7 (4.21)
	Median	30.0	30.0
	Q1, Q3	28, 33	28, 33
	Min, Max	23, 42	19, 44
Height (cm)	N	232	460
	Mean (SD)	156.8 (7.24)	156.4 (7.37)
	Median	157.0	157.0
	Q1, Q3	153, 161	153, 161
	Min, Max	127, 177	108, 177
Weight (kg)	N	232	460
	Mean (SD)	60.7 (10.14)	59.7 (9.10)
	Median	60.0	60.0
	Q1, Q3	54, 67	54, 65
	Min, Max	38, 98	32, 93
BMI (kg/m^2)	N	232	460
	Mean (SD)	24.76 (4.33)	24.51 (4.24)
	Median	24.20	24.22
	Q1, Q3	21.7, 27.4	21.9, 26.6
	Min, Max	15.6, 40.3	10.6, 56.6
Subject came from the city as the site			
Yes	n (%)	129 (55.6)	254 (55.2)

No	n (%)	103 (44.4)	206 (44.8)

-Denominator of the percentage is the number of subjects in the treatment group.
Source: Statistical table 14.1.2

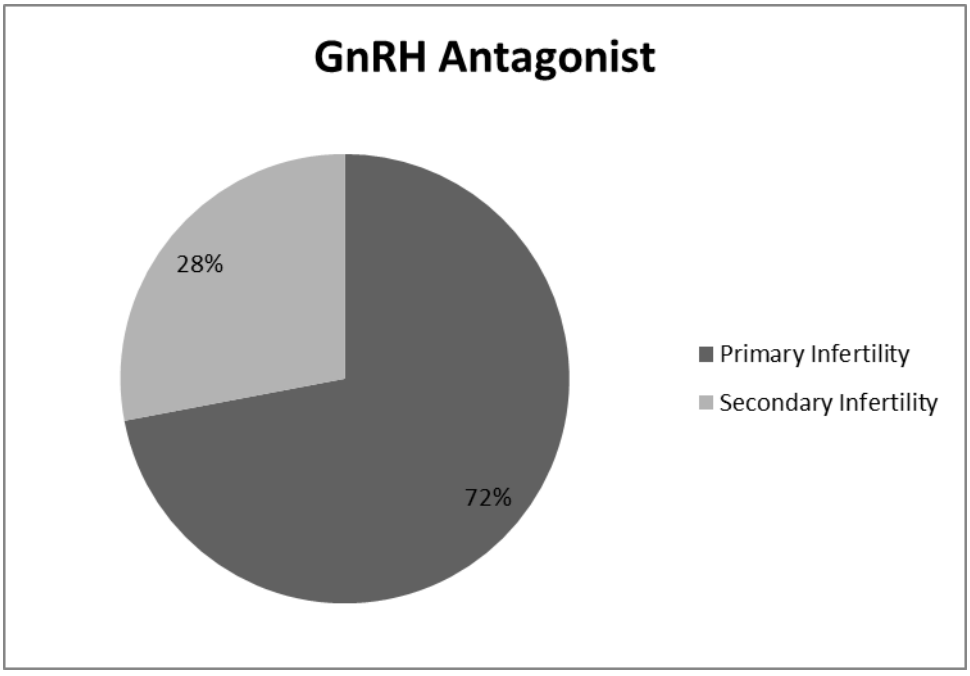
11.2.1 INFERTILITY AND FAMILY HISTORY OF SUBJECTS

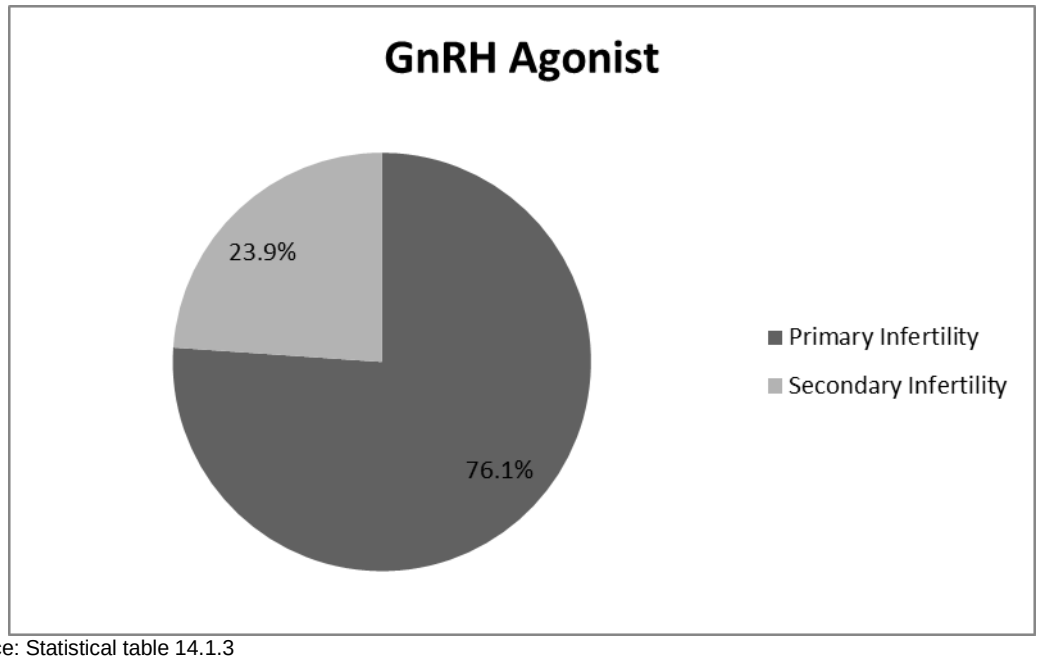
In both the groups the subjects with primary infertility were predominant. In Group A and Group B 72.0% and 76.1% subjects, had primary infertility respectively (**Figure 11-1**). Majority of the subjects of both the treatment groups did not have any family history of infertility. In present study the factors which contributed for infertility were also recorded. The cause of infertility in Group A and Group B were male factor (40.1 % and 35.2 %), Tubal factor (26.3 % and 32.0 %) and unexplained infertility (25.9 % and 21.5 %) or other reasons. The median duration of infertility was 72 months in both the groups. Both groups were comparable with respect to these patient characteristics.

A summary of infertility and family history of subjects in safety population is presented in **Table 11-2**.

For infertility and medical history listing please refer Appendix 16.2.1.

Figure 11-1 Distribution of Primary and Secondary Infertility in Both Groups





Source: Statistical table 14.1.3

Table 11-2 Summary of infertility history and family history

Characteristics	Category	Statistics	Group A	Group B
Cause of infertility	Male Factor	n (%)	93 (40.1)	162 (35.2)
	Tubal Factor	n (%)	61 (26.3)	147(32.0)
	Endometriosis	n (%)	10 (4.3)	43 (9.3)
	Ovulatory Dysfunction	n (%)	33 (14.2)	46 (10)
	Diminished Ovarian Reserve	n (%)	3 (1.3)	4 (0.9)
	Unexplained Infertility	n (%)	60 (25.9)	99 (21.5)
	Female Factors	n (%)	3 (1.3)	2 (0.4)
	Others	n (%)	6 (2.6)	12 (2.6)
Duration of Infertility (Months)		N	232	460
		Median	72	72
		Q1, Q3	47, 108	48, 108
		Min, Max	6, 252	6, 300
Total number of previous IUI cycles		N	232	460
		Mean	1.9	1.9
		Median	1	0
		Q1, Q3	0, 3	0, 3
		Min, Max	0, 15	0, 12
Total number of previous OI cycles using oral medications		N	232	460
		Mean	1.0	1.1
		Median	0	0
		Q1, Q3	0, 2	0, 2
		Min, Max	0, 10	0, 13
Total number of previous OI cycles using FSH		N	232	460
		Mean	0.7	0.7
		Median	0	0
		Q1, Q3	0, 1	0, 1
		Min, Max	0, 8	0, 8
Family history of infertility	Yes	n (%)	2 (0.9)	5 (1.1)
	No	n (%)	230 (99.1)	455 (98.9)

Denominator of the percentage is the number of subjects in the treatment group.
Source: Statistical table 14.1.3

11.2.2 MENSTRUAL HISTORY OF SUBJECTS

Summary of menstrual history in safety population is given in **Table 11-3**. The length of menstrual cycle was 16-30 days in more than 85% of subjects enrolled in both the treatment groups. Median length of cycles in both the treatment groups was 28 days. In Group A 6.5% subjects and in Group B 6.7% subjects received OC (oral contraception) in the month prior to controlled ovarian stimulation (COS).

Table 11-3 Summary of Menstrual History

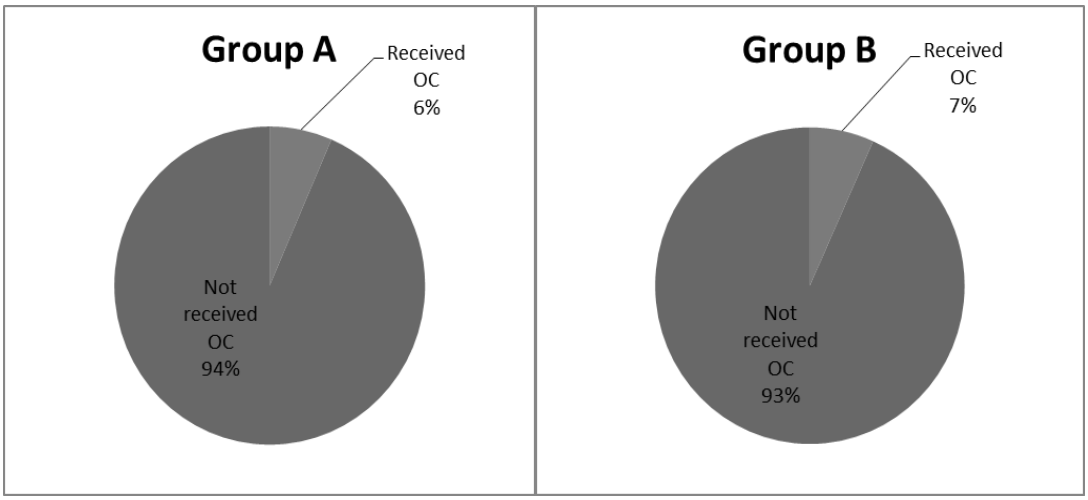
Characteristics	Statistics	Group A	Group B
Length of Cycle (days)	N	232	460
	Median	28	28
	Q1, Q3	28, 30	28, 30
	Min, Max	4, 60	4, 90
<=5	n (%)	7 (3.0)	8 (1.7)
6-15	n (%)	2 (0.9)	4 (0.9)
16-30	n (%)	208 (89.7)	392 (85.2)
31-45	n (%)	14 (6.0)	45 (9.8)
46-60	n (%)	1 (0.4)	10 (2.2)
>60	n (%)	0	0

Denominator of the percentage is the number of subjects in the treatment group
Source: Statistical table 14.1.4

Menstrual history of subjects is listed in Appendix 16.2.1.

There were 6.0% and 7.0% patients who received OC in the month prior to COS in Group A and Group B respectively (Figure 11-2).

Figure 11-2 Patients Received OC in the Month Prior to COS



Source: Statistical table 14.1.4

11.2.3 MEDICAL HISTORY OF SUBJECTS

Medical history in safety population is given in **Table 11-4**. In approximately 97% subject participants no medical history/condition was reported by the investigators in this study. There were two subjects with hypothyroidism in Group A.

Table 11-4 Medical history

Medical History/ Condition	Group A (N=232) n (%)	Group B (N=460) n (%)
Subjects with at least one medical history/condition	7 (3.0)	13 (2.8)
Subjects with no medical history/condition	225 (97.0)	447 (97.2)
Endocrine disorders	4 (1.7)	2 (0.4)
Diabetes mellitus	2 (0.9)	2 (0.4)
Hypothyroidism	2 (0.9)	0
Immune system disorders	0	1 (0.2)
Hypersensitivity	0	1 (0.2)
Infections and infestations	0	1 (0.2)
Tuberculosis	0	1 (0.2)

Psychiatric disorders	3 (1.3)	8 (1.7)
Anxiety disorder	2 (0.9)	6 (1.3)
Depression	1 (0.4)	3 (0.7)
Insomnia	1 (0.4)	0
Vascular disorders	0	2 (0.4)
Aneurysm	0	1 (0.2)
Haemorrhoidal haemorrhage	0	1 (0.2)

Denominator of the percentage is the number of subjects in the treatment group.
Source: Statistical table 14.1.5

For medical history refer the statistical listing in Appendix 16.2.1.

11.2.4 PRIOR MEDICATIONS

In more than 90% subject participants no medication or treatment history was reported by the investigators in any of the treatment groups in this study. Only one subject was on HCG for ovulation stimulation prior to her enrollment in the study (Appendix 16.2.1).A summary of prior medication in safety population is given in **Table 11-5**.

Table 11-5 Summary of Prior Medication

ATC Level 3 Medication	Group A (N=232) n (%)	Group A (N=460) n (%)
Subjects with any medication or treatment history	15 (6.5)	18 (3.9)
Subjects with no medication or treatment history	217 (93.5)	442 (96.1)
Anti-inflammatory and antirheumatic products, non-steroids	0	1 (0.2)
Nise Tab	0	1 (0.2)
Zerodol-P	0	1 (0.2)
Antiobesity preparations, excl. diet products	1 (0.4)	0
T. Orlistat	1 (0.4)	0
Antithrombotic agents	6 (2.6)	6 (1.3)
Ecosprin	6 (2.6)	6 (1.3)
Cough suppressants and expectorants, combinations	0	1 (0.2)
Honitus Syrup	0	1 (0.2)
Drugs for treatment of tuberculosis	2 (0.9)	2 (0.4)
AKT	2 (0.9)	2 (0.4)
Gonadotropins and other ovulation stimulants	1 (0.4)	0

T. Ovigyn	1 (0.4)	0
Other plain vitamin preparations	0	1 (0.2)
Evion	0	1 (0.2)
Thyroid preparations	4 (1.7)	4 (0.9)
Eltroxin	1 (0.4)	3 (0.7)
Levothyroxine	1 (0.4)	0
T. Thyroxin	0	1 (0.2)
T.Thyronorm	1 (0.4)	0
Thyrox	1 (0.4)	0
Vitamin B12 and folic acid	9 (3.9)	12 (2.6)
Folic Acid	8 (3.4)	7 (1.5)
Folinine	1 (0.4)	5 (1.1)

ATC= Anatomical Therapeutic Chemical Classification System
Denominator of the percentage is the number of subjects in the treatment group.
Source: Statistical table 14.1.6

11.3 MEASUREMENTS OF TREATMENT COMPLIANCE

At the second protocol-specified visit, the Investigator or qualified designee recorded whether treatment had been taken as per prescription in the preceding interval. If not, the date(s) and reason for each dose, non-compliance was recorded. The investigators were responsible for recording dosing and completing accountability logs.

11.4 ANALYSIS OF STUDY ENDPOINTS

11.4.1 Analysis of Primary Endpoints

This study was designed to primarily document and compare psychological, physical burden, impact on subject's well-being and impact of medication associated with COS among subjects undergoing first cycle IVF/ICSI between those receiving standard of care gonadotropin with daily administration of GnRH agonist versus recombinant gonadotropin in pen formulation with daily administration of GnRH antagonist.
Primary endpoints of this study were analysed as given below.

- **Change in psychological burden (anxiety, depression) compared between two groups using HAD scale**

To assess psychological burden (anxiety and depression) in safety population HAD scale was used. The level of anxiety and depression of individual subjects was assessed based on the

analysis of their scores on HAD scale. A score range between 0-7, 8-10 and 11-21 was regarded normal, borderline abnormal and abnormal, respectively.

In Visit 1, in Group A and Group B 63.8% (148/232) and 64.1% (295/460) subjects, respectively, were in normal category of anxiety. The subjects in normal category for depression were 69.4% (161/232) in Group A and 69.1% (318/460) in Group B. On both the visits the difference in categories for anxiety and depression was not statistically significant between the groups. A detailed analysis of psychological burden using HAD scale by visit and response category among subject participants in both the treatment groups is given in **Table 11-6**. The change in score was calculated from visit one in both the groups. The mean (±SD) change in anxiety and depression for Group A and Group B was 6.2 (±4.34) and 6.2 (±4.18), and -0.4 (±3.66) and 0.1 (±3.67), respectively. The change from visit one between both the groups was not statistically significant for anxiety (p = 0.9552) as well as depression (p =0.3562) as given in **Table 11-7**.

Listing of HADS – anxiety and depression of subjects is given in Appendix 16.2.1.

Table 11-6 Analysis of psychological burden using hospital anxiety and depression scale by visit and response category

Visit	Hospital Anxiety and Depression Scale	Response Category	Group A n (%)	Group B n (%)	P-value
Visit 1	Anxiety	Normal	148 (63.8)	295 (64.1)	0.4295*
		Borderline Abnormal	37 (15.9)	87 (18.9)	
		Abnormal	47 (20.3)	78 (17.0)	
	Depression	Normal	161 (69.4)	318 (69.1)	0.9785*
		Borderline Abnormal	40 (17.2)	82 (17.8)	
		Abnormal	31 (13.4)	60 (13.0)	
Visit 2	Anxiety	Normal	158 (68.1)	297 (64.6)	0.2704*
		Borderline Abnormal	44 (19.0)	72 (15.7)	
		Abnormal	29 (12.5)	75 (16.3)	
		Missing	1 (0.4)	16 (3.5)	
	Depression	Normal	165 (71.1)	313 (68.0)	0.7826*
		Borderline Abnormal	32 (13.8)	70 (15.2)	
		Abnormal	34 (14.7)	61 (13.3)	
		Missing	1 (0.4)	16 (3.5)	

*Chi-square Test / ^Fisher's exact test was used to calculate the significant difference between treatment groups.
Source: Statistical table 14.2.1.2

Table 11-7 Comparison of change in psychological burden using Hospital Anxiety and Depression Score

Visit	HADS	Statistics	Group A	Group B	P-value*
Visit 1	Anxiety	N	232	460	0.8492
		Mean (SD)	6.2 (4.34)	6.2 (4.18)	
		Median	5.0	6.0	
		Q1, Q3	3, 9	3, 9	
		Min, Max	0, 19	0, 21	
		Missing	0	0	
	Depression	N	232	460	0.3842

		Mean (SD)	5.5 (4.03)	5.2 (3.98)	
		Median	5.0	5.0	
		Q1, Q3	2, 9	2, 8	
		Min, Max	0, 17	0, 15	
		Missing	0	0	
Visit 2	Anxiety	N	231	444	0.6624
		Mean (SD)	5.7 (4.16)	5.9 (4.20)	
		Median	5.0	5.0	
		Q1, Q3	3, 9	2, 9	
		Min, Max	0, 21	0, 18	
		Missing	1	16	
	Depression	N	231	444	0.8764
		Mean (SD)	5.5 (4.25)	5.4 (4.09)	
		Median	5.0	5.0	
		Q1, Q3	2, 8	2, 8	
		Min, Max	0, 19	0, 21	
		Missing	1	16	
Change from visit 1	Anxiety	N	231	444	0.9552
		Mean (SD)	-0.5(3.67)	-0.4 (3.66)	
		Median	0.0	0.0	
		Q1, Q3	-2, 1	-2, 1	
		Min, Max	-17, 11	-16, 16	
	Depression	N	231	444	0.3582
		Mean (SD)	-0.1(3.57)	0.1 (3.67)	
		Median	0.0	0.0	
		Q1, Q3	-2, 1	-1, 2	
		Min, Max	-13, 13	-12, 15	

*Mann-Whitney U test was used to calculate the significant difference between treatment groups.
Source: Statistical table 14.2.1.3

- **Change in physical burden by comparison of score using HSCL scale, between the two groups**

Physical burden was analyzed in safety population using Hopkins Symptom Check List (HSCL) scale. Responses of subjects were scored on a scale of one to four. The score of one, two, three and four were rated as not-at-all, occasionally little bit, quite a bit and extremely, respectively.

In Group A, the mean (±SD) HSCL score of subjects in Visit 1 and Visit 2 was 17.9 (±5.17) and 19.1 (±5.45). The mean change in the HSCL score from Visit 1 was statistically significant (p-value<0.0001). In Group B, the mean (±SD), HSCL score of subjects in Visit 1 and Visit 2 was 18.2 (±5.19) and 18.8 (±5.23). The mean change in the HSCL score from Visit 1 was statistically significant (p-value 0.0014). (Table 11-8)

Table 11-8 Analysis of change in physical burden using Hopkins Symptom Check List (HSCL) Score by treatment group

Treatment	Statistics	Visit 1	Visit 2	Change from Visit 1	P-value*

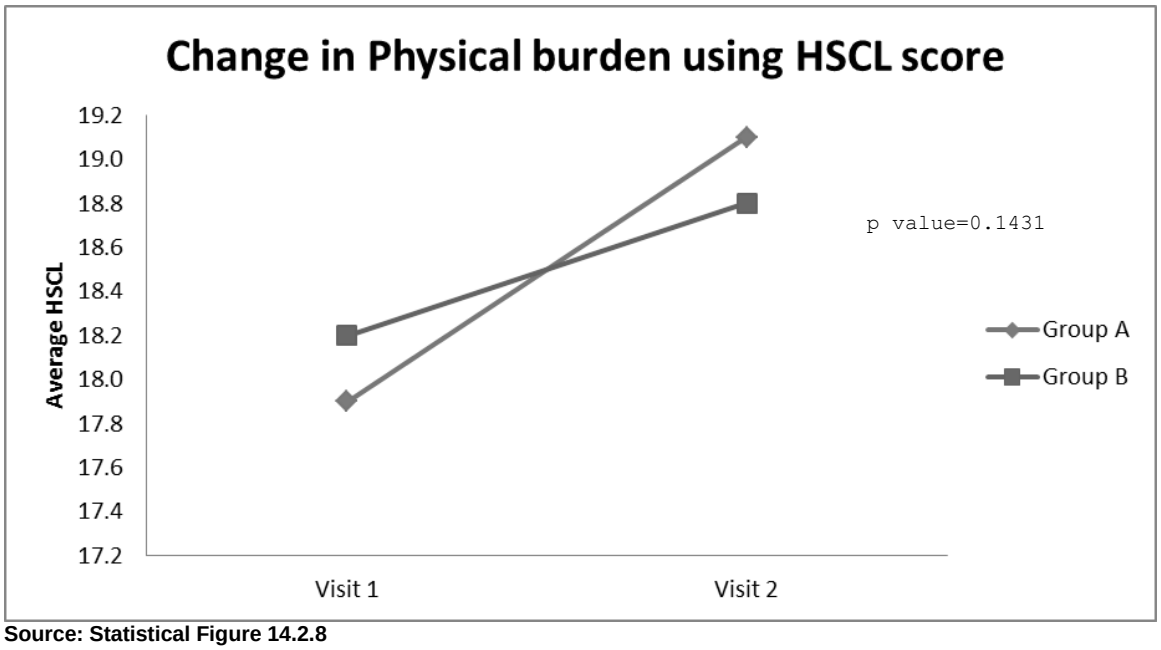
Group A	N	232	231	231	<0.0001
	Mean (SD)	17.9 (5.17)	19.1 (5.45)	1.1 (3.87)	
	Median	17.0	18.0	0.0	
	Q1, Q3	14, 21	15, 22	-1, 3	
	Min, Max	12, 37	12, 35	-17, 14	
	Missing	0	1		
Group B	N	460	444	444	0.0014
	Mean (SD)	18.2 (5.19)	18.8 (5.23)	0.6 (4.24)	
	Median	17.0	18.0	0.0	
	Q1, Q3	14, 21	15, 22	-1, 3	
	Min, Max	12, 36	12, 37	-16, 22	
	Missing	0	16		

*Wilcoxon Signed Rank test was used to calculate the significant change from Visit 1.Source: Statistical table 14.2.2.2

A detailed analysis of physical burden using each question of HSCL is presented in **Table 14-1 (Table 14-1 is presented in Section 14).**

The mean change in physical burden was not statistically significant (p value = 0.1431) when compared between two groups (Figure 11-3).

Figure 11-3 Change in Physical Burden (HSCL Score)



Source: Statistical Figure 14.2.8

Listing of HSCL score of subjects is given in Appendix 16.2.1.

- **Psychological burden and wellbeing and impact of medication by comparison of scores using COSI questionnaire between the two groups at the end of GnRH agonist or antagonist administration**

In Visit 2, the total scores for psychological burden, wellbeing and impact of medication was compared between the two treatment groups using controlled ovarian stimulation impact (COSI) questionnaire.

The mean (±SD) score of 'psychological burden', 'interference with daily life' and 'medication handling' in subjects of Group A was 19.8 (±6.35), 25.0 (±9.64) and 14.8 (±5.37), respectively. However, in Group B mean (±SD) score of 'psychological burden', 'interference with daily life' and 'medication handling' was 19.2 (±6.12), 23.8 (±8.98) and 14.4 (±5.62), respectively. No statistical significance was demonstrated between both the groups for psychological burden, interference with daily life and medication handling (**Table 11-9**)

Table 11-9 Analysis of psychological burden, wellbeing and impact of medication using Controlled Ovarian Stimulation Impact (COSI)

Visit 2	Domains	Statistics	Group A	Group B	P-value*
	Psychological burden	N	231	444	0.2033
		Mean (SD)	19.8 (6.35)	19.2 (6.12)	
		Median	20.0	18.0	
		Q1, Q3	14, 25	14, 24	
		Min, Max	9, 40	9, 41	
		Missing	1	16	
	Interference with daily life	N	231	444	0.1682
		Mean (SD)	25.0 (9.64)	23.8 (8.98)	
		Median	20.0	18.0	
		Q1, Q3	14, 25	14, 24	
		Min, Max	9, 40	9, 41	
		Missing	1	16	
	Handling of medication	N	231	444	0.4964
		Mean (SD)	14.8 (5.37)	14.4 (5.62)	
		Median	15.0	14.0	
		Q1, Q3	10, 20	10, 20	
		Min, Max	5, 25	5, 25	
		Missing	1	16	

*Mann-Whitney U test was used to calculate the significant difference between treatment groups
Source: Statistical table 14.2.3

A listing of responses of subjects for COSI questionnaire is given in Appendix 16.2.1.

11.4.2 Statistical /Analytical Issues

The general statistical approach planned for this trial has been described in Section 9.7. Detailed statistical analysis used in this study is documented in Statistical Analysis Plan (dated 30/MAY/2012) and is provided in Appendix 16.1.7.

11.4.2.1 Adjustments for Covariates

No adjustments for covariates were made.

11.4.2.2 Handling of Dropouts or Missing Data

The missing data was not imputed. Change was calculated only for subjects with non-missing data at both the time points.

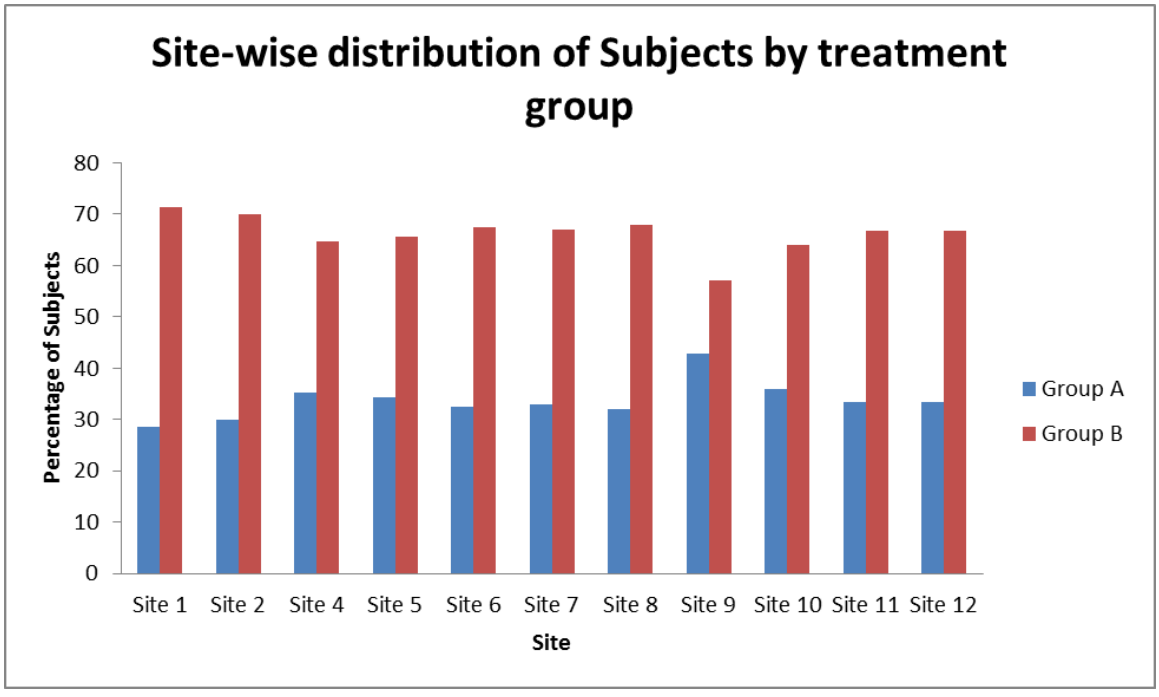
11.4.2.3 Interim Analyses and Data Monitoring

No interim analysis was done.

11.4.2.4 Multicenter Studies

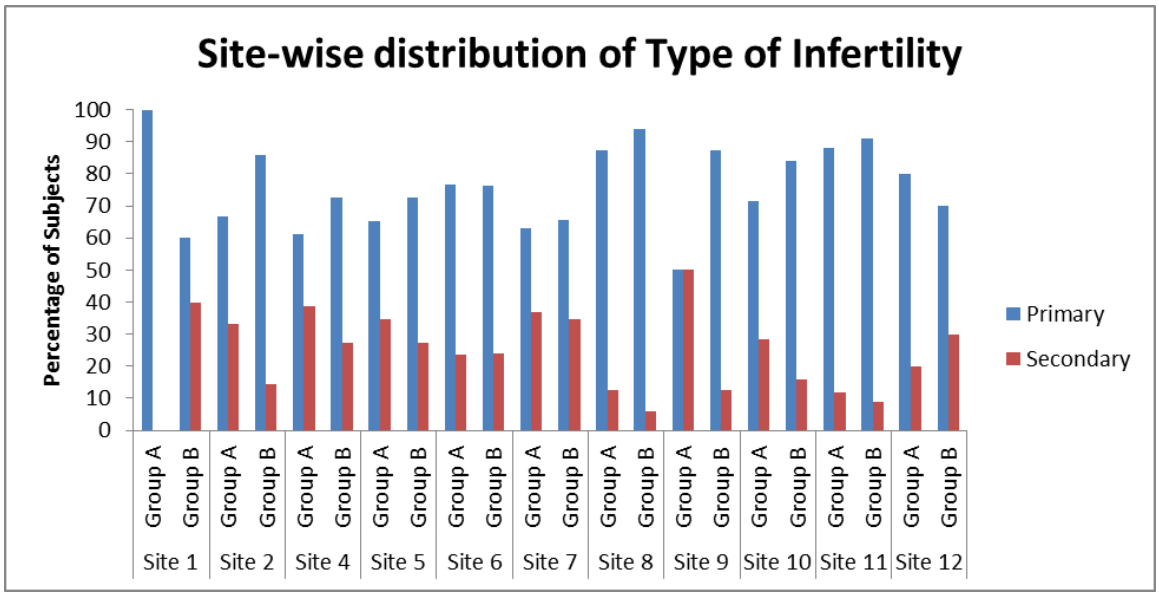
The study was conducted at 12 sites in India. The site wise enrollment is depicted in Figure 11-4.

Figure 11-4 Site wise Distribution of Subjects



All the sites demonstarted higher primary infertility than secondary infertility. The site wise distribution of primary and secondary infertility is shown in Figure 11-5 below:

Figure 11-5 Site wise Distribution of Type of Infertility



11.4.2.5 Multiple Comparison/Multiplicity

No multiplicity adjustment was planned.

11.4.2.6 Use of an 'Efficacy Subset' of Patients

Not applicable.

11.4.2.7 Active-Control Studies Intended to Show Equivalence

Not applicable.

11.4.2.8 Examination of Subgroups

This was a non-interventional study; no examination of subgroups was performed.

11.4.3 Tabulation of Individual Response Data

Not applicable.

11.4.4 Drug Dose, Drug Concentration, and Relationships to Response

Not applicable.

11.4.5 Drug-Drug and Drug-Disease Interactions

Not applicable.

11.4.6 By-Patient Displays

Not applicable.

12.0 SAFETY ASSESSMENT

The secondary objective of this study was to compare safety of controlled ovarian stimulation among subjects undergoing first cycle IVF/ICSI between those receiving standard of care gonadotropin with daily administration of GnRH agonist versus recombinant gonadotropin in pen formulation with daily administration of GnRH antagonist.

12.1 EXTENT OF EXPOSURE

This was a non-interventional, observational study. Therefore, no aspect of this study interfered with or influenced the routine medical procedures and/or medications prescribed to the subjects. Subjects were enrolled only after the treatment decision (for either GnRH agonist or antagonist protocol) had been made by the Investigator. The mean duration of medication taken by the subjects in Group A and Group B was 10.5 (±1.37) and 21.1 (±4.15) days, respectively (**Table 12-1**).

Table 12-1 Summary of Study Medication (Safety Population)

Characteristics	Statistics	Group A (N=232)	Group A (N=460)
Duration (Days)	N	232	460
	Mean (SD)	10.5 (1.37)	21.1 (4.15)
	Median	10	21
	Q1, Q3	10, 11	19, 23
	Min, Max	4, 16	7, 48

Source: Statistical table 14.3.5.2

Listing of dose administration of subjects enrolled in both treatment groups is given in Appendix 16.2.1.

12.2 ADVERSE EVENTS

12.2.1 Brief Summary of Adverse Events

This was an observational study and thus posed no risks for the subjects. The study did not expose the subjects to any experimental drug; however, assessment of safety was done on the subject participants in both the treatment groups. All the decisions regarding the assessment of AEs were based on the clinical judgment of the investigator. All the adverse events were recorded in the CRF.

Assessment of Safety Endpoints

- Number of patients with at least one adverse event, serious adverse event will be compared between the two groups.

- Incidence of ovarian hyper-stimulation syndrome (OHSS) will be compared between the two groups.

12.2.2 Display of Adverse Events

No adverse events were reported for the subjects in Group A. In Group B, there were 0.2% (1/460) subjects who reported AEs due to OHSS. **Table 12-2** summarizes all the AEs reported for safety population during this study.

Table 12-2 Summary of Adverse Events

SOC Term **Preferred Term**	**Group A (N=232) n (%)**	**Group B (N=460) n (%)**	**P-value**
Subjects with any AE	0	1 (0.2)	>0.9999^
Reproductive system and breast disorders	0	1 (0.2)	
Ovarian hyperstimulation syndrome	0	1 (0.2)	

- Denominator of the percentage is the number of subjects in the Treatment group.
- *Chi-square test / ^Fisher's Exact Test was used to calculate the P-value.
Source: Statistical table 14.3.1.1

12.2.3 Analysis of Adverse Events

The reported adverse event was due to OHSS, and OHSS of any grade was regarded as SAE in this study by the investigators. Details of the SAE are given in Section 12.3.1.2.

12.2.4 Listing of Adverse Events by Patient

Statistical listing of all adverse events reported in safety population is presented in Appendix 16.2.1.

12.3 DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

12.3.1 Listing Serious Adverse Events

Statistical listing of all subjects with OHSS is presented in Appendix 16.2.1.

12.3.1.1 Deaths

No deaths were reported during this study.

12.3.1.2 Serious Adverse Events

OHSS of any grade was considered as an SAE and expeditiously reported by the investigators. One SAE was reported from Group B due to grade I OHSS in one subject (Patient number 4002). **Table 12-3** summarizes events of OHSS for safety population.

Table 12-3 Summary of OHSS

OHSS	Grade	Group A (N=232) n (%)	Group B (N=460) n (%)	P-value
Yes		0	1 (0.2)	>0.9999^
	Grade I	0	1 (0.2)	
	Grade II	0	0	
	Grade III	0	0	
No		232 (100.0)	459 (99.6)	
Total		232 (100.0)	460 (100.0)	

- Denominator of the percentage is the number of subjects in the Treatment group.
- *Chi-square test / ^Fisher's Exact Test was used to calculate the P-value.
Grade I - Mild, Grade II - Moderate, Grade III - Severe

12.3.2 Narratives of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Subject – 04002

This 33 year old female subject was enrolled into the study and was randomized to Group B on 20/Jun/2012. The subject presented a history of infertility of 04 years and 10 months during the first visit. Further evaluation of history revealed that the subject had secondary infertility and the cause of infertility was tubal factor and polycystic ovarian syndrome (PCOS). On 05/Jul/2012 the subject was evaluated by the investigator and it was revealed she has developed mild grade OHSS. No action was taken and the subject recovered on 12/July/2012 without any sequelae. The event was determined to be unrelated to the treatment received by the subject.

12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

Summary of all the SAEs for safety population is displayed in **Table 12-4.**

As discussed earlier only one SAE was reported in this study, that is, OHSS was reported for one subject from Group B by the investigators. **Table 12-5** presents serious adverse events by severity grade for safety population. At subject level, subject with multiple occurrences of the

same event with the same severity are counted only once. The SAE reported was classified as mild.

Table 12-4 Summary of Serious Adverse Events

SOC Term Preferred Term	Group A (N=232)	Group B (N=460)	P- value
Subjects with any adverse event	0	1 (0.2)	>0.9999^
Reproductive system and breast disorders	0	1 (0.2)	
Ovarian hyperstimulation syndrome	0	1 (0.2)	

- Denominator of the percentage is the number of subjects in the treatment group.
- *Chi-square test / ^Fisher's Exact Test was used to calculate the P-value.
Source: Statistical table 14.3.2.1

Table 12-5 Summary of serious adverse events by severity

SOC Term Preferred Term	Group A (N=232)			Group A (N=460)		
	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
Subjects with any SAE	0	0	0	1 (0.2)	0	0
Reproductive system and breast disorders	0	0	0	1 (0.2)	0	0
Ovarian hyperstimulation syndrome	0	0	0	1 (0.2)	0	0

- Denominator of the percentage is the number of subjects in the Treatment group.
Source: Statistical table 14.3.2.2

The reported event of SAE was judged as not related to the treatment received by the subject (**Table14-2**). No action was taken for the reported SAE (**Table14-3**) and was resolved without sequelae (**Table14-4**). Table 14-2, 14-3 and 14-4 are presented in Section 14.

12.4 CLINICAL LABORATORY EVALUATION

12.4.1 Listing Of Individual Laboratory Measurements By Subject And Each Abnormal Laboratory Value

No laboratory measurements were done for study subjects.

12.5 VITAL SIGNS, PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY

Physical examinations were conducted as a part of screening to establish medical eligibility for the study. In Group A and Group B abnormality was detected in 1.7% (4) and 0.2% (1) subjects, respectively. It was revealed, in Group A, two subjects (Subject # 2002 and 2008), had palpable thyroid; and two other subjects (Subject # 9009 and 9010) had obesity and hirsutism. Subject # 9009 was also diagnosed with bilateral galactorrhoea. In Group B, thyroid imbalance was

detected in one subject (Subject # 2010). **Table 12-6** presents summary of physical examination for safety population. **Table 12-6** presents summary of physical examination for safety population. For physical examination listing of subjects refer Appendix 16.2.1.

Table 12-6Summary of Physical Examination

Visit	**Category**	**Group A (N=232) n (%)**	**Group B (N=460) n (%)**
Screening	Normal	228 (98.3)	459 (99.8)
	Abnormal	4 (1.7)	1 (0.2)

-Denominator of the percentage is the number of subjects in the treatment group.
Source: Statistical table 14.3.3

The details of follow-up visits of each subject are listed in Appendix 16.2.1.

12.6 SAFETY CONCLUSIONS

In this study OHSS of any grade was regarded as an SAE. There was one subject in Group B (subject # 4002) who experienced OHSS and was regarded as SAE in this study by the investigators.

The OHSS reported was of Grade I and the SAE was classified as mild. The SAE reported in this study was judged unlikely related to the treatment protocol by the investigator. There was no report of any life threatening AE or SAE throughout the study.

13.0 DISCUSSION AND OVERALL CONCLUSIONS

This study was designed to explore the impact of different COS protocols on physical and psychological burden of patients undergoing In-Vitro Fertilization/In-Vitro Cytoplasmic Sperm Injection (IVF/ICSI). This was an observational study in which 692 subjects were enrolled in the ratio 1:2 in Group A (GnRH antagonist) and Group B (GnRH agonist). In Group A 232 and in Group B 460 subjects were enrolled. In Group A and Group B, 230 and 441 subjects completed the study as per protocol, respectively. SAE was reported in one subject in Group B due to Grade I OHSS which was of mild grade and was resolved without any sequelae. The statistical analysis of the primary and secondary endpoints was done on all subjects allocated to any treatment arm in the study and was considered as safety population. The analysis demonstrated that there were changes in physical and psychological burden (Table 11-6, 11-7 and 11-8) in patients undergoing IVF/ ICSI. However, when compared between two protocols (GnRH antagonist vs GnRH agonist) it was not statistically significant (Table 11-7 and 11-8).

There was significant increase in physical burden (HSCL score) in both treatment protocols compared to baseline, though when compared between groups it was not statistically significant (Figure 11-3). Many of the studies have used analysis of psychological and physical burden in subjects undergoing IVF/ICSI, in agreement with assessment results of HADS, HSCL and COSI questionnaire (Klerk,2006, Brod, 2013). In the present study, the mean change of score from visit one for anxiety and depression were not significant (**Table 11-7**). The level of anxiety and depression varied between treatment groups. The percentage of subjects that experienced anxiety and depression was higher in the Group B than Group A, but was not statistically significant. .

In this study, subjects receiving GnRH antagonist (Group A) scored higher than the subjects receiving GnRH agonist (Group B) protocol treatment on COSI questionnaire. Unlike the study reported by Brod et al (2013), in this study, the impact of COS on subjects was not significant.

An interventional non inferiority study conducted by Heijnen et al (2007) with the primary outcome measure of pregnancy and term live birth within one year of randomization, total cost per couple and patient discomfort compared the two protocols similar to the present study i.e., the mild treatment strategy for IVF and standard treatment. However the present study was an observational study and analyzed only one cycle as compared to three to four cycle in the study by Heijnen et al (2007); yet both studies demonstrated that there were no significant differences in anxiety, depression and physical discomfort between both the protocols.

Systematic review (Al-Inany, 2011) have shown that use of antagonist compared with long GnRH agonist protocols was associated with a large reduction in OHSS and there was no evidence of a difference in live-birth rates. Consistent with the findings of previous studies, one subject from

Group B treatment group experienced an unrelated SAE due to OHSS during this study and in Group A no cases of OHSS was reported.

The present study was an observational open label study to evaluate the psychological and physical burden in subjects for first cycle. This study reflected psychological burden of patients of infertility receiving IVF/ICSI treatment, as has been previously noted in other such studies (Demyttenaere K, 1998; Smeenk, 2001). Generally previous studies have reported the high psychological and physical burden to account for the infertility treatment effect. The previous studies (Heijnen et al 2007; Klerk et al 2006; Demyttenaere et al., 1998) were interventional randomized trials and the change was observed over a period of time where treatment lasts for more than one cycle. Hence the change in psychological stress was significant as compared to the present study. It was observed that psychological burden increase due to difficulty in tolerating the negative emotions for extending time periods, uncertainty and strain of repeated ART cycles. In a study by Boivin et al (2012) it was suggested that causes of burden can originate in patient, clinic or treatment. This psychological and physical burden can be decreased by comprehensive educational materials, screening to identify highly distressed patients, provision of tailored coping tools and improvements in the clinic environment and medical interventions.

Some researchers have proposed that the frequent treatment visits daily injections, scans and invasive procedures, such as oocyte retrieval, may be responsible for the high psychological and physical burden (Eyal et al., 1996). However, in this study, the psychological burden was not statistically significant compared to baseline score, but the physical burden was increased post treatment protocols similar to the previous study by Klerk et al 2006. These results can be due to the fact that all the participants were first cycle IVF treatment patients and were comparatively well adjusted psychologically in comparison of subjects who had experienced unsuccessful IVF treatment previously. The role of physical and psychological burden in infertility and infertility treatment outcome is not very clear. Both men and women experience anxiety during an IVF-treatment, independent of the stage of the procedure (first time or repeated cycle) (Eugster et al., 1999). However, in a report Domar et al. have agreed to the fact that psychological and physical burden may have some impact on the outcome of the IVF treatment (Domar et al., 2011).

In conclusion, this was the first study in Indian population comparing different protocols to evaluate psychological and physical burden in patients undergoing IVF/ICSI treatment. The study demonstrated significant physical burden with both treatment protocols. However, a significant difference between the protocols is not demonstrated in both psychological and physical burden. One case of OHSS was reported in the GnRH Agonist treated group. This reiterates importance

of comprehensive education and counseling to reduce physical burden as well as safety aspects of different stimulation protocol which can improve quality of life and treatment outcome.

14.0 TABLES AND FIGURES AND GRAPHS REFFERED TO BUT NOT INCLUDED IN THE TEXT

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Table 14-1 Analysis of physical burden using each question of HSCL

Visit	How have you felt during the past seven days including today	Rating scale	Group A n (%)	Group B n (%)	P-value
Visit 1	I feel faintness or dizziness	Not at all	142 (61.2)	299 (65.0)	0.6749*
		From time to time occasionally	65 (28.0)	123 (26.7)	
		A lot of time	22 (9.5)	33 (7.2)	
		Most of the time	3 (1.3)	5 (1.1)	
	I feel numbness or tingling in parts of my body	Not at all	169 (72.8)	301 (65.4)	0.2482*
		From time to time occasionally	44 (19.0)	115 (25.0)	
		A lot of time	13 (5.6)	32 (7.0)	
		Most of the time	6 (2.6)	12 (2.6)	
	I feel a lump in the throat	Not at all	183 (78.9)	368 (80.0)	0.2489*
		From time to time occasionally	31 (13.4)	115 (25.0)	
		A lot of time	11 (4.7)	32 (7.0)	
		Most of the time	7 (3.0)	12 (2.6)	
	I feel low in energy or slowed down	Not at all	100 (43.1)	217 (47.2)	0.6040*
		From time to time occasionally	98 (42.2)	170 (37.0)	
		A lot of time	26 (11.2)	57 (12.4)	
		Most of the time	8 (3.4)	16 (3.5)	
	I feel pain in the heart or chest	Not at all	167 (72.0)	340 (73.9)	0.3430*
		From time to time occasionally	48 (20.7)	77 (16.7)	
		A lot of time	12 (5.2)	36 (7.8)	
		Most of the time	8 (3.4)	7 (1.5)	
	I feel soreness of muscles	Not at all	159 (68.5)	272 (59.1)	0.1169*
		From time to time occasionally	55 (23.7)	144(31.3)	
		A lot of time	13 (5.6)	33 (7.2)	
		Most of the time	5 (2.2)	11 (2.4)	
	I get hot or cold spells	Not at all	133 (57.3)	270 (58.7)	0.8138*
		From time to time occasionally	74 (31.9)	133 (28.9)	
		A lot of time	18 (7.8)	39 (8.5)	
		Most of the time	7 (3.0)	18 (3.9)	
	I get headaches	Not at all	121 (52.2)	225 (48.9)	0.4682*
		From time to time occasionally	83 (35.8)	191 (41.5)	
		A lot of time	21 (9.1)	33 (7.2)	
		Most of the time	7 (3.0)	11 (2.4)	
	I get pain in the lower part of my back	Not at all	128 (55.2)	236 (51.3)	0.4335*

		From time to time occasionally	69 (29.7)	154 (33.5)	
		A lot of time	29 (12.5)	50 (10.9)	
		Most of the time	6 (2.6)	20 (4.3)	
	I have a feeling of weakness in parts of body	Not at all	121 (52.2)	214 (46.5)	0.3481*
		From time to time occasionally	80 (34.5)	169 (36.7)	
		A lot of time	28 (12.1)	59 (12.8)	
		Most of the time	3 (1.3)	18 (3.9)	
	I have heavy feelings in arms or legs	Not at all	164 (70.7)	299 (65.0)	0.3481*
		From time to time occasionally	44 (19.0)	110 (23.9)	
		A lot of time	18 (7.8)	33 (7.2)	
		Most of the time	6 (2.6)	18 (3.9)	
	I have trouble getting my breath	Not at all	176 (75.9)	357 (77.6)	0.9208*
		From time to time occasionally	41 (17.7)	72 (15.7)	
		A lot of time	11 (4.7)	22 (4.8)	
		Most of the time	4 (1.7)	9 (2.0)	
Visit 2	I feel faintness or dizziness	Not at all	112 (48.3)	258 (56.1)	0.0319*
		From time to time occasionally	100 (43.1)	142 (30.9)	
		A lot of time	17 (7.3)	40 (8.7)	
		Most of the time	2 (0.9)	4 (0.9)	
		Missing	1 (0.4)	16 (3.5)	
	I feel numbness or tingling in parts of my body	Not at all	144 (62.1)	283 (61.5)	0.4824*
		From time to time occasionally	65 (28.0)	119 (25.9)	
		A lot of time	19 (8.2)	29 (6.3)	
		Most of the time	3 (1.3)	13 (2.8)	
		Missing	1 (0.4)	16 (3.5)	
	I feel a lump in the throat	Not at all	173 (74.6)	349 (75.9)	0.0242*
		From time to time occasionally	30 (12.9)	70 (15.2)	
		A lot of time	21 (9.1)	20 (4.3)	
		Most of the time	7 (3.0)	5 (1.1)	
		Missing	1 (0.4)	16 (3.5)	
	I feel low in energy or slowed down	Not at all	104 (44.8)	198 (43.0)	0.1912*
		From time to time occasionally	81 (34.9)	178 (38.7)	
		A lot of time	30 (12.9)	52 (11.3)	
		Most of the time	16 (6.9)	16 (3.5)	
		Missing	1 (0.4)	16 (3.5)	
	I feel pain in the heart or chest	Not at all	143 (61.6)	275 (59.8)	0.3792*
		From time to time occasionally	65 (28.0)	138 (30.0)	
		A lot of time	16 (6.9)	25 (5.4)	
		Most of the time	7 (3.0)	6 (1.3)	
		Missing	1 (0.4)	16 (3.5)	
	I feel soreness of muscles	Not at all	135 (58.2)	260 (56.5)	0.7691*
		From time to time occasionally	66 (28.4)	125 (27.2)	
		A lot of time	27 (11.6)	48 (10.4)	
		Most of the time	3 (1.3)	11 (2.4)	

		Missing	1 (0.4)	16 (3.5)	
	I get hot or cold spells	Not at all	136 (58.6)	264 (57.4)	0.9983*
		From time to time occasionally	66 (28.4)	126 (27.4)	
		A lot of time	27 (11.6)	45 (9.8)	
		Most of the time	3 (1.3)	9 (2.0)	
		Missing	1 (0.4)	16 (3.5)	
	I get headaches	Not at all	110 (47.4)	203 (44.1)	0.2997*
		From time to time occasionally	95 (40.9)	195 (42.4)	
		A lot of time	19 (8.2)	41 (8.9)	
		Most of the time	7 (3.0)	5 (1.1)	
		Missing	1 (0.4)	16 (3.5)	
	I get pain in the lower part of my back	Not at all	103 (44.4)	224 (48.7)	0.2751*
		From time to time occasionally	95 (40.9)	153 (33.3)	
		A lot of time	20 (8.6)	47 (10.2)	
		Most of the time	13 (5.6)	20 (4.3)	
		Missing	1 (0.4)	16 (3.5)	
	I have a feeling of weakness in parts of body	Not at all	106 (45.7)	179 (38.9)	0.4189*
		From time to time occasionally	79 (34.1)	158 (34.3)	
		A lot of time	38 (16.4)	93 (20.2)	
		Most of the time	8 (3.4)	14 (3.0)	
		Missing	1 (0.4)	16 (3.5)	
	I have heavy feelings in arms or legs	Not at all	137 (59.1)	265 (57.6)	0.7990*
		From time to time occasionally	61 (26.3)	120 (26.1)	
		A lot of time	21 (9.1)	43 (9.3)	
		Most of the time	12 (5.2)	16 (3.5)	
		Missing	1 (0.4)	16 (3.5)	
	I have trouble getting my breath	Not at all	177 (76.3)	314 (68.3)	0.3638*
		From time to time occasionally	38 (16.4)	98 (21.3)	
		A lot of time	12 (5.2)	25 (5.4)	
		Most of the time	4 (1.7)	7 (1.5)	
		Missing	1 (0.4)	16 (3.5)	

*Chi-square Test/ ^Fisher's exact test was used to calculate the significant difference between treatment groups.
Source: Statistical table 14.2.2.3

Table 14-2 Summary of serious adverse events by relationship with study drug

SOC Term Preferred Term	Group A (N=232)				Group B (N=460)			
	Probable n (%)	Possible n (%)	Probably not n (%)	Not Related n (%)	Probable n (%)	Possible n (%)	Probably not n (%)	Not Related n (%)
Subjects with any SAE	0	0	0	0	0	0	0	1 (0.2)
Reproductive system and breast disorders	0	0	0	0	0	0	0	1 (0.2)
Ovarian hyperstimulation syndrome	0	0	0	0	0	0	0	1 (0.2)

- Denominator of the percentage is the number of subjects in the Treatment group.
Source: Statistical table 14.3.2.3

Table 14-3 Summary of serious adverse events by action taken

SOC Term Preferred Term	**Group A (N=232)**			**Group A (N=460)**		
	None n (%)	**Concomitant Medication n (%)**	**Non-Drug Treatment n (%)**	**None n (%)**	**Concomitant Medication n (%)**	**Non-Drug Treatment n (%)**
Subjects with any SAE	0	0	0	1 (0.2)	0	0
Reproductive system and breast disorders	0	0	0	1 (0.2)	0	0
Ovarian hyperstimulation syndrome	0	0	0	1 (0.2)	0	0

- Denominator of the percentage is the number of subjects in the treatment group.
Source: Statistical table 14.3.2.4

Table 14-4 Summary of serious adverse events by outcome

SOC Term Preferred Term	**Group A (N=232)**				**Group B (N=460)**			
	Recovered / resolved without sequelae n (%)	**Recovered / resolved with sequelae n (%)**	**Death n (%)**	**Unknown n (%)**	**Recovered / resolved without sequelae n (%)**	**Recovered / resolved with sequelae n (%)**	**Death n (%)**	**Unknown n (%)**
Subjects with any SAE	0	0	0	0	1 (0.2)	0	0	0
Reproductive system and breast disorders	0	0	0	0	1 (0.2)	0	0	0
Ovarian hyperstimulation syndrome	0	0	0	0	1 (0.2)	0	0	0

- Denominator of the percentage is the number of subjects in the treatment group.
Source: Statistical table 14.3.2.5

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16.0 APPENDICES

16.1 Study Information

16.1.1 Protocol and protocol amendments

16.1.2 Sample case report form

16.1.3 IEC / IRB Documents and Sample Informed Consent Form

16.1.4 Curriculum Vitae (CVs) of Study Personnel

16.1.5 Signatures of PI/coordinating Investigator(s) or sponsor's medical officer

16.1.6 Audit certificates (if available) (Certification from QA)

16.1.7 Documentations of Statistical Methods

16.1.8 Documentation of inter-laboratory standardization methods and quality assurance procedures if used

16.2 Patient Data Listings

16.2.1 Statistical Tables, Listings and Figures

16.3 Case Report Forms (CRFs)

16.3.1 CRFs for Deaths, other serious adverse events and withdrawals for AE

16.3.2 Other CRFs submitted