Clinical Trial Protocol

Clinical Trial Protocol Number	MS700623_0020
Title	A prospective, randomized controlled study to investigate the cumulative live birth rates (CLBRs) of gonadotrophin-releasing hormone (GnRH) antagonist protocol compared with the standard GnRH agonist long protocol for controlled ovarian stimulation in supposed normal ovarian responders
Phase	IV
IND Number	N/A
EudraCT Number	N/A
Principal Investigator	Peking University Third Hospital, Beijing, China
Sponsor	Center for Reproductive Medicine, Peking University Third Hospital Medical Responsible: Address: No. 49 Huayuan North Road, Haidian District, Beijing (phone) 010-82265080 (fax) 010-62010334
Sponsor Legal Representative in the European Union	N/A
Clinical Trial Protocol Version	15 Jan 2018/ Version 1.1
Replaces Version	N/A

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List of Abbreviations

ADR	Adverse drug reaction
AE	Adverse event
AFC	Antral follicle count
ART	Assisted reproductive technology
β -hCG	Beta-human chorionic gonadotropin
COS	Controlled ovarian stimulation
CRO	Contract research organization
eCRF	Electronic case report form
ET	Embryo transfer
FET	Frozen embryo transfer
E_2	Estradiol
FSH	Follicle stimulating hormone
Gn	Gonadotropin
GnRH-a	Gonadotropin-releasing hormone agonist
GnRH-ant	Gonadotropin-releasing hormone antagonist
hCG	Human chorionic gonadotropin
iCOS	Individualized controlled ovarian stimulation
ICSI	Intracytoplasmic sperm injection
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IU	International Unit
IVF	In vitro fertilization
LH	Luteinizing hormone
MII	Metaphase II
OHSS	Ovarian hyperstimulation syndrome
PCOS	Polycystic ovary syndrome
r-LH	Recombinant luteinizing hormone
r-FSH	Recombinant human follicle stimulating hormone
SAE	Serious adverse event
SmPC	Summary of product characteristics

1 Synopsis

Clinical Trial Protocol Number	MS700623_0020
Title	A prospective, randomized controlled study to investigate the cumulative live birth rates (CLBRs) of gonadotrophin-releasing hormone (GnRH) antagonist protocol compared with the standard GnRH agonist long protocol for controlled ovarian stimulation in supposed normal ovarian responders
Trial Phase	Phase IV
IND Number	Not applicable
FDA covered trial	No
EudraCT Number	Not applicable
Principal Investigator	Peking University Third Hospital
Sponsor	Center for Reproductive Medicine, Peking University Third Hospital
Sponsor Legal Representative in the European Union	Not applicable
Trial centers/countries	This study will be conducted in approximately 5 centers in China
Planned trial period (first subject in-last subject out)	About 34 months
Trial Registry	Register study information on ClinicalTrials.gov

Objectives:

Primary objectives

• To investigate the cumulative live birth rates in infertile women ≤ 38 years old with normal ovarian reserve using GnRH antagonist or agonist protocol for COS in ART treatment

Secondary Objectives

• To investigate the safety and pregnancy outcomes of GnRH antagonist and agonist protocols after the fresh embryo transfer

Methodology:
This is a Phase IV, prospective, randomized controlled study to investigate the cumulative live birth rates (CLBRs) of gonadotrophin-releasing hormone (GnRH) antagonist protocol (GnRH-ant group) compared with the standard GnRH agonist long protocol (GnRH-a group) for controlled ovarian stimulation in supposed normal ovarian responders.

In this study, patients who are planning to undergo IVF/ICSI cycle aged ⩽38 years old with normal ovarian reserve will be considered for enrollment. Approximately 888 patients will be enrolled at approximately 5 centers in China over a period of 10 months.

About 12-20 visits will be performed in this study for each patient.

The CLBR with first live birth resulting from one initiated COS cycle will be compared between GnRH-a group and GnRH-ant group.

Planned number of subjects: 888

Primary endpoints:

CLBR with first live birth resulting from one initiated COS cycle

Secondary endpoints:

- Number of oocytes retrieved
- Good-quality embryo rate (The Istanbul Consensus[29])
- hCG positive rate
- Implantation rate
- Clinical pregnancy rate
- Ongoing pregnancy rate
- Live birth rate
- Cumulative clinical pregnancy rate
- Miscarriage rate
- Ectopic pregnancy rate
- Cycle cancelled rate and reason
- Rate and severity of OHSS
- Time to pregnancy
- Time to live birth

Pharmacokinetics: Not applicable

Other assessments:

To explore the relationship between the number of oocytes retrieved and number of embryos or times of embryo transfer or CLBR

Diagnosis and key inclusion and exclusion criteria:
Diagnosis: Infertile women planning to undergo IVF/ICSI cycle aged ≤38 years old with normal ovarian reserve

Inclusion criteria:

1. Infertile women planning to undergo IVF/ICSI cycle using conventional GnRH agonist long protocol or GnRH antagonist protocol
2. Age ≤ 38 years old
3. Basal AFC 8~20
4. Basal FSH≤10 IU/L
5. Basal E_2<200pmol/L

6. Normal uterus and at least one side of the normal ovary
7. Informed consent form signed
8. Willing to follow the study protocol, and able to complete this study

Exclusion criteria:

1. Previous IVF/ICSI cycles >2
2. Severe hydro-salpinx (Ultrasound shows hydro salpinx > 2cm)
3. Severe endometriosis (Grade III – IV)
4. Polycystic ovarian syndrome (PCOS)
5. History of recurrent miscarriages (>2 times of miscarriages)
6. Plan to undergo ovarian stimulation for preimplantation genetic diagnosis or preimplantation genetic screening, oocyte donation, and social or medical freezing of oocytes
7. Any major systemic disease that as per Investigator's discretion precludes subject for participation in the study
8. With pregnancy contraindications
9. Alcoholism, drug abuse, drug addiction or patients with uncured sexually transmitted disease
10. According to the judgment of the Investigator, any medical condition or any concomitant surgery/medications that would interfere with evaluation of study medications
11. Simultaneous participation in another clinical study
12. Plan to use urinary gonadotrophin during COS treatment

Investigational Medicinal Product:

GnRH-a group: The GnRH-a (Diphereline® or Decapetyl®) 0.1mg will be administered for about 14 to 20 days for down-regulation. Recombinant FSH (Gonal-f®) will be administrated as routinely practiced by investigators. GnRH-a types, GnRH-a and FSH doses will be adjusted according to the clinical experiences of investigators in each site.

GnRH-ant group: Recombinant FSH (Gonal-f®) will be administrated as routinely practiced by investigators. FSH doses will be adjusted according to the clinical experiences of investigators. The GnRH-ant (Cetrotide®) will be initiated in a fixed protocol on stimulation days 5 or 6 per the investigator's ART protocol.

Reference therapy:

LH supplementation: If there is slow/suboptimal response in follicular development observed by investigators, the rLH (Luveris®) will be administrated as required. LH supplementation is based on one of the following criteria[1] :

- Having no follicle >10 mm by day 6;
- Low estradiol concentration <200 pg/ml or <732 pmol/L by day 6;
- Poor progression or slowing of follicle growth, i.e., previously 1–2 mm progression/day slowing to less than 2 mm in 3 days.

Planned trial and treatment duration per subject:

Two years (from the administration of FSH)

Statistical methods:

For this non-inferiority trial, a sufficient number of subjects will be enrolled to have at least 80% power to demonstrate the non-inferiority of GnRH antagonist protocol vs GnRH agonist protocol regarding the CLBR using a two-sided 95% confidence interval. The CLBR is expected to be 60% in both groups, and the non-inferiority margin is -10% (absolute). Based on these assumptions, a sample size of 377 evaluable subjects per arm would provide 80% power to demonstrate the non-inferiority of GnRH antagonist protocol vs GnRH agonist protocol regarding the CLBR. As a result, totally about 888 subjects will be randomized, that is 444 for each treatment group after considering 15% dropout rate.

The primary analyses will be performed on the PP population, and will be confirmed on the ITT. Safety analysis will be based on the safety population.

In general, continuous variables will be presented with number of subjects, mean, standard deviation, median, minimum, and maximum. Categorical variables will be presented with number and percentage of subjects within each specific category.

The result of the analysis of the primary endpoint (CLBR) is essential for the non-inferiority claim. The conservative CLBR will be used to test the hypothesis in a confirmatory way. Conservative CLBR with the corresponding 95% confidence interval (CL) will be based on binominal distribution. The two treatments will be compared by using Chi-square test for conservative CLBR. The difference between the two treatments and its associated 95% CI based on asymptotic normal distribution will be presented. If the lower-limit of the 95% confidence interval is greater than the non-inferiority limit (-10%), the null hypothesis will be rejected and it would be claimed that GnRH antagonist protocol is non-inferior to GnRH agonist protocol regarding to the cumulative live birth rate.

Optimal CLBR will be analyzed using Kaplan-Meier product-limit method, the rate and its 95% CI will be provided. For optimal CLBR, the two treatments will be compared using Kaplan-Meier product-limit estimates, the difference between the two treatments and its associated 95% CI will be also presented.

The analyses of the secondary rate endpoints will use the same methods as the conservative CLBR and the analysis of secondary time-to-event variables will use the similar methods as the optimal CLBR, which are intended to provide additional characterization of the treatment effect.

Number of oocytes retrieved will be summarized and compared basing on analysis of variance (ANOVA) including treatment and center as factors. The treatment difference and the two-sided 95% confidence interval will be reported.

Furthermore, univariate/multivariate logistic or cox regression analysis will be performed to evaluate the dependence of Age (≤35 or >35 years), AFC, AMH, number of oocytes retrieved, number of usable embryos, times of embryo transfer, and BMI in relation to pregnancy rate or CLBR.

Table X Schedule of Assessments

Procedure Visit	Screening/Baseline	Gn Initiation	Triggering Day	Oocytes pick up	Embryo Transfer		HCG Test	Clinical pregnancy assessment	Ongoing Pregnancy（fresh cycle）	Live Birth	End of Observation	2 years Follow up Visit
					fresh cycle	FET						
Demography	×											
Medical history	×											
Inclusion and exclusion criteria	×											
Signed informed consent form	×											
Physical examination and vital signs	×											
Clinical and gynecological examination	×											
FSH levels within last 3 months	×											
E_2 level within last 3 months	×											
AMH*	×											
AFC within last 3 months	×											
Administration of GnRH-a（ long protocol group）		×	×									
Administration of Gonal-f® new pen		×	×									
Administration of GnRH-ant (GnRH-ant protocol group)			×									
LH levels		×										
r-LH supplementation if need			×									
HCGtrigger			×									
E_2 level		×										
Oocytes pick up				×								

Procedure Visit	Screening/Baseline	Gn Initiation	Triggering Day	Oocytes pick up	Embryo Transfer		HCG Test	Clinical pregnancy assessment	Ongoing Pregnancy（fresh cycle）	Live Birth	End of Observation	2 years Follow up Visit
					fresh cycle	FET						
Embryo transfer					×	×						
Pregnancy assessment by serum β-hCG test							×					
Clinical Pregnancy assessment by ultrasound scan						×		×				
Ongoing pregnancy									×			
Live birth										×		
Safety												
OHSS			×	×								
AEs		×	×	×	×		×	×	×	×		
Concomitant medication		×	×	×	×		×	×	×	×		

* After randomization.

After each embryo transfer in the fresh cycle / frozen embryo transfer (FET), HCG test, clinical pregnancy assessment, ongoing pregnancy (only in the fresh cycle) and live birth assessment should be performed and recorded.

2 Sponsor, Investigators and Trial Administrative Structure

This clinical trial will be sponsored by: Center for Reproductive Medicine, Peking University Third Hospital

The trial will be conducted at about 5 sites in China.

The Principal Investigator (Professor Jie Qiao, Peking University Third Hospital), represents all Investigators for decisions and discussions regarding this trial, consistent with the Good Clinical Practice (GCP). The Principal Investigator will provide expert medical input and advice relating to trial design and execution and is responsible for the review and signoff of the clinical trial report.

Signature pages for the Principal Investigator as well as a list of Sponsor responsible persons are in Appendix1.

It is planned to perform the study at approximately 5 sites across China. A Contract Research Organization (CRO) will be appointed for the conduct of the trial (including trial management, monitoring, data management, statistical analysis and medical writing).

3 Background Information

In the last 50 years, development of assisted reproduction and unprecedented success has given hope to couples who were considered sub-fertile and constituted 10-15% of the general population. In the developed nations 1% of the children are thought to be conceived with the help of assisted reproductive technology (ART) (Larcher V, 2007). Since the birth of Louise Brown, first "test tube baby"， more than five million babies have been born worldwide with the help of ART (Qiao J, 2014). Joint research and collaboration between diversified scientific fields like biology, physiology, endocrinology, embryology, laboratory science and clinical medicine resulted in development of ART of today (Feinberg EC, 2005). Howard and Jones in USA and Trounson from Australia pioneered COH (controlled ovarian hyperstimulation) by using gonadotropins derived from the urine and provided a useful tool for in vitro fertilization (IVF) (Trounson AO, 1981. Brinsden PR, 2009; Zhao Y, 2011). These injectable gonadotropins made it possible to expose ovarian follicles to higher hormonal levels and make a larger number of ovarian follicles to mature into oocytes which can be retrieved predictably in a large number from a single IVF cycle (Zhao Y, 2011).

Higher number of oocytes retrieved has been linked with greater chances of pregnancy (Fleming R, 1996) and will increase the efficacy and efficiency of the reproductive treatment. This is done by hyper stimulation of the ovaries by external recombinant gonadotrophins (Commenges-Ducos M, 1998. Macklon NS, 2006). Average number of follicles recruited in an ovarian stimulation cycle have risen to ten, twenty or more, which have led to the yield of enhanced number of oocytes per cycle (Edwards RG, 1996). Manipulation of menstrual physiology with the help of drugs and surgery is the key to success in ART (Matzuk M, 2008).

In clinical practice, the most common used protocols in controlled ovarian stimulation include the long protocol (GnRH-a will be used) and short protocol (GnRH-ant will be used). GnRH analogues are given to the women undergoing ovarian hyper-stimulation to obviate LH surge which may

cause the follicles to ovulate prematurely. In order to suppress internal secretion of pituitary gonadotropin, GnRH agonists are used which help in revolutionizing the process and procedure of stimulation of the ovaries and prevention of LH (luteinizing hormone) surge. GnRH agonists utilize agonistic analogues of gonadotropins which have some amino acids substitutions in their amino acid sequence which happen to make them more competent and enhance their half lives in comparison with the natural hormones. GnRH agonists provide release of gonadotropin secretion (Copperman AB, 2013), but after 5-7d continuous application, the pituitary is no longer respond to the stimulation then become desensitization, achieve the down-regulation (JING X, 2012). So called long protocol consist of giving external gonadotropin along with GnRH agonists and causing suppression of pituitary FSH and LH. By this protocol cancellation rate is reduced and there is increase in recruitment of the follicles and getting larger number of oocytes. The incidence of premature surges of LH is also remarkably reduced. Ovarian stimulation, through the use of GnRH agonists, helps to improve pregnancy rate as a result of IVF (Macklon NS, 2006). GnRH antagonists cause sudden chemical suppression of the pituitary, thereby causing shutdown of LH (luteinizing hormone) and FSH (follicle stimulating hormone) secretion (Shrestha D, 2015). GnRH antagonists are given in the mid-cycle which prevents an early LH surge (Gordts S, 2010). No suppression occurs in the beginning of follicular phase which is an important time for recruitment of the follicles. Ovarian stimulation by GnRH antagonist protocol is not only short but also cost effective (Depalo R, 2012). Perfect synchronization of female endocrines, endometrial physiology and embryonic factors form the basis of molecular communication between the uterine endometrium and upcoming embryo which helps in implantation and subsequent conception (Cartwright JE, 2010). Changes in morphology of the endometrium and hormonal secretion ensure proper embryo transfer and implantation capable of progression to pregnancy (Gellersen B, 2014).

Both GnRH agonist and GnRH antagonist protocols are widely used in controlled ovarian stimulation (COS); however, there is a persistent debate concerning the reproductive outcomes when comparing the two analogue treatments (Toftager M, 2016). In the most recent Cochrane review, the GnRH antagonist protocol was associated with comparable live birth rate (LBR) and a substantial reduction in the incidence of OHSS when compared to GnRH agonist long protocol in women undergoing ART in none selected population (Hesham G AI,2016).

Comparing with GnRH agonist protocol, the GnRH antagonist protocol is associated with fewer oocytes retrieved, lower OHSS incidence whereas the ongoing pregnancy rate and LBR were similar in supposed normal responders in the recent systematic review and meta-analysis (JS Xiao, 2014). However, the data published in the same year found that among good-prognosis patients, agonist protocol decreased cancellation risk and increased odds of implantation and live birth compared with antagonist protocol using the national surveillance data (D. Grow, 2014).

Overall, there is an ongoing debate regarding the superiority of these two COS protocols in supposed normal responders.

In the other aspect, IVF success has generally been calculated and reported on the basis of LBRs per treatment attempt involving either an intended fresh or frozen-thawed embryo transfer (FET). The continued improvement in reproductive technology has seen an increase in the number of FETs and their associated pregnancy rates. This, combined with an emphasis on reducing multiple pregnancies and increasing single embryo transfers (SETs), means that outcomes per fresh embryo transfer are no longer meaningful to patients and clinicians who want to know their chance of live birth over an entire IVF program. The most appropriate way of reporting this is to estimate the

cumulative chances of success per woman after a number of complete cycles—defined as all fresh and FET attempts resulting from one episode of ovarian stimulation. CLBRs are increasingly proving to be the currency of IVF (DJ. McL 2016).

From fertility counselling perspective, patients undergoing IVF treatments should be informed not only the opportunity of success rate in fresh cycle transfer but also the probability to achieve a live birth after utilization of all cryopreserved embryos.

The retrospective data from Peking University Third Hospital showed that the CLBR was about 50% in unselected population (unpublished data). The CLBR was about 60% with 11-15 oocytes retrieved in Chinese population from retrospective published data (Jingjuan J, 2013).

The latest published data regarding the CLBRs of these two protocols in a prospective study showed comparable results (34.1% in the GnRH-antagonist group vs 31.2% in the GnRH-agonist group) in unselected population (Toftage M., 2017). However, the CLBR in this study was just a secondary endpoint and it is much lower than the data expected in Chinese population.

In China, there is no prospective randomized study so far to compare the CLBR between GnRH-antagonist protocol and GnRH-agonist protocol in COS. Local study and data generation is in need to provide more evidence regarding to these two protocols to guide the clinicians in their daily practice and also provide valuable data for patients counselling.

4 Trial Objectives

4.1 Primary Objectives

To investigate the cumulative live birth rates in infertile women ≤ 38 years old with normal ovarian reserve using GnRH antagonist or agonist protocol for COS in ART treatment

4.2 Secondary Objectives

To investigate the safety and pregnancy outcomes of GnRH antagonist and agonist protocols

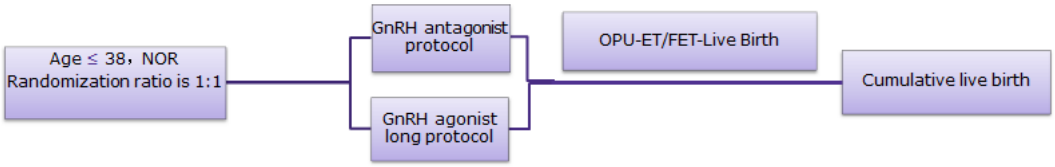
4.3 Other Objectives

To explore the relationship between the number of oocytes retrieved and number of embryos or times of embryo transfer or CLBR

5 Investigational Plan

5.1 Overall Trial Design and Plan

This is a multicenter prospective study which will observe the cumulative live birth rates (CLBRs) of gonadotrophin-releasing hormone (GnRH) antagonist protocol compared with the standard GnRH agonist long protocol for controlled ovarian stimulation in supposed normal ovarian responders in China. The recruitment period is planned to start on March, 2018 and to last for 2 years, last-subject-out is expected in December 2020.



This study is planned to involve 5 hospitals and recruit 888 female subjects. Relevant data according to study requirements will be recorded in standard case report form (eCRF). When the study initiates, each reproductive center will screen and enroll qualified subjects to enter the treatment. If a subject has entered the study and later discontinue from the treatment cycle, the reason of discontinuing the treatment should be recorded in eCRF.

Each subject will be followed up to 2 years until she has one live birth or all her embryos are used up after one initiated COS, including fresh & frozen-thawed embryo transfers. Subjects who do not obtain live birth but with embryos left for FET in the 2 years follow up will not be analyzed as drop-out cases either and the CLBR for those patients will be calculated and analyzed in appropriate statistical methods.

5.2 Discussion of Trial Design

Both GnRH agonist and GnRH antagonist protocols are widely used in controlled ovarian stimulation (COS); however, there is a persistent debate concerning the reproductive outcomes when comparing the two analogue treatments (Toftager, M 2016). In the most recent Cochrane review, the GnRH antagonist protocol was associated with comparable live birth rate (LBR) and a substantial reduction in the incidence of OHSS when compared to GnRH agonist long protocol in women undergoing ART in none selected population (Hesham G Al-I,2016).

Comparing with GnRH agonist protocol, the GnRH antagonist protocol is associated with fewer oocytes retrieved, lower OHSS incidence whereas the ongoing pregnancy rate and LBR were similar in supposed normal responders in the recent systematic review and meta-analysis (Jin-song Xiao, 2014). However, the data published in the same year found that among good-prognosis patients, agonist protocol decreased cancellation risk and increased odds of implantation and live birth compared with antagonist protocol using the national surveillance data (Grow D, 2014).

Overall, there is an ongoing debate regarding the superiority of these two COS protocols in supposed normal responders.

The retrospective data from Peking University Third Hospital showed that the CLBR was about 50% in unselected population (unpublished data). The CLBR was about 60% with 11-15 oocytes retrieved in a Chinese population from retrospective published data (Jingjuan Ji, 2013).

The latest published data regarding the CLBRs of these two protocols in a prospective study showed comparable results (34.1% in the GnRH-antagonist group vs 31.2% in the GnRH-agonist group) in unselected population (Toftager M, 2017). However, the CLBR in this study was just a secondary endpoint and it is much lower than the data expected in Chinese population.

5.2.1 Inclusion of Special Populations

Not applicable.

5.3 Selection of Trial Population

Only patients meeting all inclusion criteria and no exclusion criteria may be enrolled into the trial as subjects. Prior to performing any trial assessments which is not part of the subject's routine medical care, the investigator will ensure that the subject or the subject's legal representative has provided written informed consent following the procedure described in Section 9.2.

5.3.1 Inclusion Criteria

Eligible patients for this study should meet all of the following inclusion criteria:

1. Infertile women planning to undergo IVF/ICSI cycle using conventional GnRH agonist long protocol or GnRH antagonist protocol
2. Age ≤ 38 years old
3. Basal AFC 8~20
4. Basal FSH≤10 IU/L
5. Basal E_2<200pmol/L
6. Normal uterus and at least one side of the normal ovary
7. Informed consent form signed
8. Willing to follow the study protocol, and able to complete this study

5.3.2 Exclusion Criteria

Patients are not eligible for this trial if they fulfill any of the following exclusion criteria:

1. Previous IVF/ICSI cycles >2
2. Severe hydrosalpinx (Ultrasound shows hydrosalpinx > 2cm)
3. Severe endometriosis (Grade III – IV)
4. Polycystic ovarian syndrome (PCOS)
5. History of recurrent miscarriages (>2 times of miscarriages)
6. Plan to undergo ovarian stimulation for preimplantation genetic diagnosis or preimplantation genetic screening, oocyte donation, and social or medical freezing of oocytes
7. Any major systemic disease that as per Investigator's discretion precludes subject for participation in the study
8. With pregnancy contraindications
9. Alcoholism, drug abuse, drug addiction or patients with uncured sexually transmitted disease

10. According to the judgment of the Investigator, any medical condition or any concomitant surgery/medications that would interfere with evaluation of study medications
11. Simultaneous participation in another clinical study
12. Plan to use urinary gonadotrophin during COS treatment

5.4 Criteria for Initiation of Trial Treatment

When subjects enter this study, they will be randomized to either of the two treatment groups at ratio 1:1 by the randomization schedule generated by a computer program. Considering these two treatments have differences in both administration route and dose, this study is open-label, randomized, controlled clinical study.

5.5 Criteria for Subject Withdrawal

5.5.1 Withdrawal from Trial Therapy

A subject must be withdrawn from trial therapy if any of the following occur:

- Subject withdrew consent
- Subject lost to follow up
- Participation in another clinical trial
- Any events that unacceptably endanger the safety of the subject.

5.5.2 Withdrawal from the Trial

Subjects may withdraw from the trial at any time without giving a reason. Withdrawal of consent will be considered withdrawal from the trial.

A subject must be withdrawn if any of the following occur during the trial

- Subject withdrew consent
- Participation in another clinical trial

5.6 Premature Termination of the Trial

At any time of the study, due to adverse events, investigators determine risks outweigh the benefits. The Sponsor may discontinue the trial if it becomes unjustifiable for medical or ethical reasons, for poor enrollment, or because of comparator from the market for safety reasons. Patients need to receive treatment of forbidden combined medications.

Health Authorities and Independent Ethics Committees (IECs) will be informed about the discontinuation of the trial in accordance with applicable regulations.

5.7 Definition of End of Trial

Subjects who meet primary endpoints or complete 2 years follow-up can complete the study. Primary endpoint is cumulative live birth rates with first live birth resulting from one initiated COS cycle.

A clinical trial may not be considered closed as long as:

- Visits specified by the protocol are still taking place,
- Procedures or interventions according to the protocol are still being undertaken in any subject,
- The post-treatment follow up period, defined in the clinical trial protocol as being part of the trial, has not yet been completed for any subject.

6 Investigational Medicinal Product and Other Drugs Used in the Trial

6.1 Description of the Investigational Medicinal Product

This trail aims to compare GnRH antagonist or agonist **protocols** (described in section 6.2) for COS in ART treatment, not focusing on compare the efficacy and safety for **drugs** used in these two protocols. Drugs used in this study are introduced as followed.

NOTE: All the following introductions are excerpted from the full prescribing information. Dose adjustments can be performed depends on the clinical practice and the special details of each patient.

Cetrorelix acetate for injection (Cetrotide®) is a gonadotropin-releasing hormone (GnRH) antagonist used to prevent premature ovulation in controlled ovarian stimulation prior to assisted reproductive technologies (ART). Treatment with Cetrotide® should be carried out by a doctor who has experience in this type of fertility treatment. Cetrotide® is given by injection under the skin of the lower abdomen (belly). The recommended dose is 0.25 mg given every 24 hours, either in the morning or in the evening. Treatment starts on day 5 or 6 of ovarian stimulation, and is continued throughout the ovarian stimulation period, until the evening before or the morning of the day when the induction of ovulation (the release of eggs) is planned. Because of the risk of severe allergic reactions, the first injection should be supervised by a doctor, and the patient closely watched for 30 minutes. Further injections may be given by the patient herself, as long as she is made aware of the signs of allergic reaction and what to do if they appear. The medicine should be injected slowly at different places on the abdomen every day.

Triptorelin embonate (Diphereline® or Decapeptyl®) belongs to a group of medicines called Gonadotrophin Releasing Hormone analogues (GnRHa), often be used in ART in combination with gonadotrophins for COS in vitro fertilization and embryo transfer (IVF-ET). GnRH-a should be administered for about 14 to 20 days for down-regulation.

Follitropin alfa (Gonal-f®): As a r-FSH agent, Gonal-f® is used for COS. It is a prefilled ready to use pen device containing follitropin alfa for injection and is designed for subcutaneous self-

administration by patients undergoing COS for ART. It is available as dose presentations of 300 IU and 450 IU. The investigators and/or his/her delegate/s will explain the use of new Gonal-f® prefilled pen, the dose and route of administration (subcutaneous) to the patients to administer the injections at home. Trainings will be provided to study nurses about how to use Gonal-f® new pen. Study nurse in turn will provide training to patients on how to self-inject the new Gonal-f® pen subcutaneously. The 75IU Gonal-f® can also be used as required. If in the course of treatment, in the clinical judgment of the investigator, once the patient meets the criteria of suboptimal ovarian response, the patient needs to receive luteinizing hormone (LH) supplementation, this is permitted as long as no urinary products are used as stated in the exclusion criteria. The daily dose of LH data will be captured in the eCRF.

Lutropin alfa (Luveris®) is a luteinizing hormone (recombinant human LH) for the treatment of female infertility. The physicochemical, immunological, and biological activities of Luveris® are comparable to those of human pituitary LH. In the ovaries, during the follicular phase, LH stimulates theca cells to secrete androgens, which will be used as the substrate by granulosa cell aromatase enzyme to produce estradiol, supporting Follicle-Stimulating Hormone (FSH)-induced follicular development. Luveris® is administered concomitantly with Gonal-f® (follitropin alfa for injection) to stimulate development of a potentially competent follicle and to indirectly prepare the reproductive tract for implantation and pregnancy.

6.2 Dosage and Administration

GnRH-a group: GnRH-a types, GnRH-a and FSH doses will be adjusted according to the clinical experiences of investigators in each site. GnRH-a（Diphereline® or Decapetyl®）0.1mg administered for about 14 to 20 days for down-regulation is recommended if applicable. Gonal-f® will be administrated as routinely practiced by investigators.(Daily dose should follow China PI)

GnRH-ant group: The GnRH-ant (Cetrotide®) will be initiated in a fixed protocol on stimulation days 5 or 6 per the investigator's ART protocol. Recombinant FSH (Gonal-f®) will be administrated as routinely practiced by investigators. FSH doses will be adjusted according to the clinical experiences of investigators.

LH supplementation: If there is slow/suboptimal response in follicular development observed by investigators, the rLH (Luveris®) will be administrated as required. LH supplementation is based on one of the following criteria:

- Having no follicle >10 mm by day 6;
- Low estradiol concentration <200 pg/ml or <732 pmol/L by day 6;
- Poor progression or slowing of follicle growth, i.e., previously 1–2 mm progression/day slowing to less than 2 mm in 3 days.

6.3 Assignment to Treatment Groups

An Interactive Web Response System will be used in this study for the randomization procedure. Subjects will be randomized and assigned to GnRH-a group or GnRH-ant group. Statistical aspects of randomization, including stratification, will be described in Section 8.2.

6.4 Non-investigational Medicinal Products to be Used

Not applicable

6.5 Concomitant Medications and Therapies

Concomitant medications related with COS taken by the subject during the trial, from the date of signature of informed consent are to be recorded in the appropriate section of the eCRF, noting the name, dose, duration and indication of each drug. Nondrug interventions and any changes to a concomitant medication or other intervention related with COS should also be recorded in the eCRF.

6.5.1 Permitted Medicines

Any medications that are considered necessary to protect subject welfare and will not interfere with the trial medication may be given at investigator's discretion.

6.5.2 Prohibited Medicines

Drugs will interfere with the trial medication and other ART treatment drugs (for example uFSH, hMG, etc.).

6.5.3 Other Interventions

Not applicable

6.5.4 Special Precautions

Cetrotide®, Diphereline®, Decapetyl®and Gonal-f® are all prescribed by the physicians and bought by patients themselves.

Luveris® will be provided for free once patients meet at least one of following criteria

- Having no follicle >10 mm by day 6;
- Low estradiol concentration <200 pg/ml or <732 pmol/L by day 6;
- Poor progression or slowing of follicle growth, i.e., previously 1–2 mm progression/day slowing to less than 2 mm in 3 days.

6.5.5 Management of Specific Adverse Events or Adverse Drug Reactions

Not applicable

6.6 Packaging and Labeling of the Investigational Medicinal Product

All IMPs will be packaged and labeled in commercial packaging.

6.7 Preparation, Handling, and Storage of the Investigational Medicinal Product

Drug preparation

Investigational drug:

All investigational drugs are prescribed for subjects in clinic by investigators. The study site does not provide Cetrotide®, Diphereline®, Decapetyl®and Gonal-f® for free, but in some specific situation Luveris® will be provided for free, which was listed in section 6.5.4.

Drug storage

Drugs will be stored in clinical study sites. Drugs are prescribed by investigators and subjects get them in the pharmacy, see Section 6.5.4.

6.8 Investigational Medicinal Product Accountability

All drugs involved in the study are prescribed to subjects by investigators and subjects go to the pharmacy of clinic and buy drugs according to the prescription.

6.9 Assessment of Investigational Medicinal Product Compliance

Investigators check investigational drug usage of subjects regularly and record it in original medical record.

6.10 Blinding

Not applicable.

6.11 Emergency Unblinding

Not applicable.

6.12 Treatment of Overdose

An overdose is defined as any dose greater than the highest daily dose included in a clinical trial protocol or planned for an individual subject enrolled in the trial, even if it does not meet other criteria for an SAE. If investigational drug is overdose, the subject will be judged by investigators and determined whether to continue in the study or not. And usage, dose and date of overdose will be recorded in original medical record. Any overdose must be recorded in the trial medication section of the eCRF and reported to Drug Safety in an expedited manner using the SAE Report Form, and following the procedure in Section 7.4.

6.13 Medical Care of Subjects after End of Trial

Conduct according to clinical practice.

7 Trial Procedures and Assessments

7.1 Schedule of Assessments

All subjects' data will be collected in anonymity. The subjects are assigned to the two treatment groups at the ratio 1:1 using blocked randomization method according to a randomization schedule generated by the statistician using a computer program. Each subject will have a unique subject number assigned to her and this will be referenced throughout the study as the subject's identifier. The Investigator should keep a separate code identification list with subjects' information to be retained at the site.

After randomization, the subjects will receive either GnRH-a long protocol or GnRH- ant protocol for COS in supposed normal ovarian responders.

The data collection time points for two protocols are as follows:

Screening/Baseline

Gonadotrophin (Gn) Initiation

Triggering Day

Oocytes Pick up

Embryo Transfer

HCG test: Serum β-hCG test after 11 to 17 days of ET

Clinical Pregnancy Assessment: Ultrasound examination after 4 to 6 weeks of ET

Ongoing Pregnancy Assessment (fresh cycle)

Live Birth Assessment

FET cycles

Follow up Visit

In each frozen embryo transfer (FET) cycle, the data regarding hCG results, clinical pregnancy and live birth will be assessed and collected.

7.2 Visit procedure

All subjects who don't withdraw from this study, will be followed up for 2 years.

7.2.1 Screening/Baseline

At the initial study visit, the subject will be informed of the study objectives and overall requirements, and written informed consent will be obtained prior to any study specific assessments. The subject will then undergo a brief clinical evaluation to ensure compliance with the inclusion and exclusion criteria to determine the eligibility (see Section 5.2).

Data for all subjects will come from the subjects' Screening or Baseline Visits and the subjects' medical records:

The following must be completed before Gn Initiation:

- Visit date
- Subject Name and hospital subject number will be recorded and kept confidentially in the clinic solely for the purposes of generating a unique study subject number which will be used to anonymously identify each subject in the study.
- Demographic details including age, gender, date of birth and ethnic origin
- Weight and height
- Clinical and gynecological examination
- Gynecological history: duration of infertility, menstrual cycle, History of miscarriages, history of pelvic surgery; history of ovarian surgery.
- Medical history and concomitant illness
- Any concomitant medication taken by the subject when entering the study
- Concomitant medications prescribed and reasons
- Ability to conceive and times of IVF attempts
- In vitro fertilization-embryo transfer and ICSI indications assessment
- The following data should be collected (data within 3 months before Screening is accepted)
    - FSH and estrogen (E2) levels during the early follicular phase (Cycle Day 2 to 4)
    - AFC (follicles $\geq$ 2 mm and < 11 mm) assessed in the early follicular phase (Cycle Day 2 to 4)

After randomization, blood samples for AMH test should be collected in each site, and the analysis will be performed in central lab. The analysis result of AMH test will be used in final statistical analysis, not for guiding the clinical medication.

7.2.2 Gn Initiation

After randomization, the subjects will receive either long GnRH-a protocol or GnRH- ant protocol for COS in supposed normal ovarian responders, the procedures are described as follows:

1: GnRH agonist long protocol

GnRH-a will be administered for about 14 to 20 days until down-regulation is satisfied as judged by Investigator. Satisfied down regulation criteria can be defined as: LH ≤ 5 IU, E2 ≤ 50 pg/ml, and endometrium thickness ≤ 6mm. r-FSH (Gonal-f®) will be initiated and regimen will be as routinely practiced by Investigators and according to licensed summary of product characteristics (China) label.

The following data will be collected:

- Date of initiation of GnRH-a
- Initial Dose of GnRH-a
- Details of dose adjustments of GnRH-a if any
- LH and E2 levels before Gonal-f® initiation
- Date of initiation of Gonal-f®
- Initial dose of Gonal-f®
- Recording of AEs
- Concomitant medications prescribed and reasons.

2: GnRH antagonist protocol

r-FSH (Gonal-f®) will be initiated and regimen will be as routinely practiced by Investigators and according to licensed SmPC label.

The following data will be collected:

- LH and E2 levels before Gonal-f® initiation (if measured)
- Date of initiation of Gonal-f®
- Initial dose of Gonal-f®
- Recording of AEs
- Concomitant medications prescribed and reasons.
-

7.2.3 Triggering Day

1: GnRH agonist long protocol

Follicular development will be monitored according to the Investigator site's ART practice until the criteria to administer r-hCG (Ovidrel®) are met to induce final oocyte maturation. r-hCG administration is to be performed according to the site's routine clinical practice.

The following data will be collected:

- No. and sizes of follicles, E2 level and LH level on the day of hCG administration
- Details of dose adjustments of GnRH-a if any
- Treatment days of GnRH-a
- Details of dose adjustments of Gonal-f® new pen/ powder injection (75IU) (Sequence and timing of dose adjustment)
- Daily dose and total dose of Gonal-f®
- Total number of Gonal-f® stimulation treatment days
- Date and dose of hCG administrated / other methods performed.

  or
- Reason for not administering hCG / take other action such as no optical follicle development, elevated levels of E2 or Progesterone or subject's decision etc.
- If r-LH supplementation is required, as per clinical judgment of the Investigator, indicate the initial dose and date of initiation
- Dose adjustment of r-LH and total dose
- Total number of r-LH treatment days
- Recording of AEs
- Concomitant medications prescribed and reasons.

2: GnRH antagonist protocol

The GnRH-ant will be initiated in a fixed protocol on stimulation days 5 to 6 as per the Investigator site's ART protocol. Follicular development will be monitored according to the Investigator site's ART practice until the criteria to administer hCG are met to induce final oocyte maturation. hCG administration is to be performed according to the site's routine clinical practice.

The following data will be collected:

- No. and sizes of follicles, E2 level and LH level on the day of hCG/GnRH-a administration
- LH and E2 levels prior to GnRH-ant administration and on the day of GnRH-ant initiation if measured
- Date of initiation of GnRH-ant
- Initial Dose of GnRH-ant
- Total dose of GnRH-ant
- Total treatment days of GnRH-ant
- Dose adjustment of GnRH-ant
- Details of dose adjustments of Gonal-f® new pen/ powder injection (75 IU) (Sequence and timing of dose adjustment)
- Daily dose and total dose of Gonal-f®

- Total number of Gonal-f® stimulation treatment days
- Date and dose of hCG administrated

  or

- Reason for not administering hCG such as no optical follicle development, elevated levels of E2 or Progesterone or subject's decision etc.
- If r-LH supplementation is required, as per clinical judgment of the Investigator, indicate the initial dose and date of initiation
- Dose adjustment of r-LH and total dose
- Total number of r-LH treatment days
- Recording of AEs
- Concomitant medications prescribed and reasons

7.2.4 Oocytes pick up

The cycle will be canceled if there is no oocyte gained in this visit or the oocytes pick up procedure is not performed, the patient will withdraw from this study and all procedures related to End of Study Visit should be performed..

Oocyte pick up will be performed according to the site's routine practice.

The following data will be collected:

- Date of oocyte pick up
- No. of oocytes retrieved
- No. of metaphase II (MII) oocytes retrieved
- Recording of AEs
- Concomitant medications prescribed and reasons.

7.2.5 Embryo Transfer in fresh cycle

IVF/ICSI, ET and luteal phase support will be performed according to the site's routine practice. Luteal phase support will be started after oocytes retrieval.

The following data will be collected:

- Date of oocyte insemination
- Number of oocytes inseminated
- Endometrial assessment
- Embryo quality
- Methods of insemination
- Number of oocytes fertilized

- Total number of good quality embryos
- Total number of embryos
- Date of embryo transfer
- No. of embryos transferred
- No. of embryos cryopreserved
- Recording of AEs
- Concomitant medications prescribed and reasons.

If the procedure of insemination is not conducted due to any reason, reasons should be specified and all procedures related to End of Study Visit should be performed.

If the procedure of ET in fresh cycle is not conducted and there are no embryos preserved for frozen embryo transfer (FET), reasons should be specified and all procedures related to End of Study Visit should be performed.

If the procedure of ET in fresh cycle is not conducted but there are embryos preserved for FET, further FET visit should be performed.

7.2.6 FET Visit

- The time of FET visits will be determined by the status of embryo transfer and pregnancy outcomes.
- FET-1 Visit: ET(endometrial preparation, number of embryos transferred, embryo quality,etc), hCG results, clinical pregnancy results and live birth results
- FET-2 Visit: ET(endometrial preparation, number of embryos transferred, embryo quality,etc), hCG results, clinical pregnancy results and live birth results
- FET-n Visit: ET(endometrial preparation, number of embryos transferred, embryo quality,etc), hCG results, clinical pregnancy results and live birth results
- Note: The data recorded in the medical records and prescription records during subject's visit will be transcribed onto eCRF by the Investigator or suitably qualified authorized designee.
- If the procedure of FET is not conducted due to any reason, reasons should be specified and all procedures related to End of Study Visit should be performed.
- Prior to performing any trial assessments that are not part of routine medical care for the subject, the Investigator will obtain written informed consent as described in Section 9.2.

7.2.7 HCG Test

Subjects treated by ART are routinely monitored for early detection of pregnancy by measuring serum β-hCG concentration on a specific day, according to site's routine clinical practice.

After about 11 to 17 days of ET, early detection of pregnancy will be done by β-hCG blood test and the results will be recorded.

The following data will be collected:

- Date of pregnancy assessment
- Test results (positive or negative)
- Recording of AEs
- Concomitant medications prescribed and reasons.

For negative result of pregnancy and without embryos for FET, all procedures related to End of Study Visit will be performed.
For negative result of pregnancy but with embryos for FET, further FET visit will be performed.

7.2.8 Clinical pregnancy assessment

A positive test of pregnancy will be confirmed by clinical pregnancy assessment (ultrasound examination) 4 to 6 weeks after ET.

The following data will be collected:

- Date of pregnancy assessment
- Pregnancy status
- Positive pregnancy status has to be confirmed by ultrasound examination (presence or non-presence of gestational sac(s), gestational sacs with or without heartbeat, gestational stage at which ultrasound is performed is to be recorded and ectopic pregnancy).
- Gestational age
- Singleton pregnancy / multiple pregnancy
- Recording of AEs
- Concomitant medications prescribed and reasons.

If the negative of clinical pregnancy is confirmed, and without embryos for FET, all procedures related to End of Study Visit will be performed.

If the negative of clinical pregnancy is confirmed, but with embryos for FET, further FET visit will be performed.

7.2.9 Ongoing Pregnancy assessment (by telephone)

Ongoing pregnancy is defined as intrauterine pregnancy continued for 12 gestational weeks.

The following data will be collected:

- Singleton pregnancy / multiple pregnancy
- Status of ongoing pregnancy
- Early Miscarriage
- Recording of AEs
- Concomitant medications prescribed and reasons.

If the negative of ongoing pregnancy is confirmed, and without embryos for FET, all procedures related to End of Study Visit will be performed.

If the negative of ongoing pregnancy is confirmed, but with embryos for FET, further FET visit will be performed.

Once the negative of ongoing pregnancy is related to abortion, the reason of abortion should be recorded.

7.2.10 Live Birth assessment (by telephone)

The following data will be collected:

- Date of live birth
- No. of live birth(Singleton pregnancy / Multiple pregnancy)
- Type of live birth(Caesarean delivery/ Spontaneous vaginal delivery)
- Any abnormal pregnancy outcome (e.g. spontaneous abortion, congenital anomalies).
- Recording of AEs
- Concomitant medications prescribed and reasons.

If the negative of live birth is confirmed, and without embryos for FET, all procedures related to End of Study Visit will be performed.

If the negative of live birth is confirmed, but with embryos for FET, the data regarding to further FET visit should be collected.

If the negative of live birth is related to abortion, the reason of abortion should be recorded,

7.2.11 End of Study visit (by telephone)

The observation period will be completed when:

- The subject achieve a live birth in live birth visit (in either the fresh ET or the FET)
- IVF/ICSI treatment is terminated (cycle cancellation) due to:
  - Incidence of OHSS
  - Risk of OHSS
  - Lack of ovarian response to stimulation treatment
  - No oocytes retrieved
  - No fertilization
  - Other, to be specified (e.g. Investigator's or subject's decision)
- Subjects who complete 2 years follow up.
- No embryos for further FET
- Subject is lost to follow up
- AE / serious adverse event (SAE)
- There is an occurrence of an exclusion criterion
- Subject withdraws consent.

The date and reason of observation completion will be collected.

7.2.12 2 years follow up Visit (by telephone)

All subjects who don't withdraw from this study, will be followed up telephonically at the end of 2 years to check their pregnancy status and outcome.

- Date of Visit
- Fresh embryo transfer from the COS in this study(yes/no)
- FET from the COS in this study(yes/no)
- Total times of embryo transfer from the COS in this study
- Pregnancy status (yes/no), if yes
  - Gestational age
  - Singleton pregnancy / Multiple pregnancy
  - Due date
- Live birth (yes/no), if yes
  - Date of live birth
  - No. of live birth(Singleton pregnancy / Multiple pregnancy)
  - Type of live birth(Caesarean delivery/ Spontaneous vaginal delivery)
- Embryos for further FET(yes/no)

Only the Pregnancy status and live birth resulted from the COS in this study will be recorded.

7.3 Efficacy Assessments

7.3.1 Primary Endpoint

- CLBR with first live birth resulting from one initiated COS cycle

Definition of CLBR:

- Numerator is the No. of women got their first live birth; the Denominator is the No. of women who attempt the ovarian stimulation.
- There will be two ways to calculate the CLBR:
    - The conservative estimate of the cumulative live birth rate, which is based on the assumption that none of the women who do not return for a subsequent embryo transfer would have had a live birth.
    - The optimal estimate of the cumulative live birth rate, which is based on the assumption that women who do not return for a subsequent embryo transfer would have had the same live birth rates as those who do return.

7.3.2 Secondary endpoints

COS and Pregnant outcomes, including:

- Number of oocytes retrieved
- Good-quality embryo rate(The Istanbul Consensus1)
- hCG positive rate
- Implantation rate
- Clinical pregnancy rate
- Ongoing pregnancy rate
- Live birth rate
- Cumulative clinical pregnancy rate
- Miscarriage rate
- Ectopic pregnancy rate
- Cycle cancelled rate and reason
- Rate and severity of OHSS
- Time to pregnancy
- Time to live birth

7.3.3 Exploratory Endpoint

- To explore the relationship between the number of oocytes retrieved and number of embryos or times of embryo transfer or CLBR.

7.4 Assessment of Safety

Safety reporting will be conducted according to local pharmacovigilance practices.

The safety profile of the IMP will be assessed through the recording, reporting and analysis of baseline medical conditions, adverse events (AEs), physical examination findings including vital signs and laboratory tests.

Comprehensive assessment of any apparent toxicity experienced by each subject will be performed from the time of giving informed consent and throughout the trial. The investigator will report any AEs, whether observed by the Investigator or reported by the subject (see Section 7.4.1.2). The reporting period for AEs is described in Section 7.4.1.3.

7.4.1 Adverse Events

7.4.1.1 Adverse Event Definitions

Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, regardless of causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

The Investigator is required to grade the severity or toxicity of each AE.

Qualitative Severity (or Toxicity) Scale:

Investigators must assess the severity of AEs according to the Qualitative Toxicity Scale, as follows:

Mild: The subject is aware of the event or symptom, but the event or symptom is easily tolerated.

Moderate: The subject experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.

Severe: Significant impairment of functioning: the subject is unable to carry out his or her usual activities.

Investigators must also systematically assess the causal relationship of AEs to IMP(s)/study treatment (including any other non-IMPs, radiation therapy, etc.) using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the <IMP/study treatment>

include, but may not be limited to, temporal relationship between the AE and the < IMP/study treatment>, known side effects of <IMP/study treatment>, medical history, concomitant medication, course of the underlying disease, trial procedures.

Unrelated: Not reasonably related to the IMP/study treatment. AE could not medically (pharmacologically/clinically) be attributed to the IMP/study treatment under study in this clinical trial protocol. A reasonable alternative explanation must be available.

Related: Reasonably related to the IMP/study treatment. AE could medically (pharmacologically/clinically) be attributed to the IMP/study treatment under study in this clinical trial protocol.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (for example, on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (for example, anemia, increased ALT) must be reported as the AE rather than the abnormal value itself.

Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening. (Note: The term "life-threatening" refers to an event in which the subject is at risk of death at the time of the event, not an event that hypothetically might have caused death if it was more severe.)
- Requires inpatient hospitalization or prolongs an existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is otherwise considered to be medically important. (Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasia or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)

For the purposes of reporting, any suspected transmission of an infectious agent via an IMP is also considered an SAE, as described in Section 7.4.1.4

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify trial treatment or trial procedures are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (for example, undesirable effects of any administered treatment) must be documented and reported as SAEs.

Events Not to Be Considered as AEs/SAEs

Medical conditions present at the initial trial visit that do not worsen in severity or frequency during the trial are defined as Baseline Medical Conditions, and are not to be considered AEs.

7.4.1.2 Methods of Recording and Assessing Adverse Events

At each trial visit, the subject will be queried on changes in her condition. During the reporting period, any unfavorable changes in the subject's condition will be recorded as AEs, whether reported by the subject or observed by the investigator.

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the eCRF. All SAEs must be additionally documented and reported using the appropriate Report Form as described in Section 7.4.1.4.

Specific guidance can be found in the eCRF Completion and Monitoring Conventions provided by the Sponsor.

7.4.1.3 Definition of the Adverse Event Reporting Period

The AE reporting period for safety surveillance begins when the subject is initially included in the trial (date of first signature of informed consent/date of first signature of first informed consent) and continues until the end of trial visit.

Any SAE assessed as related to IMP must be reported whenever it occurs, irrespective of the time elapsed since the last administration of IMP

7.4.1.4 Procedure for Reporting Serious Adverse Events, Adverse Events of Special Interest and Dose Limiting Toxicities

Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum of 24 HOURS after becoming aware of the event) inform the Sponsor or its designee in writing. All written reports should be transmitted using the SAE Report Form, which must be completed by the Investigator following specific completion instructions.

In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone; in these cases, a written report must be sent immediately thereafter by fax or e-mail. Names,

addresses, and telephone and fax numbers for SAE reporting will be included in the trial-specific SAE Report Form.

Relevant pages from the eCRF may be provided in parallel (for example, medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (for example, laboratory results, hospital report, and autopsy report). In all cases, the information provided on the SAE Report Form must be consistent with the data about the event recorded in the eCRF.

The Investigator must respond to any request for follow-up information (for example, additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor/designee may have on the AE within the same timelines as those noted above for initial reports. This is necessary to ensure prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

7.4.1.5 Safety Reporting to Health Authorities, Independent Ethics Committees/ Institutional Review Boards and Investigators

The Sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) involving trial subjects to the IEC/IRB that approved the trial.

In accordance with ICH GCP and local GCP, the Sponsor/designee will inform the Investigator of "findings that could adversely affect the safety of subjects, impact the conduct of the trial or alter the IEC's/IRB's approval/favorable opinion to continue the trial." In particular and in line with respective regulations, the Sponsor/designee will inform the Investigator of AEs that are both serious and unexpected and are considered to be related to the administered product ("suspected unexpected serious adverse reactions" or SUSARs). The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations with regard to Safety Report notifications to Investigators will be taken into account.

When specifically required by regulations and guidelines, the Sponsor/designee will provide appropriate Safety Reports directly to the concerned lead IEC and will maintain records of these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC of any Safety Reports provided by the Sponsor/designee and of filing copies of all related correspondence in the Investigator Site File.

The Sponsor's responsibilities regarding the reporting of SAEs/SUSARs/Safety Issues will be carried out in accordance with that Directive and with the related Detailed Guidance documents.

7.4.1.6 Monitoring of Subjects with Adverse Events

AEs are recorded and assessed continuously throughout the trial (see Section 7.4.1.3) and are assessed for final outcome at the end of trial visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up". Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

7.4.2 Pregnancy and In Utero Drug Exposure

Not applicable

7.4.3 Clinical Laboratory Assessments

Anti-Mullerian hormone(AMH) analysis will be performed in central lab.

Other lab data such as hematology, biochemistry and urinalysis laboratory in each site will be used and normal ranges of laboratory examinations will be provided by each site.

7.4.4 Vital Signs, Physical Examinations, and Other safety Assessments

Routine clinical examination will be performed.

7.5 Pharmacokinetics

Not applicable

7.6 Biomarkers

Anti-Mullerian hormone (AMH)

The result of AMH test will be used in final statistical analysis.

7.7 Other Assessments

Not applicable

8 Statistics

8.1 Sample Size

For this non-inferiority trial, a sufficient number of subjects will be enrolled to have at least 80% power to demonstrate the non-inferiority of GnRH antagonist protocol vs GnRH agonist protocol regarding the CLBR using a two-sided 95% confidence interval. The CLBR is expected to be 60% in both groups, and the non-inferiority margin is -10% (absolute). Based on these assumptions, a

sample size of 377 evaluable subjects per arm would provide 80% power to demonstrate the non-inferiority of GnRH antagonist protocol vs GnRH agonist protocol regarding the CLBR. As a result, totally about 888 subjects will be randomized, that is 444 for each treatment group after considering 15% dropout rate.

8.2 Randomization

Subjects will be randomized at a 1:1 ratio to GnRH-a group and GnRH-ant group.

The trial is designed as a multicenter trial, and randomization will be conducted by using the IWRS.

Randomization numbers will be computer generated by a statistician at FMD. Sites will log into EDC system to have randomization numbers assigned according to the sequence of screening. A unique randomization number will be allocated to the subject together with the assignment of the group.

8.3 Endpoints

8.3.1 Primary Endpoints

- CLBR with first live birth resulting from one initiated COS cycle

8.3.2 Secondary Endpoints

COS and pregnant outcomes, including:

- Number of oocytes retrieved
- Good-quality embryo rate(The Istanbul Consensus1)
- hCG positive rate (in fresh cycle)
- Implantation rate (in fresh cycle)
- Clinical pregnancy rate (in fresh cycle)
- Ongoing pregnancy rate(in fresh cycle)
- Live birth rate(in fresh cycle)
- Cumulative clinical pregnancy rate
- Miscarriage rate(in fresh cycle)
- Ectopic pregnancy rate(in fresh cycle)
- Cycle cancelled rate and reason(in fresh cycle)
- Rate and severity of OHSS(in fresh cycle)
- Time to pregnancy
- Time to live birth

8.3.3 Other Endpoints

To explore the relationship between the number of oocytes retrieved and number of embryos or times of embryo transfer or CLBR

8.4 Analysis Sets

Three analysis sets will be used: the Per Protocol population (PP population), Intention-To-Treat (ITT) population, and the Safety population.

The primary immunogenicity analyses will be performed on the PP population, and will be confirmed on the ITT. In ITT, subjects will be analyzed by the treatment group to which they were randomized.

Intention-to-treat (ITT) Population

An Intention-to-Treat Population (ITT) analysis will be performed including all subjects who receive at least one injection of randomized treatment IMP.

Safety Population

The safety population will include all subjects who have received at least one dose of IMP.

Per Protocol (PP) population

The PP population includes all subjects who have been treated according to the Clinical Trial

Protocol and fulfill the following criteria:

- Compliance with all entry criteria.
- Absence of major Clinical Trial Protocol violations with respect to factors likely to affect the efficacy of treatment.
- Adequate compliance with trial medication.

The PP population will consist of all subjects who do not have a major protocol deviation. The PP population is the primary analysis population. A supportive analysis will be performed using the ITT population only if the PP population is < 90% of the ITT population.

8.5 Description of Statistical Analyses

8.5.1 General Considerations

Descriptive Statistics

For continuous parameters, the following statistics will be presented: Number (N) of subjects, mean, standard deviation (SD), median, first quartile (q1), third quartile (q3), minimum, and

maximum. Number of subjects with missing values ('Missing') will be added for the analyses based on observed case data. An overall column will also be added, where appropriate.

For categorical parameters, the total number ('N') of subjects and percentages will be presented. Number of subjects with missing values ('Missing') will be added for analyses based on observed case data. An overall column will also be added, where appropriate.

Method of handling missing data

Normally, missing data will not be imputed. If the subject does not have the required evidence for ovulation, follicular development, or pregnancy then the subject will be counted as a failure for the particular endpoint.

Should a specific endpoint need another method of handling missing data, this will be specified in the Statistical Analysis Plan.

8.5.2 Analysis of Primary Endpoints

The result of the analysis of the primary endpoint (CLBR) is essential for the non-inferiority claim. The conservative CLBR will be used to test the hypothesis in a confirmatory way.

Definition of the primary endpoint: CLBR with first live birth resulting from one initiated COS cycle.

Numerator is the No. of women got their first live birth, the Denominator is the No. of women who attempt the ovarian stimulation.

There will be two ways to calculate the CLBR:

- The conservative estimate of the cumulative live birth rate, which is based on the assumption that none of the women who do not return for a subsequent embryo transfer would have had a live birth.

- The optimal estimate of the cumulative live birth rate, which is based on the assumption that women who do not return for a subsequent embryo transfer would have had the same live birth rates as those who do return.

Conservative CLBR with the corresponding 95% confidence interval (CL) will be based on binominal distribution. The two treatments will be compared by using Chi-square test for conservative CLBR. The difference between the two treatments and its associated 95% CI based on asymptotic normal distribution will be presented. If the lower-limit of the 95% confidence interval is greater than the non-inferiority limit (-10%), the null hypothesis will be rejected and it would be claimed that GnRH antagonist protocol is non-inferior to GnRH agonist protocol regarding to the cumulative live birth rate.

Optimal CLBR will be analyzed by using Kaplan-Meier product-limit method, the rate and its 95% CI will be provided. For optimal CLBR, the two treatments will be compared using Kaplan-Meier

product-limit estimates, the difference between the two treatments and its associated 95% CI will be also presented.

Number of oocytes retrieved will be summarized and compared basing on analysis of variance (ANOVA) including treatment and center as factors. The treatment difference and the two-sided 95% confidence interval will be reported.

Furthermore, univariate/multivariate logistic or cox regression analysis will be performed to evaluate the dependence of Age (≤35 or >35 years), AFC, AMH, number of oocytes retrieved, number of usable embryos, times of embryo transfer, and BMI in relation to pregnancy rate or CLBR.

8.5.3 Analysis of Secondary Endpoints

Definition of some important secondary endpoints:

Clinical pregnancy: a pregnancy diagnosed by ultra-sonographic visualization of one or more gestational sacs or definitive clinical signs of pregnancy. It includes ectopic pregnancy. Note: Multiple gestational sacs are counted as one clinical pregnancy.

Clinical pregnancy rate: the number of clinical pregnancies expressed per 100 initiated cycles, aspiration cycles, or embryo transfer cycles. Note: When clinical pregnancy rates are given, the denominator (initiated, aspirated, or embryo transfer cycles) must be specified.

Cumulative clinical pregnancy rate: Numerator is the No. of women got their first clinical pregnancy, the Denominator is the No. of women who attempt the ovarian stimulation.

Live birth rate: Numerator is the No. of women got live birth resulting from fresh cycle (multiple births considered as one live birth), the Denominator is the No. of women who attempt the ovarian stimulation.

Implantation rate: the number of gestational sacs observed divided by the number of embryos transferred.

Ongoing pregnancy: intrauterine pregnancy continued for 12 gestational weeks (detection of presence of gestational sac with fetal heartbeat by transvaginal ultrasound examination in week 12).

Time to pregnancy: time from Gn Initiation to the first clinical pregnancy.

Time to live birth: time from Gn Initiation to the first live birth.

Cancelled cycle: an ART cycle in which ovarian stimulation or monitoring has been carried out with the intention to treat, but which did not proceed to follicular aspiration or, in the case of a thawed embryo, to embryo transfer.

Miscarriage, also known as spontaneous abortion and pregnancy loss, is the natural death of an embryo or fetus before it is able to survive independently

The analysis of the secondary endpoints are intended to provide additional characterization of the treatment effect.

Number, time, percentages and related CIs will also be reported for the following secondary endpoints:

- Number of oocytes retrieved
- Good-quality embryo rate(The Istanbul Consensus1)
- hCG positive rate (in fresh cycle)
- Implantation rate (in fresh cycle)
- Clinical pregnancy rate (in fresh cycle)
- Ongoing pregnancy rate(in fresh cycle)
- Live birth rate(in fresh cycle)
- Cumulative clinical pregnancy rate
- Miscarriage rate(in fresh cycle)
- Ectopic pregnancy rate(in fresh cycle)
- Cycle cancelled rate and reason(in fresh cycle)
- Rate and severity of OHSS(in fresh cycle)
- Time to pregnancy
- Time to live birth

8.5.4 Analysis of Safety and Other Endpoints

Safety Analyses will be performed using the Safety population.

Data on AEs will be collected at scheduled and unscheduled visits, based on information spontaneously provided by the subject and/or through questioning of the subject. The Medical Dictionary for Regulatory Activities (MedDRA) and the World Health Organization Drug Dictionary (WHODRUG) coding dictionaries will be used for AEs, medical conditions, and previous and concomitant medications. Count and percentage of AEs and SAEs will be presented according to System Organ Class and preferred term of the MedDRA dictionary. Shift tables will be presented for hematology, biochemistry and urinalysis laboratory parameters.

8.6 Interim and Additional Planned Analyses

Not applicable.

9 Ethical and Regulatory Aspects

9.1 Responsibilities of the Investigator

The Investigator is responsible for the conduct of the trial at the site and will ensure that the trial is performed in accordance with this protocol, the ethical principles outlined in the Declaration of Helsinki, GCP, and Chinese relevant regulations requirements. The Investigator must ensure that only subjects who have given informed consent (ICF) are included in the trial.

9.2 Subject Information and Informed Consent

An unconditional prerequisite for each subject prior to participation in the trial is written informed consent, which must be given before any trial-related activities are carried out. Adequate information must therefore be given to the subject by the Investigator or an appropriate designee (if local regulations permit) before informed consent is obtained.

A subject information sheet must be prepared in the local language in accordance with ICH GCP and local GCP, will be provided by the Sponsor for the purpose of obtaining informed consent. In addition to providing this written information to a potential subject, the Investigator or a designate will inform the subject verbally of all pertinent aspects of the trial, using language chosen so that the information can be fully and readily understood by laypersons. The subject will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification.

If permitted by national regulations, a person other than the Investigator may inform the subject about the trial and sign the Informed Consent Form, as above.

After the information is provided by the Investigator, the Informed Consent Form must be signed and dated by the subject and the Investigator.

The signed and dated declaration of informed consent will remain at the Investigator's site, and must be safely archived so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. A copy of the signed and dated information and Informed Consent Form should be provided to the subject prior to participation.

Whenever important new information becomes available that may be relevant to informed consent, the Investigator will revise the subject information sheet and any other written information to be provided to the subjects and submit them to the IRB for review and opinion. Using the approved revised subject information sheet and other written information, The Investigator will explain the changes to the previous version to each trial subject and obtain new written consent for continued participation in the trial. The subject will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification about the changes.

9.3 Subject Identification and Privacy

Study staffs should keep subjects' identification confidential. It is not allowed to indicate subjects' name in case report form or sponsor's documents, but initial of name and number of subjects can be referred.

Principle investigator should keep another document about identification, number and address of subjects, which should be preserved well by the principal investigator strictly complying with confidentiality.

9.4 Emergency Medical Support and Subject Card

Not applicable

9.5 Clinical Trial Insurance and Compensation to Subjects

Insurance covers all the subjects who are included in the study. From the subject is selected for the study, appropriate insurance should be conducted according to requirements of law, GCP guideline and relevant provisions of hospitals in the study.

Patients allowance will be provided to all the subjects.

9.6 Independent Ethics Committee or Institutional Review Board

Prior to commencement of the trial at a given site, this clinical trial protocol will be submitted together with its associated documents (ICF, investigator's brochure, etc.) to the responsible IEC for its favorable opinion or approval, which will be filed in the Investigator Site File. A copy will be filed in the Sponsor Trial Master File at sponsor.

The IEC will be asked to document the date of the meeting at which the favorable opinion or approval was given and the members and voting members present. Written evidence of favorable opinion or approval that clearly identifies the trial, the clinical trial protocol version and the Subject Information and Informed Consent Form version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

Amendments to this clinical trial protocol will also be submitted to the concerned IEC or IRB, before implementation of substantial changes (see Section 10.5). Relevant safety information will be submitted to the IEC or IRB during the course of the trial in accordance with national regulations and requirements.

9.7 Health Authorities

The clinical trial protocol and any applicable documentation (for example, Subject Information and Informed Consent Form) will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

10 Trial Management

Monitors from contract research organization (CRO) monitor the whole process of the study, collect

completed case report forms. CRO will conduct central data input, analyze data in completed eCRF from all the study sites and complete the statistical report. For eCRFs which are not completely filled or with missing data, monitors from CRO will contact investigator to clarify.

Investigators should conduct the study according to the study protocol, ICH-GCP guideline, requirements of IEC and applicable local guidelines and legislations, and follow precautions and indications in medical practice.

10.1 Case Report Form Handling

Refer to the Manual of Operations for eCRF handling guidelines.

The main purpose of the eCRF is to obtain data required by the clinical trial protocol in a complete, accurate, legible and timely. The data in the eCRF should be consistent with the relevant source documents.

The Investigator or designee is responsible for ensuring that the data collected in the course of this trial is accurate and documented appropriately on all applicable forms. They will then be processed, evaluated, and stored in anonymous form in accordance with applicable data protection regulations. The Investigator must ensure that the eCRFs and any other associated documents forwarded to Sponsor or its designated organization contain no mention of any subject names.

The data will be entered into a validated database. The Sponsor or its designee will be responsible for data processing, in accordance with the Sponsor's data management procedures. Database lock will occur once quality control and quality assurance procedures have been completed. PDF files of the eCRFs will be provided to the Investigators at the completion of the trial.

10.2 Source Data and Subject Files

The Investigator must keep a file (medical file, original medical records) on paper or electronically for every subject in the trial. It must be possible to identify each subject by using this subject file. This file will contain the demographic and medical information for the subject listed below and should be as complete as possible.

- Subject's full name, date of birth, sex, height, weight
- Medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the trial)
- Trial identification, that is, the Sponsor trial number for this clinical trial, and subject number
- Dates for entry into the trial (informed consent) and visits to the site
- Any medical examinations and clinical findings predefined in this clinical trial protocol
- All AEs
- Date that the subject left the trial including any reason for early withdrawal from the trial or IMP (if applicable).

All documents containing source data must be filed, including, but not limited to CT or MRI scan images, ECG recordings, and laboratory results. Such documents must bear the subject number and the date of the procedure. If possible, this information should be printed by the instrument used to perform the assessment or measurement. As necessary, medical evaluation of such records should be performed; all evaluations should be documented, signed, and dated by the Investigator.

Electronic subject files will be printed whenever the Monitor performs source data verification. Printouts must be signed and dated by the Investigator, countersigned by the Monitor and kept in a safe place at the site.

10.3 Investigator Site File and Archiving

Upon initiation of the trial, the Investigator will be provided with an Investigator Site File containing all necessary trial documents, which will be completed throughout the trial and updated as necessary. The file must be available for review by the Monitor, during Sponsor audits and for inspection by Health Authorities during and after the trial, and must be safely archived for at least 5 years (or longer, per local requirements or as otherwise notified by the Sponsor) after the end of the trial. The documents to be archived include the Subject Identification List and the signed subject Informed Consent Forms. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor/designee.

All original subject files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, local GCP whichever is longer. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

10.4 Monitoring, Quality Assurance and Inspection by Health Authorities

This trial will be monitored in accordance with the GCP, and any other applicable regulations. The site Monitor will perform visits to the trial site at regular intervals.

The clinical trial protocol, each step of the data captures procedure, and the handling of the data, including the final clinical trial report, will be subject to independent Quality Assurance activities. Audits may be conducted at any time during or after the trial to ensure the validity and integrity of the trial data. Representatives of the Quality Assurance unit from the Sponsor or a designated organization, as well as Health Authorities, must be permitted to access all trial documents and other materials at the site, including the Investigator Site File, the completed eCRFs, all IMP and IMP accountability records, and the original medical records or files for each subject.

10.5 Changes to the Clinical Trial Protocol

Changes to the clinical trial protocol will be documented in writing. Substantive amendments will usually require submission to the Health Authorities and to the relevant IEC for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

Minor (nonsubstantial) protocol amendments, including administrative changes, will be filed by the Sponsor and at the site. They will be submitted to the relevant IEC or to Health Authorities only where requested by pertinent regulations. Any amendment that could affect the subject's agreement to participate in the trial requires additional informed consent prior to implementation following the process as described in Section 9.2.

10.6 Clinical Trial Report and Publication Policy

10.6.1 Clinical Trial Report

After completion of the trial, a clinical trial report will be written by the Principal Investigator following the regulation/guideline in China.

10.6.2 Publication

The first publication will include the results of the analysis of the primary endpoints and will include data from all trial sites. The Investigator will inform the Sponsor in advance about any plans to publish or present data from the trial. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by Investigators or their representatives will require review by the Sponsor before submission. The Sponsor will not suppress publication, but maintains the right to delay publication in order to protect intellectual property rights.

Study information in this study will be registered on ClinicalTrials.gov.

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Signature Page – Protocol Lead

Trial Title:	A prospective, randomized controlled study to investigate the cumulative live birth rates (CLBRs) of gonadotrophin-releasing hormone (GnRH) antagonist protocol compared with the standard GnRH agonist long protocol for controlled ovarian stimulation in supposed normal ovarian responders
Clinical Trial Protocol Date / Version:	15 June 2017/ Version 1.0

Protocol Lead:

I approve the design of the clinical trial:

_____ _____

Signature Date of Signature

Name, academic degree:

Function / Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address:

Signature Page –Coordinating Investigator

This signature page should only be included for multicenter trials.

A Coordinating Investigator must be appointed for each multicenter trial irrespective of where it is undertaken according to GCP an Investigator assigned the responsibility for the coordination of Investigators at different centers participating in a multicenter trial. For single center trials, the Principal Investigator signature page may be adapted to reflect that the investigator approves the design of the trial.

Trial Title	A prospective, randomized controlled study to investigate the cumulative live birth rates (CLBRs) of gonadotrophin-releasing hormone (GnRH) antagonist protocol compared with the standard GnRH agonist long protocol for controlled ovarian stimulation in supposed normal ovarian responders
Clinical Trial Protocol Date / Version	15 June 2017/ Version 1.0

I approve the design of the clinical trial and I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Conference on Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

_____ _____

Signature Date of Signature

Name, academic degree:

Function / Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address:

Signature Page – Principal Investigator

Trial Title	A prospective, randomized controlled study to investigate the cumulative live birth rates (CLBRs) of gonadotrophin-releasing hormone (GnRH) antagonist protocol compared with the standard GnRH agonist long protocol for controlled ovarian stimulation in supposed normal ovarian responders
Clinical Trial Protocol Date / Version	15 June 2017/ Version 1.0
Center Number	
Principal Investigator	

I, the undersigned, am responsible for the conduct of the trial at this site and affirm that I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, GCP and all applicable Health Authority requirements and national laws.

_____ _____

Signature Date of Signature

Name, academic degree:

Function / Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address:

The signature page above is a generic page in the master clinical trial protocol. For multicenter trials, each Principal Investigator will sign a copy of this page. subinvestigators will not sign the clinical trial protocol.

The original signed signature sheets will be filed in the Trial Master File.