CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-197

MEDICAL REVIEW(S)

JUL 28 2000

Medical Officer's NDA Review

General Information

NDA: 21-197

Applicant: Asta Medica, Inc.
890 East Street
Tewksbury, MA 01876-1496
978-851-5981
Brian A. Green (Manager, Regulatory Affairs)

Submission/review dates

Date of Submission: October 28, 1999
CDER stamp date: October 29, 1999
HFD 580 date: November 1, 1999
Review begun: December 13, 1999
Review Completion Date: July 27, 2000

Drug identification

Generic name: cetrorelix acetate
Proposed trade name: Cetrotide™
Molecular formula: Acetyl-D-3- (2'-naphtyl) -alanine-D-4-chlorophenylalanine-D-3- (3'-pyridyl) -alanine-L-serine-L-tyrosine-D-citruline-L-leucine-L-arginine-L-proline-D-alanine-amide
Molecular weight: 1431.06
Other names: SB-075 acetate, D-20761 (acetate salt)

Pharmacologic category: gonadotropin-releasing hormone antagonist

Dosage form: lyophilized powder

Route of administration: subcutaneous injection

Proposed indication: "Cetrotide™ (cetrorelix acetate for injection) is indicated for the prevention of premature ovulation in women undergoing controlled ovarian stimulation."

Proposed dosage and administration:

"Single Dose Regimen

Ovarian stimulation therapy with gonadotropins (FSH, HMG) is started on cycle Day 2 or 3. Cetrotide™ 3mg is administered subcutaneously on stimulation Day 7.

When assessment by ultrasound shows a sufficient number of follicles of adequate size, hCG is administered to induce ovulation and final maturation of the oocytes.

If hCG has not been administered within four days after injection of Cetrotide™ 3mg, Cetrotide™ 0.25mg should be administered once daily, beginning 96 hours after the injection of Cetrotide™ 3mg until and including the day of hCG administration.

Multiple Dose Regimen

Ovarian stimulation therapy with gonadotropins (FSH, HMG) is started on cycle Day 2 or 3. Daily subcutaneous administration of Cetrotide™ 0.25mg is started at the early to mid follicular phase (Day 5 or 6 of stimulation). Treatment with Cetrotide™ 0.25mg is continued until and including the day of hCG administration.

When assessment by ultrasound shows a sufficient number of follicles of adequate size, hCG is administered to induce ovulation and final maturation of the oocytes."

Preparations:

0.25mg Cetrotide™ is supplied as a sterile lyophilized powder that is reconstituted with sterile water in a 1.0ml pre-filled syringe. The powder vial contains 0.26-0.27mg cetrorelix acetate, equivalent to 0.25mg cetrorelix, and 54.80mg mannitol.

3.0mg Cetrotide™ is supplied as a sterile lyophilized powder that is reconstituted with sterile water in a 3.0ml pre-filled syringe. The powder vial contains 3.12-3.24mg cetrorelix acetate, equivalent to 3.0mg cetrorelix, and 164.40mg mannitol.

Injection site: The proposed dosing listed above is intended for subcutaneous injection in the lower abdominal wall after reconstitution with water.

Related drug (GnRH antagonist):

Ganirelix
Route: Subcutaneous injection
Proprietary Name: ANTAGON
Applicant: ORGANON INC
Strength: 0.25mg BASE/0.5ML,
Indication: Inhibition of premature LH surges in women undergoing controlled ovarian stimulation
NDA: 21-057
Approval Date: Jul 29, 1999

Material reviewed:

NDA 21-197, volumes (1, 73-131)
Other documents ——— all submissions, ——— –all submissions, all meeting minutes and correspondence, all responses to requests for information, 4-month safety review report D-20761/8670000026 and included reports 8680000018, 850000008, 8683039029, and 8663046030)

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1.0 Resume

The sponsor has submitted safety and efficacy data on the use of the GnRH-antagonist Cetrotide™ for the prevention of premature ovulation during controlled ovarian stimulation/assisted reproductive technology (COS/ART). This drug is designed to be used either as a single dose of 3.0mg subcutaneously on the seventh stimulation day or multiple doses of 0.25mg given subcutaneously from the 5^{th}-6^{th} stimulation day up to the day of hCG injection.

For this application the sponsor submitted information from sixteen phase I studies, seven phase II COS/ART studies, and three phase III COS/ART studies. The dosage range from all studies varied from 0.1mg to 20mg. The dosage duration from all studies varied from 1 to 84 days. The dosage range in the pivotal COS/ART studies varied from 0.1mg to 3.0mg. The dosage duration in the COS/ART studies varied from 1 to 7 days

The phase I studies demonstrated the gonadotropin suppression ability of Cetrotide™ in both males and females. From these studies the dose finding phase II COS/ART studies were planned. In addition to the physiologic hypogonadotrophic effects, the principle adverse event identified in phase I trials was a transient injection site reaction.

The phase II COS/ART studies established the minimal effective single and daily doses. Study 2986 established that the 3.0mg single dose would prevent the LH surge for a four-day window. Study 2997 established the minimal effective daily dose as 0.25mg. An exploratory phase II study (3097) found no significant difference in outcomes whether Cetrotide™ was used with human menopausal gonadotropin (HMG) or recombinant FSH.

There were three pivotal phase III COS/ART studies. Two of these studies evaluated the 0.25mg daily dose (3010, 3020) and one study evaluated the 3.0mg single dose (3030). One of the 0.25mg dosing studies was non-controlled (3020) and the other (3010) used an active comparator (GnRH agonist -buserelin nasal spray). The phase III 3.0mg study (3030) utilized an active comparator (GnRH agonist- triptorelin injection)

All three pivotal phase III studies demonstrated the efficacy of Cetrotide™ in the inhibition of LH surges (LH>10 IU, progesterone >1.0ng/mL) and the allowance of subjects to reach the day of hCG injection. Cycle cancellation rates (1.7-7.5%) were significantly lower than historical controls (22.7-28.5%) derived from Society of Assisted Reproductive Technology (SART) registry data which included data collected with and without GnRH agonist use.

The safety evaluation for Cetrotide™ includes 1243 subjects presented in the integrated summary of safety plus an additional 142 subjects presented in the 4 month safety update. Among 949 subjects in the ten COS/ART studies, the only serious adverse event occurring in more than one subject was ovarian hyperstimulation syndrome, which is regarded as a complication of COS. There were no reported deaths in the COS/ART studies.

There were reports of deaths in prostatic and ovarian carcinoma studies employing Cetrotide™, but these deaths were felt to be disease related.

Cetrotide™ antibody formation was reported in a few subjects from the prostatic and ovarian cancer studies with long term use. Antibody formation was not reported in the COS/ART studies. One patient in the ovarian cancer study had an anaphylactic reaction following Cetrotide™ injection. No anaphylactic reactions were reported in the COS/ART studies.

The most commonly reported non-serious adverse event was injection site reaction. This consisted primarily of erythema with occasional symptoms of

itching and swelling. The injection site reactions were transient and mild in intensity. Headache and nausea were rarely reported (less than 1%)

Enzyme elevations (SGOT, SGPT, GGT, Alk Phos) were found in approximately 1-2% of the COS/ART subjects following initiation of Cetrotide™. The elevations ranged up to 2-3 times the upper limit of normal but were not associated with hyperbilirubinemia or long term hepatic toxicity.

There was no increased incidence in the number of pregnancy complications or congenital anomalies for subjects taking Cetrotide™.

2.0 Background information

2.1 Clinical Background

The role for GnRH-antagonists in infertility management revolves around their ability to inhibit unwanted LH surges during controlled ovarian stimulation. These surges are associated with premature ovulation, follicular luteinization, reduced oocyte numbers, and poor oocyte quality.

The development of use of antagonists for this indication follows the off-label use of GnRH-agonists for the same purpose. Beginning in the late 1980's, GnRH-agonists were employed in controlled ovarian stimulation because it was recognized that women with significant estrogen, androgen, and gonadotropin levels may not respond well to ovulatory stimulants.

GnRH-agonists provide a method to turn off a woman's endogenous reproductive hormone production and essentially provide more complete control of the amount of gonadotropins present during the stimulation. Premature LH surges leading to premature ovulation, early luteinization, poor follicular response, and subsequent cycle cancellation could theoretically be prevented. An equally important development with GnRH-agonists was the ability of infertility clinics to be able to schedule patients for oocyte retrieval in a much more controlled and timely fashion.

This use of GnRH-agonists in controlled ovarian stimulation protocols as mentioned above, developed in an off-label manner, but is presently employed in over 90% of infertility clinics. The agonists were already approved for other indications, such as endometriosis. Some researchers in the late 1980's and early 1990's felt that the medical benefits of GnRH-agonists were overrated in terms of cancellation and pregnancy results. These arguments will be elaborated more fully in the medical review summary.

Different dosages and timing of GnRH-agonist drug delivery have been studied. Longer protocols started the medication in the previous cycle (either proliferative or luteal phase). Other protocols utilized the agonist shortly before gonadotropins were started. The comparative phase III studies in this NDA employed a protocol starting the agonist in the preceding luteal phase.

Cetrotide™ represents the second GnRH-antagonist proposed to the agency for the indication of inhibiting LH surges in controlled ovarian stimulation protocols. Antagon (ganirelix) received approval by the FDA in the summer of 1999.

2.2 Regulatory history

The initial [redacted] for cetrorelix was received at the FDA on October 11, 1994. The proposed clinical trial D-20761-2980 was to assess the efficacy and safety of two dose schedules of daily injections of cetrorelix in previously untreated male patients with benign prostatic hypertrophy (BPH).

Most clinical studies of cetrorelix have occurred outside of the U.S. with phase I patients undergoing controlled ovarian stimulation began in Germany in 1992.

Other studies occurring in the U.S., aside from BPH, have included studies assessing the safety and efficacy of cetrorelix in patients with prostatic and ovarian cancer.

On October 30, 1997, a guidance meeting with Asta Medica was held to discuss clinical development of cetrorelix for the prevention of premature ovulation in patients undergoing fertilization treatments. At this meeting the use of historical controls and the use of the endpoint of reaching the hCG day were discussed. The agency accepted these proposals with the reservation that secondary endpoints (ie, pregancy rate) support the efficacy analysis.

A Pre-NDA guidance meeting was held on September 29, 1998. The use of historical controls was judged to be adequate for submission. Guidance was provided to the sponsor in terms of confidence intervals required. Study endpoints were again discussed because the SART registry did not have the data endpoint of reaching the day of hCG. The endpoint of proportion of subjects to reach oocyte retrieval with the calculation of the rate of cycle cancellation (failure to reach retrieval) was discussed and agreed upon. A 10% success rate difference between historical controls and Cetrotide™ treated subjects in reaching oocyte retrieval was considered to be clinically significant and to qualify for efficacy approval. The sponsor was also asked to perform antibody screening in up to three cycles.

On January 8, 1999 a pre-NDA guidance meeting addressed the issue of stability lots made in Germany. The proposed stability protocol employing a Belgium company to perform the final steps in the manufacture of the drug substance was deemed acceptable.

On July 15, 1999 a pre-NDA meeting discussed deficiencies at the Lubeck site as identified by internal audit. The agency felt that data from the Lubeck site should not be included in the efficacy analysis for cetrorelix. Safety data from the Lubeck site could be retained in the ISS. The sponsor planned to include data with and without the Lubeck site in the ISE. The Lubeck site was used in one half of the subjects in the pharmacokinetic studies (but not dose finding) and in two phase II pilot studies

The NDA for cetrorelix (Cetrotide™, NDA 21-197) was received by the agency on October 29, 1999.

The filing meeting for NDA 21-197 was on December 6, 1999. The application was accepted as fileable by all review disciplines.

On December 30, 1999, the sponsor submitted [redacted] for a cetrorelix study in the United States for additional safety and efficacy information on the 3mg single dose regimen. A similar regimen for the 3mg dose was evaluated in the pivotal study (3030) in France.

2.3 Chemistry/Manufacturing Controls: please refer to chemistry review

2.4 Animal Pharmacology/Toxicology: please refer to pharm-tox review

2.5 Microbiology: please refer to pertinent chemistry review sections

2.6 Human Pharmacokinetics/Pharmacodynamics: please refer to biopharmaceutics review

2.7 Foreign experience:

The 0.25mg and 3.0 mg dosage forms of cetrorelix were approved in the following countries in 1999 for use in prevention of premature ovulation in patients undergoing controlled ovarian stimulation:

European Community – April 13, 1999
Estonia – August 27, 1999
Latvia – September 8, 1999
Czech Republic – September 22, 1999

3.0 Description of the clinical data source

A listing of completed and ongoing clinical studies of Cetrotide™ are provided in Table 1. The studies for controlled ovarian stimulation that are important to support safety and efficacy of Cetrotide™ in this application are bolded.

Table 1. Completed and ongoing clinical studies of Cetrotide™

Study #	Indication	Study Phase	Patients
0001	Evaluate hormone activity	1	25 males
0002	Evaluate hormone activity	1	30 males
0003	Evaluate hormone activity	1	12 males
0004	Evaluate hormone activity	1	28 males
0007b	Evaluate hormone activity	1	16 males
0010	Evaluate hormone activity	1	15 males
0013	Evaluate hormone activity	1	10 males, 10 females
3031	Evaluate hormone activity	1	37 females
3047	Evaluate hormone activity	1	18 males
3082	Biliary excretion	1	3 males, 4 females
J95001	Evaluate hormone activity	1	15 females
3124	Evaluate hormone activity	1	48 females
0006	Evaluate hormone activity	1	5 females
0007a	Evaluate hormone activity	1	4 males
0009a	COS/ART pilot	1	7 females
2962	Cetrorelix pamoate, slow release formulation	1	24 females
2947	Cetrorelix pamoate, slow release formulation	1	37 males
3124	Evaluate hormone activity	1	48 females
C6	Male contraception		8 males
0008	COS/ART	2	19 females
0009b	COS/ART	2	21 females
0012	COS/ART	2	22 females
IC93005	COS/ART	2	18 females
2986	**COS/ART**	**2**	**65 females**
2997	**COS/ART**	**2**	**90 females**
3097	COS/ART HMG vs. recombinant FSH	2	62 females
3010	**COS/ART**	**3**	**188 females (Cetrotide™)** **86 females (buserelin)**
3020	**COS/ART**	**3**	**346 females**
3030	**COS/ART**	**3**	**115 females (Cetrotide™)** **39 females (triptorelin)**
2980	Benign prostatic hypertrophy	2	79 males
3043	Chemotherapy refractory ovarian cancer		17 females
0011	Prostate cancer		11 males
3053	Prostate cancer		7

3046	Unstimulated cycle study	2	34 females
3039	COS/ART HMG vs. rec FSH	2	60
J98003	Uterine leiomyomata	2	29 females

4.0 Clinical Study 2986 (phase II dose-finding)

4.1 Objective

The objective of this study was to identify the minimally effective dose for the single dose regimen.

Reviewer's comment: Previous studies had indicated the effectiveness of the 5.0mg dose in suppressing LH. In this study the researchers selected the 3.0mg dose as the starting dose with plans to decrease or increase the dosage level as needed to find the minimal effective dose for prevention of LH surges.

4.2 Design

4.2.1 Dosage selection

This study was performed as an open-label trial. The dosages were to be given until occurrence of LH-surge or on reaching the planned maximum group size of 30 subjects without occurrence of LH-surge. Then the next higher or lower dosage group, respectively, was to be started. The first group was to start with 3mg Cetrotide™ as single dose. In case of down-titration - as it actually occurred - the dose steps foreseen were 2.0mg, 1.0mg, and 0.5mg. Cetrotide™ was to be injected subcutaneously into the anterior abdominal wall as a single dose on HMG day 7.

4.2.2 Ovarian stimulation

The treatment with human menopausal gonadotropin (HMG) was to be started with two ampules (Humegon® - Lab. Organon, standardised to 75 I.U. FSH) on the second day of the menstrual cycle and continued daily. After Day 8 the regimen was to be adjusted individually on the basis of current estradiol levels. HMG was administered intramuscularly, usually in the evening.

4.2.3 HCG administration

For induction of the final maturation of the dominant follicles, 10,000 I.U. human chorionic gonadotropin (hCG, Gonadotrophins® / Lab. Organon, standardised to 5,000 I.U. hCG) were to be administered as soon as the lead follicle reached a size of 18 to 20 mm and the estradiol levels signified an adequate maturation of the follicles (>250 pg/ml per follicle >15 mm).

4.2.4 Oocyte retrieval, fertilization, embryo transfer, luteal phase support

Follicles were to be punctured 36 hours after hCG administraton. IVF was to be performed and embryo transfer was to occur 48 hours following oocyte retrieval. A maximum of three embryos will be transferred per patient. Luteal phase support was to be provided using Utrogestan®.

4.2.5 Hormonal lab assessment

Hormone levels of LH, FSH, estradiol, and progesterone were to be measured just before and after Cetrotide™ administration until the day of embryo transfer. The analyses were performed at each center's lab.

4.2.6 Cetrotide™ lab assessment

The plasma levels of Cetrotide™ were to be measured beginning on HMG day 6 and continue through the day of oocyte pick-up. The concentration of Cetrotide™ in the follicular fluid (sampling and pooling 2 ml from the three largest follicles) was to be assessed on the day of oocyte pick-up.

4.2.7 Safety evaluation

The safety evaluation consisted of physical examinations, assessment of safety laboratory parameters, vital signs, ECGs, and monitoring for risk factors associated with OHSS.

4.3 Inclusion and exclusion criteria

Inclusion:

- At least 18 but not older than 37 years of age at the time of screening
- Infertility cause solvable by controlled ovarian stimulation and ART, with or without intracytoplasmic sperm injection (ICSI)
- Menstrual cycle within a range of 24-35 days
- No more than 3 IVF procedures in the respective center in the past

- No previous stimulation within the last 3 months
- Normal uterus and at least one functioning ovary
- Satisfactory physical health
- Body weight within normal range ±20 %
- Written informed consent

Exclusion:

- Polycystic ovary syndrome (PCOS), corpus luteum insufficiency, impaired ovarian functions, severe endometriosis class III, IV.
- Myoma uteri.
- Serious systemic disorders such as high blood pressure.
- Contraindications to HMG or hCG administration.
- Clinically relevant allergic reactions (e.g. asthma, drug allergy), and history of allergy to LH antagonists.
- Abuse of alcohol or drugs.
- Participation in another clinical study within the last 2 months.
- Lack of willingness or ability to co-operate.

Reviewer's comments: Of all the pivotal studies, this was the only one to have an age range of 18-37. All the other studies used 18-39. This slight variation could have had a small effect in increasing pregnancy rate but does not impact the dose finding analysis of prevention of LH surge.

The exclusion of patients with polycystic ovarian syndrome (PCOS) is based on the fact that these patients may require a more prolonged and careful stimulation protocol and have an increased risk for ovarian hyperstimulation syndrome. This exclusion however may not accurately reflect the selection and treatment process that occurs in fertility clinics. The exclusion of PCOS patients necessitates a labeling comment. A well-controlled prospective study is needed to establish the best controlled ovarian stimulation protocol for these patients that incorporates accepted definitions of the syndrome along with determinations of androgenicity and its affect on success rates.

The concept of excluding patients with corpus luteum insufficiency does not impact on the efficacy analysis. One could argue whether this exclusion needs to be stated. Corpus luteum insufficiency may not be present in all cycles of women with this diagnosis. It is also a condition that can be created by the medications that are used in controlled ovarian stimulation protocols. Most patients undergoing these procedures have some form of luteal phase support anyway.

The exclusion of patients with "impaired ovarian function" is nebulous and not well defined by the sponsor. As discussed further in this review, the label should say that patients with low or no ovarian reserve were excluded.

The other pivotal clinical studies in this NDA submission specified submucous leiomyomata as the exclusion criteria rather than "myoma uteri" that was listed in study 2986. Submucous leiomyomata, if felt to be contributory to infertility, are treated by hysteroscopic removal and represent an acceptable exclusion.

Assisted reproductive technologies have improved the pregnancy rate for minimal to mild endometriosis. Less is known about the effect for severe disease because of the lack of randomized controlled studies.

4.4 Efficacy endpoints

Prevention of LH surge was the primary parameter of efficacy. The protocol defined an LH surge as LH>10 U/l, following several (antecedent) rising points and confirmed afterwards by consecutive rise in progesterone.

Secondary endpoints included:
• Ultrasonography scanning of the ovaries to measure number and size of follicles.
• Number and quality of the oocytes (mature, immature, or degenerated).
• Number and quality of embryos obtained (ideal cleavage, good, irregular cleavage) and transferred; number of embryos frozen.
• Pregnancy rate and follow-up of live births.

Reviewer's comments: The efficacy endpoint in this study varied slightly from the other four pivotal trials. This trial took into account several antecedent rising points with progesterone confirmation, but did not provide a specified progesterone level. Most of the other trials used an LH of ≥10.0 IU and a progesterone of ≥ 1.0ng/mL as the definition of an LH surge without assessment of antecedent rising points.

4.5 Patient disposition

A total of 65 patients were recruited and exposed to study medication. The trial was started with 31 patients treated with 3 mg Cetrotide™, the next 31 patients were treated with 2 mg Cetrotide™ and the last 3 patients were treated with 3 mg Cetrotide™. The two investigational dose groups of Cetrotide™ were unequally distributed between the two centers: center 1 (Prof. Frydman) contributed mainly to the 3 mg Cetrotide™ group, while center 2 (Prof. Salat-Baroux) contributed mainly to the 2 mg Cetrotide™ group. All except one of the 65 patients received

one single dose only of either 2 or 3 mg Cetrotide™. One patient (#2/231) received two injections of 2 mg Cetrotide™.

Reviewer's comment: It is conceivable that the investigation of the two doses at different centers may have affected the dosage analysis, however , there is no evidence from the data that the unequal distribution adversely affected the study's conclusion regarding the selection of the appropriate dose for the single dose regimen.

4.6 Compliance and withdrawals

All the planned doses of study medication were administered. Ten patients did not return for the final visit. Four of these patients did not undergo embryo transfer. No reason was listed for the other six patients.

Reviewer's comment: There is no evidence to suggest that lack of data from these ten patients affects the overall safety and efficacy analysis

4.7 Protocol violations

Protocol violations provided by the sponsor included:

- Exceeding the limits set for the height, weight, Broca index, or age (4 cases);
- Administration of more than 3 HMG ampules right from the start of stimulation (1 case);
- Cetrotide™ administered despite estradiol not being >400 pg/ml (11 cases);
- Cetrotide™ administered outside of cycle day 8, 9, or 10 (10 cases);
- No hCG administration despite at least 1 follicle exceeded 18 mm and adequate maturation (indicated by estradiol ≥250 pg/ml per follicle >15 mm; 7 cases).

Reviewer's Comment: There is no evidence that the protocol violations adversely affected the study's conclusions regarding the selection of the appropriate dose for the single dose regimen.

4.8 Efficacy analysis

4.8.1 Demographics

There was no significant demographic differences in the treatment groups aside from a history of ectopic pregnancies which were found to be more frequent in the 3mg treatment dose.

Reviewer's comments: The inclusion in the 3mg dose of more subjects with a history of ectopics does not impact the dose finding analysis.

4.8.2 Ovarian stimulation

For hormonal stimulation with HMG, various regimen were applied: some patients received 3 ampules every day, while others started with 2 ampules and were then titrated up to 6 ampules per day. HMG was administered for a minimum of 6 and a maximum of 16 days, the (pooled) mean was 9.3 days. The number of ampules used in the 3 mg group (mean 25.5) was slightly lower than in the 2 mg group (mean 30.5). There was no obvious difference in the HMG regimen between the centers.

Reviewer's comments: The variance in the number of ampules is primarily related to individual patient responsiveness. Patients who required many ampules with a previous attempt would be started with a higher number of ampules to begin with. Though the study design called for starting patients on 2 ampules, the starting of 3 ampules is consistent with normal clinical practice and is not thought to impact the decision concerning the minimal effective dose. The establishment of the 3mg dose was also based on the hormonal analysis carried through a four day period which demonstrated an LH rise on the 2mg dosing.

4.8.3 Cetrotide™ dosing

On average Cetrotide™ was injected on HMG day 7 to 8 (range 5 - 11 days). While in the 3 mg group, almost all patients received Cetrotide™ on HMG day 7, it was injected in the 2 mg group on HMG day 7 to 9 in most patients.

4.8.4 LH surge and cycle cancellation

While patient #2/223 was receiving the 2mg dose, a rise in LH above 10 [U/l] occurred at the day of hCG. A rise in progesterone to 2.5ng/mL was noted the day after the LH rise. An LH rise was not demonstrated after subjects initiated the 3mg dose.

Screening of the data base revealed five cases with LH levels above 10U/L just before the Cetrotide™ injection: #1/205, #1/312, #1/326, #2/217, #2/218. Cetrotide™ successfully controlled the LH levels in all these cases. In these five cases Cetrotide™ successfully reduced the LH levels and no premature ovulation occurred. hCG was given in one of these

patients (#1/312) on the same day as Cetrotide™, in three patients two days following Cetrotide™ and in one patient 3 days later (#2/217).

No cycles were cancelled in this study.

Reviewer's comment: These findings established the 3.0 mg dose as the minimal effective dose.The data also illustrates that although an LH surge can begin earlier in the cycle in some subjects, Cetrotide™ will still suppress the surge and allow the cycle to continue.

4.8.5 Follicular development/hCG/oocyte retrieval

On average, 2.5 follicles greater than 18 mm were found in each patient at the day of hCG. The hCG dose was 10,000 U in all but one patient (#2/319), who received 5,000 U.

In all 65 patients, who received Cetrotide™, the puncture was done and oocytes were obtained. In all cases mature oocytes could be retrieved. From all 65 patients, cumulus/oocyte complexes (COC) were obtained. The mean number of oocytes classified was 7.3. The mean proportion of mature oocytes was 81%.

4.8.6 Fertilization/ embryo transfer/luteal phase support

Most oocytes (95%) were normally fertilised. All oocytes were fertilised initially using the IVF method. Oocytes of four patients from center 2 were additionally fertilised by the ICSI method. Embryo transfer was performed in all but five patients. Luteal phase support was given to all patients with successful embryo transfer.

4.8.7 Pregnancy Results

Nineteen pregnancies were reported overall (pregnancy rate 29%). Of these nineteen pregnancies, there were 16 deliveries of 21 liveborn infants. There was one triplet pregnancy and three sets of twins. The treatment cycle pregnancy rate for the 3.0mg dose was 32%.

Reviewer's comments: The pregnancy rate compares favorably with historical controls (with and without GnRH agonist).

4.8.8 Pharmacodynamics

There was no difference in the estradiol profiles of the two Cetrotide™ dosage groups. The data provide no insight into possible effects of Cetrotide™ upon estradiol, since the HMG dosage was increased at the day of Cetrotide™ in most patients. The FSH levels were more than doubled after start of HMG treatment compared to pre-treatment values; after the initial increase, these values remained fairly stable despite the Cetrotide™ injection. Until the hCG administration, there were virtually no changes in progesterone values. A remarkable effect of Cetrotide™ was only seen on LH levels.

Reviewer's comment: It is difficult to establish during a COS/ART trial whether an antagonist has subtle effects on FSH and estradiol, since subjects show varied responsiveness to HMG and HMG dosages are adjusted accordingly. The laboratory analysis presented by the sponsor consistently shows that the major impact is on LH and there is no evidence to suggest that the antagonist at the dosages selected significantly counteracts the HMG effect on estradiol and FSH.

The antagonist effect on normal cycling women not receiving HMG is a different situation. Phase I studies of Cetrotide™ demonstrated a dose related decrease in FSH and estradiol.

4.8.9 Pharmacokinetics/follicular fluid analysis

The concentration of Cetrotide™ was nearly the same in plasma and in the follicular fluid (ratio C follicle/C plasma about 0.9). Low plasma concentrations of Cetrotide™ were found at the time point of embryo transfer (around limit of quantification).

Reviewer's comments: The sponsor felt from the pharmacokinetic data that if embryo exposure occurred it would only be a low and short-lasting exposure. Though the data supports very low Cetrotide™ levels or levels below the level of quantification, the more critical analysis resides in the evaluation of congenital and chromosomal anomalies that develop compared to the normal incidence.

4.10 Safety analysis

4.10.1 Total adverse events

A total of 30 newly occurring or worsening adverse events (= treatment emergent signs and symptoms) were recorded at any time after the first

injection of CET in 29 patients (aside from the pregnancy and newborn events listed below)

4.10.2 Serious adverse events

No serious adverse events occurred. No cases of ovarian hyperstimulation syndrome were reported in this study.

4.10.3 Pregnancy and newborn adverse events

Two spontaneous abortions and one ectopic pregnancy were reported. No congenital anomalies were reported. No abnormal development has been reported in the infant follow-up.

4.10.4 Other adverse events

Injection site reactions were reported in 28 patients. One patient experienced nausea. Another patient reported fatigue.

Reviewer's comments: The injection site reaction is the most commonly reported adverse event occurring with Cetrotide™. It is occasionally associated with itching. There were no reports of long lasting skin reactions such as nodule formation.

4.10.5 Laboratory abnormalities

Enzyme changes were reported in one patient (02/217). SGPT increased from 56.0 to 143.0. However, in this case, there was a pre-existing elevation of GGT and Alk phos.

Reviewer's comment: There were no significant biochemical or hematologic laboratory abnormalities noted aside from the enzyme change in pt. 2/217. See the other studies and final summary comments on enzyme elevation change.

4.11 Summary of study

This study, which was performed at two centers in France, identified the 3.0mg single dose of Cetrotide™ as the minimal effective dose in suppressing the LH

surge (for at least four days) when employed in women undergoing controlled ovarian stimulation.

LH levels decreased after the administration of Cetrotide™ and were approximately equal for 72 hours after Cetrotide™ injection of either 2.0 or 3.0 mg. However, three days after Cetrotide™ administration, the two curves split indicating a slight re-increase of the LH levels in the Cetrotide™ 2.0mg dose group only. In patients with an injection of 3.0mg Cetrotide™, LH levels remained low for at least 4 days.

Erythema around the injection site occurred in most patients. There was one reported case of nausea associated with Cetrotide™. There was no adverse effect on vital signs. No serious adverse events were reported.

4.12 Reviewer's comments on safety and efficacy:

Safety

There were no reports of OHSS in this study. Analysis of study data indicated no significant elevation of estradiol or the presence of excess follicular development.

Small areas of erythema are seen in most of the injection sites. Reporting of this event varied between the study sites. Because it is a common finding, some centers may be reporting only certain reactions or subject initiated reports. The reactions are transient with no long-term sequelae.

Efficacy

Study data of LH levels, progesterone levels, oocyte retrieval and pregnancy rates support the sponsor's selection of the 3.0 mg dosing form of Cetrotide™ for the "single dose" regimen to inhibit the LH surge during controlled ovarian stimulation. This dose was found to suppress LH for at least four days. Most patients will reach the day of hCG administration within this window of time. All patients receiving Cetrotide™ in this study had oocyte retrieval performed.

5.0 Clinical Study 2997 (phase II dose-finding)

5.1 Objective

The objective of this study was to identify the minimally effective daily dose for the multiple dose regimen.

5.2 Design

5.2.1 Dosage selection

In this dose finding study, 0.5mg Cetrotide™ was selected as the starting dose. If no LH surge occurred among the first 30 subjects treated with the same dose, then the next lower step was to be used (0.25mg, 0.1mg). If, however, an LH surge occurred, then the next higher step was to be started in the next subject.

The starting date for Cetrotide™ administration was HMG day 6. Daily Cetrotide™ was planned for 3-7 days up to and including the day of hCG.

5.2.2 Ovarian stimulation

The protocol standardised the basic treatment for the controlled ovarian hyperstimulation as follows: Two to three ampules - according to the discretion of the investigator - human menopausal gonadotropin (HMG, Humegon® - NV Organon, NL, 1 ampule containing 75 IU FSH and 75 IU LH) were to be administered i.m. into the buttocks. The HMG was to be administered daily on the menstrual cycle days 2 - 6 or 3 - 7, respectively. Thereafter the dose was flexible. Amendment 2 allowed other HMG preparations with the same content as Humegon® was withdrawn from the market during the study; the other preparations were: Pergonal®, Serono, and Menogon ®, Ferring.

Reviewer's comment: The use of different HMG products does not effect the minimal effective dosage selection.

5.2.3 HCG administration

For ovulation induction and for the final maturation of the dominant follicles, 10,000 IU human chorionic gonadotropin (hCG, Pregnyl ® / NV Organon, NL, standardised to 5,000 IU) were to be administered as soon as 3 follicles with a mean diameter of at least 17 mm were observed by ultrasound.

5.2.4 Oocyte retrieval, fertilization, embryo transfer, luteal phase support

Follicles were to be punctured 36 hours after hCG administraton. IVF and ICSI fertilization procedures was to be performed and embryo transfer was to occur 48 hours following oocyte retrieval. A maximum of three embryos were to be transferred per patient. Luteal phase support was to be provided using Utrogestan® Luteal phase support was allowed after the first six patients according to the discretion of the investigator (if estradiol was below 1000 ng/l). Utrogestan ® tablets (600 mg progesterone) or hCG i.m. (1,500 IU) were allowed for administration starting the day after of hCG until 2 to 3 days after ET.

Reviewer's comments: This assessment of the need for luteal support in the first six patients does not impact the efficacy analysis for Cetrotide™ in regard to prevention of LH surge. It could have a small impact on the pregnancy rate, though the pregnancy rate in this study compares well to historical controls.

5.2.5 Hormonal assessment

Hormone levels of LH, FSH, estradiol, and progesterone were to be measured just before and after Cetrotide™ administration until the day of embryo transfer.The analyses were performed at each center's lab.

5.2.6 Safety evaluation

The safety assessments performed were the same as study 2986.

5.3 Inclusion and exclusion criteria

The inclusion criteria are the same as study 2986 except for the age range of patients. Study 2997 had an age range from 18-39.

The exclusion criteria are similar to study 2986 except for these additions:

- Exclusion of specific leiomyomata (submucous type)
- FSH level >10 IU/L at screening
- History of low ovarian response to HMG/FSH
- Any ovarian or abdominal abnormality that would interfere with adequate ultrasound investigation
- Lactation or within a period of 2 months after a delivery or abortion. Use of an injectable hormonal method of contraception within a period of 6 months or use of any hormonal contraceptive within a period of 8 weeks prior to the start of controlled ovarian stimulation treatment

- PAP smear of III or higher within 2 years prior to or at screening
- Any hematological or biochemical value outside the normal reference range at screening. For serum liver enzyme concentrations values up to 30% above the upper reference limit were allowed
- Participation in another clinical study within the last 2 months.

5.4 Efficacy endpoints

A patient was considered as a non-responder to the respective dose of Cetrotide™, if an LH surge, which is defined by LH >10 IU/l and progesterone >1ng/mL, occurred.

In addition, the following secondary efficacy-related observations were recorded:
- Ultrasonography scanning (USS) of the ovaries to measure number and size of follicles.
- Number and quality of the oocytes.
- Cycle outcome, pregnancy rate and children follow-up.

5.5 Patient disposition

In one study center in Belgium a total of 90 subjects were recruited and exposed to study medication. Cetrotide™ was administered in daily doses of 0.5 mg to 32 patients (group 1), in doses of 0.25 mg to 30 patients (group 2L), and in doses of 0.1mg to 8 patients (group 3L).

5.6 Compliance and withdrawals

Two patients were discontinued while on Cetrotide™ treatment. One patient on the 0.1mg dose discontinued due to LH surge. Another patient on the 0.1mg dose was discontinued due to insufficient follicles.

5.7 Protocol violations

The following protocol violations were observed:
- Instead of recruiting 30 patients in the group 1, the investigator recruited 32.
- The weight of six patients were more than 20% below normal range
- In one patient each the diastolic blood pressure or the heart rate were outside the range given in the exclusion criteria,
- Patient #1/11 started HMG at cycle day 6 instead of cycle day 2,
- Total bilirubin values for patients #1/11 and #1/17 at screening were elevated at
- Creatinine kinase values at screening were elevated for some patients:

Reviewer's comments: The protocol violations do not affect the establishment of the minimally effective daily dose.

5.8 Efficacy analysis

5.8.1 Demographics

No demographic differences appeared in the separate treatment groups.

5.8.2 Ovarian stimulation

HMG was administered in all patients for a minimum of 8 and a maximum of 18 days; on average 10 to 11 days.

The hCG dose was 10,000 U in all but one patient (#3L/3), who received 5,000 U. Luteal phase support was given to most patients from #1/7 onwards, all received 1,500 U hCG at one to three occassions as single injections: two, six, and ten days after OPU.

5.8.3 Cetrotide™ dosing

On average, all 90 patients were treated with Cetrotide™ for 5 to 6 days; the minimum was 3 and the maximum 13 days. 46 subjects received 0.25 mg Cetrotide™ alone or were increased to 0.25mg Cetrotide™, 32 subjects received 0.5 mg Cetrotide™, and 8 subjects received 0.1mg Cetrotide™ alone.

5.8.4 LH surge and cycle cancellation

No patient of the 0.5mg Cetrotide™ or the 0.25mg Cetrotide™ groups experienced an LH-surge during treatment. One patient experienced an LH surge according to the protocol definition during treatment with 0.1 mg Cetrotide™. Thereafter, four patients already on treatment with 0.1 mg Cetrotide™ were switched to 0.25mg Cetrotide™ and the next 16 patients were treated using 0.25 mg Cetrotide™.

In three patients a rise in LH beyond 10 IU/l without simultaneous rise in progesterone was observed after the first injection of Cetrotide™; one after 0.25 mg Cetrotide™ (#3L/27) and two after 0.1 mg Cetrotide™ (#3L/1; #3L/4). In patients #3L/27and #3L/1 the hCG injection was done and two mature oocytes and 9 metaphase II oocytes, respectively, were

picked-up. The hCG injection was not done in patient #3L/4 due to low oestrogen values.

One patient experienced a definite LH surge before start of the Cetrotide™ administration. This case was controlled by treatment with 0.5 mg Cetrotide™. Twelve patients experienced a rise in LH beyond 10 IU/l without increased progesterone just before initiation of Cetrotide™ treatment: five in 0.5 mg Cetrotide™ group, seven in the 0.25 mg Cetrotide™ group, and three in the 0.25 mg Cetrotide™ group. In each of these cases, Cetrotide™ successfully controlled the elevated LH levels, and in all except one patient (#1/32) oocytes were obtained.

The cycle cancellation rate reported by the sponsor in this study is 6.3%

Reviewer's comments: The 0.25mg dose was appropriately established as the minimally effective dose for the daily regimen. The cycle cancellation rate reported by the sponsor compares favorably to the cancellation rates in the SART historical registry data prior to widespread use of GnRH-agonist to prevent LH surges. The comparative analysis will be discussed in more detail at the end of the review.

5.8.5 Follicular development/hCG/oocyte retrieval

An effect of the various Cetrotide™ doses on follicle size or number of follicles was not evident. Eighty-eight patients received hCG. The hCG dose was 10,000 units in all but one patient who received 5,000 units.

Oocytes were obtained from 87 patients. The mean number of oocytes retrieved was 14. The mean proportion of metaphase II oocytes was 84% and germinal vesicle stage oocytes 11%. A dose-relationship to Cetrotide™ was not evident.

5.8.6 Fertilization/embryo transfer/luteal phase support

Most oocytes were normally fertilized. 71 subjects had ICSI performed. 16 subjects had IVF performed. Embryo transfer was performed in 85 subjects. Luteal phase support was given in 78 of these subjects. It was not given in the first six patients according to protocol. Patient #1/6 received no luteal phase support due to high estradiol. The duration of luteal phase support was 3 days for 64 patients, 2 days for 9 patients and 1 day for 5 patients.

5.8.7 Pregnancy results

25 pregnancies were reported overall (pregnancy rate = 28% per stimulated cycle). The pregnancy rate per transfer in the ICSI group was 29.0%. The pregnancy rate per transfer in the IVF group was 31.3%. There were 18 deliveries with 24 live births. There were six sets of twins. The treatment cycle pregnancy rate for the 0.25mg dose of Cetrotide™ was 30%

5.8.8 Pharmacodynamics

Cetrotide™ mainly showed an effect on the LH level. There is no apparent effect on FSH, estradiol, and progesterone at this level.

5.10 Safety analysis

5.10.1 Total adverse events

A total of 63 adverse events were reported (includes 7 serious adverse events, 10 minor adverse events, and 46 injection site reactions). The pregnancy and newborn adverse events are listed separately.

5.10.2 Serious adverse events

Six cases of ovarian hyperstimulation syndrome (OHSS) occurred in this study. All the patients were hospitalized. One of these OHSS patients also developed severe right renal colic. Four of these six cases occurred in conjunction with pregnancy. Four of the cases were graded severe and two were graded as moderate. All the cases resolved without further sequelae.

Reviewer's comments:

The cases of OHSS are listed in the following table:

Table 2. OHSS in study 2997

Pt. #	Dose mg	OHSS grade	Pregnancy	Highest E2 (pg/mL)	Follicular status
1/18	0.5	III	Yes		20 follicles>15mm
1/28	0.5	III	Yes		9 follicles>15mm (17>11mm)
1/29	0.5	III	Yes		11 follicles>15mm
1/30	0.5	III	Yes		12 follicles>15mm
2/18	0.25	II	No		17 follicles>15mm (35>11mm)
3/19	0.25	II	No		16 follicles>15mm (28>11mm)

The phase III studies advised that the hCG injection was not to be given to subjects with 12 or more follicles with a mean diameter of >15 mm or an estradiol level >4000 pg/ml. These values were exceeded in 4 of the 6 patients who developed OHSS in this phase II study.

The percentage of moderate to severe OHSS (6.6%) from this study is higher than that reported in COS/ART conception cycles prior to GnRH agonist use.

5.10.3 Pregnancy and newborn adverse events

Four spontaneous and three induced abortions were reported. One induced abortion was performed for fetal death in utero at 24 weeks gestation. No anomalies were seen. In the second induced abortion (pt#218), a trisomy 21, +Klinefelter was reported. This patient had ICSI performed. In the third induced abortion (pt# 225) a polymalformation syndrome was reported. ICSI was also performed in this case. Two ectopic pregnancies were reported.

No congenital anomalies were reported in the initial newborn physical examination. In the baby follow-up data, one report of a twin pregnancy indicated a VSD in the male and motor delay in the female. Minor congenital skin nevi and hemangioma were also reported. One sudden infant death syndrome was reported at 4 months.

5.10.4 Other adverse events

4 cases of nausea, 3 cases of headache and one each of sinusitis, hypotension, and pharyngitis were reported.

In 46 patients (51%) a local redness at the injection site of Cetrotide™ was seen, accompanied by itching in 27 (30%) and swelling in 5 (6%) patients. Redness was more frequently reported in the first 60 patients then in the last 30.

5.10.5 Laboratory abnormalities

Liver enzyme changes were reported in four patients (01/09, 2L/08, 2L/12, and 3L/09) See Table 3.

Table 3: Enzyme elevation in study 2997

Pt. #	Pre-existing elevation at screening	Enzyme abnormality
01/09	No	GGT = [illegible] (normal 14-41)
2L/08	Yes (alk phos)	SGOT = [illegible] (9-41) SGPT = [illegible] (4-39)
2l/12	No	GGT [illegible] (14-41)
3L/09	No	SGOT [illegible] (9-41) SGPT = [illegible] (4-39) GGT [illegible] 14-41)

Reviewer's comment: After excluding the patient with pre-existing enzyme elevation the number of patients in study 2997 with enzyme elevation following initiation of Cetrotide™ is 3/90 (3.3%)

All the other biochemical and hematology measurements determined at screening and final visit were within normal limits.

5.11 Summary of study

This study, which was performed in one center in Belgium, identified the 0.25mg dose of Cetrotide™ as the minimal effective dose in suppressing LH surges during controlled ovarian stimulation for the daily dose regimen. A pregnancy rate of 28% was reported in this trial.

Six cases of ovarian hyperstimulation syndrome were reported. The most common minor adverse event was an injection site reaction. Enzyme elevations were reported in four patients (4.4%)

5.12 Reviewer's summary comments

Safety

The number of cases of OHSS exceeds the usual reported incidence. Four of the six cases had significant elevation of estradiol and/or follicles, which may indicate an over-aggressive stimulation or pronounced sensitivity in the individual patient.

The modest increase in enzymes should be noted and be included in labeling. The etiology is not known. The sponsor's suggestion that the elevation is related to controlled ovarian stimulation has some theoretical merit but has not been previously reported either in the medical literature or prior COS studies received by the agency. Thus, the possibility that Cetrotide™ is contributing to this change cannot be ruled out. It is reassuring to see that there was no evidence of hyperbilirubinemia or long term hepatic toxicity.

Though studies to date have not indicated an excess of chromosomal/congenital anomalies with ICSI aside from sex chromosome related problems, this procedure still needs to be considered as a potential risk.

The finding of the trisomy 21, +Klinefelters individual, though rare, may be associated with the ICSI procedure and paternal status. Patients with Klinefelter's syndrome with oligozoospermia have an increased risk of both sex chromosome and autosome aneuploidy in their progeny.

Efficacy

This study's findings support the sponsor's decision to propose the 0.25mg subcutaneous dose of Cetrotide™ as the "daily dose regimen" to prevent LH surge during controlled ovarian stimulation. An LH surge after treatment initiation was noted in the 0.1mg dosage group but not in the 0.25mg dose. The definition for LH surge in this study is LH $\geq$10 U/L and progesterone $\geq$1.0ng/mL. This was the same definition used in the phase III studies.

Though an LH surge (as defined by both LH & progesterone) did not occur during treatment ~~with the~~ 0.25mg dose, there were isolated LH rises without a concomitant rise in progesterone.

Attention should be paid to the fact that an LH surge and elevations of LH without concomitant elevations of progesterone can occur before HMG day 6. The study data indicates that Cetrotide™ decreased these elevations in most cases and that the quality and number of oocytes did not suffer. The sponsor proposed either an HMG day 5 or 6 start for the 0.25mg dose in the labeling.

The pregnancy rate (28%) and oocyte retrieval data compare favorably to historical controls.

6.0 Clinical study 3010 (phase III, controlled)

6.1 Objective

To investigate the safety and efficacy of the once daily, multiple 0.25mg Cetrotide™ regimen in COS/ART compared to the use of four time daily intranasal 0.15mg buserelin spray.

The ultimate aim of such treatment with Cetrotide™ was to guarantee a controlled ovulation and the retrieval of at least one mature (used for IVF) or metaphase II (M II, used for ICSI) oocyte suitable for ART. Cetrotide™ as an GnRH-antagonist was expected to prevent a premature ovulation triggered by an LH surge. Both a short treatment protocol with Cetrotide™ (GnRH-antagonist) and "long term protocol" with buserelin (GnRH-agonist) were expected to prevent premature ovulation triggered by an LH surge.

6.2 Design

6.2.1 Overall design

This pivotal study was planned using a prospective, randomised, open-label, 2 parallel groups design and was performed as a multicenter and multinational trial. The randomisation was done using a 2:1 ratio (Cetrotide™:buserelin)

6.2.2 Replacement policy

Patients randomised to buserelin or Cetrotide™ were to be replaced, if they did not return to the visit HMG-Day-1 within three months after screening, i.e. if no controlled ovarian stimulation was initiated (Amendment 1).

The replacement patients would receive a number added multiple of 100, i.e. patient #7 would have to be replaced by patient #307, using the same treatment.

6.2.3 Ovarian stimulation

All of the following prerequisites were to be matched prior to the initiation of the HMG stimulation:

- Menstrual bleeding, confirmed by cycle length (not obligatory for buserelin patients)
- Exclusion of pregnancy
- Exclusion of an ovarian cyst with a diameter ≤2 cm,
- hCG ≤10 U/l
- progesterone ≤1 ng/ml
- estradiol ≤50 pg/ml (for buserelin patients only)
- LH≤ 10 U/l (for buserelin patients only)
- FSH ≤10 U/l

Human menopausal gonadotropin (HMG), ampules containing 75 IU FSH and 75 IU LH. Menogon® from Ferring, Germany, was purchased by the sponsor and supplied to all centers except #22 and #27, which used Pergonal® (Serono, #22) and Humegon® (Organon, #27). The HMG was started on cycle day 2 at a dosage of two ampules (150 IU each of FSH and LH) per day for the first five days. The dosage could be increased thereafter according to the individual response regarding the hormonal stimulation verified by the daily hormone analyses or the ultrasound measurements of the ovaries. HMG was to be given until the day of hCG. All HMG injections were to be administered intramuscularly into the buttocks in the morning.

Reviewer's comment: The use of different HMG products does not effect the efficacy analysis.

6.2.4 Cetrotide™ dosing

Cetrotide™ was to be injected once daily in the morning in doses of 0.25 mg subcutaneously into the lower abdominal wall, starting from day 6 of HMG treatment of the controlled ovarian stimulation cycle until and including the day of hCG. In case of a premature LH surge prior to HMG day 6, Cetrotide™ should be administered as soon as possible in order to interrupt a possible ovulation and to rescue the cycle. Each Cetrotide™ injection was to be done after taking a blood sample for hormone assessments in intervals of 24 ± 2 hours. It was anticipated that the duration of Cetrotide™ treatment would be 3 to 7 days in most cases, with a maximum being 14 days.

6.2.5 Buserelin dosing

The buserelin spray was to be administered four times daily in doses of 0.15 mg each (0.6 mg/d) intranasally, starting on day 18 to 22 (i.e. the mid-luteal phase) of the pre-controlled ovarian stimulation/ART cycle. Those patients who do not reach the required hormone levels of estradiol<50pg/mL with 15 days or after a further 7 days in case of cyst formation were discontinued. Treatment with buserelin was to be continued during the stimulation period with HMG including the day of administration of hCG. The total duration of buserelin treatment was expected to be 24 to 35 days.

6.2.6 HCG administration

Before proceeding with the hCG administration, at least 1 follicle with diameter ≥20 mm or an estradiol level ≥1200 pg/ml was stipulated by the protocol.

The hCG injection was not to be done in case of 12 or more follicles with a mean diameter of ≥15 mm or an estradiol level ≥4000 pg/mL.

Each center was allowed to use the commercially available preparation of hCG that would normally be employed at their center. HCG was given in a single dose of 10,000 IU for the induction of the ovulation and for the final maturation of the dominant follicles.

If an LH surge occurred during the HMG stimulation phase, the investigators were always allowed to rescue the cycle by continuing with hCG (10'000 IU) and oocyte-pick-up.

Reviewer's comments: A strong argument against the use of "reaching the day of HCG" as primary efficacy endpoint is illustrated here. Rescuing the cycle despite an LH surge may be very important for the individual patient, but it makes the efficacy analysis difficult when historical controls are use for efficacy analysis. SART registry data did not comment on patients reaching HCG administration but rather listed cancellation rates. Use of cancellation rates compared to historical controls was approved for efficacy analysis.

6.2.7 Oocyte retrieval, fertilization, and embryo transfer

Follicles were to be punctured 36 hours after hCG administraton. IVF and ICSI fertilization procedures were to be performed and embryo transfer

was to be occur 48 hours following oocyte retrieval. A maximum of three embryos were to be transferred per patient.

6.2.8 Luteal phase support

Either:
Injections of hCG according to the center's rule, however, not when estradiol >2,000
or
Vaginal administration of progesterone (e.g. 200 mg b.i.d., t.i.d. or 400 mg b.i.d.).

6.2.9 Hormonal laboratory assessment

Hormone levels of LH, FSH, estradiol, and progesterone were to be measured daily each morning before the Cetrotide™ injection or on respective HMG days for the buserelin patients; on the day of hCG injection blood samples were drawn in the morning and evening. Blood samples were drawn for both on site laboratory evaluation and central laboratory evaluation.

6.2.10 Cancellation Criteria

The circumstances which could lead to cancellation of the controlled ovarian stimulation/ART were:

- Estradiol too low,
- Insufficient follicular size
- Premature LH surge before or on the days of Cetrotide or buserelin administration
- Poor tolerability
- Intercurrent diseases
- Occurrence of exclusion criteria
- Non-compliance

Reviewer's comment: Despite having a cycle cancellation criteria for premature LH surge before or on Cetrotide™ the investigators, at their discretion, were allowed to attempt a rescue of the LH surge. This makes the use of "reaching the day of hCG" as a primary endpoint difficult.

In case of cycle cancellation before hCG administration it was recommended to continue with Cetrotide™ or buserelin administration, respectively, for one week in order to prevent spontaneous ovulation with the release of multiple oocytes leading to multiple pregnancies, and to prevent the development of an ovarian hyperstimulation syndrome.

Reviewer's comment: This recommendation has a theoretical basis but a controlled clinical trial, appropriately powered, is required before labeling indications can be approved.

6.2.11 Safety evaluation

The safety evaluation consisted of physical examinations, assessment of safety laboratory parameters, vital signs, ECGs, and monitoring for risk factors associated with OHSS.

6.3 Inclusion and exclusion criteria

Inclusion criteria

- healthy, physically and mentally,
- at least 18 but not older than 39 years of age at the time of screening,
- infertility cause solvable by COS and ART, with or without ICSI,
- normal menstrual cycle with a range of 24-35 days and an intra-individual variation of ± 3 days,
- no more than 3 IVF procedures in the past,
- normal uterus and at least one functioning ovary,
- able and willing to comply with the treatment and assessment regimen designed for this study,
- written informed consent.

Exclusion criteria

- A previous cycle within this study.
- Polycystic ovary syndrome (PCOS), corpus luteum insufficiency, impaired ovarian function, severe endometriosis class III or IV, submucosal myoma uteri.
- FSH level ≥10 IU/L at screening (around day 5 of the previous cycle).
- Known history of low ovarian response to HMG/FSH.
- Contraindications for the use of gonadotropins.