- 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 COS treatment.
- PAP smear of III or higher within 2 years prior to or at screening.
- Arterial hypertension: systolic blood pressure >150 mm Hg or diastolic blood pressure >90 mm Hg.
- Any significant cardiovascular, pulmonary, neurologic, allergic, hepatic, or renal disease at present or in the past, if recurrence of sequel is possible.
- History of alcohol or drug abuse.
- Any laboratory parameter (e.g. clinical chemistry, haematology) clinically relevant outside the normal range.
- Administration of investigational drugs within 60 days prior to screening.

6.4 Efficacy endpoints

The primary parameter was the response rate defined as: reaching the day of hCG.

(There was an inconsistency in the protocol in this respect: "prevention of premature LH surge" was initially defined primary objective. However, this was redefined as "reaching the hCG day". The estimates for the incidences, the sample size calculation, and the analysis strategy were based upon the latter definition.)

- The secondary parameters were:
- Prevention of premature LH surge*, which was defined as serum levels of LH ≥10 [U/l] together with progesterone ≥1 [ng/ml] (between day 6 of HMG treatment until and including the day of ovulation induction (day of hCG)
- Pre- and postovulatory endocrine profiles of LH, FSH, estradiol, and progesterone
- Number and size of follicles at the day of hCG
- Number and quality of oocytes and transferable embryos
- Number and dose of HMG ampules (containing 75 IU each of FSH and LH).
- Duration of stimulation period with HMG until the day of hCG
- Ovarian ~~cyst~~ formation before stimulation period
- Cycle outcome and pregnancy rate
- Luteal phase support
- Tolerability (adverse events, laboratory tests, occurrence of ovarian hyperstimulation syndromes (OHSS) according to WHO criteria)
- A follow-up analysis of pregnancy and the newborn children

6.5 Patient disposition

The center sites and patient distribution are listed in Table 4.

Table 4: Study sites and patient distribution for study 3010

Country	Center #	Cetrotide™ pts	Buserelin pts
Belgium	21-Brussels	31	14
UK	22-Cambridge	12	6
UK	23-Sheffield	14	7
UK	24-Glasgow	29	11
UK	25-Edinburgh	41	17
Netherlands	26-Maastricht	21	10
Denmark	27-Frederikberg	40	20

Reviewer's Comment: Efficacy information will be listed excluding the Glasgow site. DSI made plans to review Glasgow but cancelled the review when the sponsor could not provide originial sonographic study data. For the critical efficacy data, separate numbers and rates will be specified that exclude the Glasgow site. Data from the Glasgow site will be retained for safety analysis. Excluding Glasgow reduces the intent to treat patients to 159 in the Cetrotide™ treated arm and 74 in the buserelin treated arm.

6.6 Compliance and withdrawals

Cetrotide™ was started in all patients on day 6, except in one patient (day 7, #25/11). In one patient, one dose of Cetrotide™ was missed (#24/1); another one (#23/18) received no Cetrotide™ the day of hCG, however, the hCG injection was done within 36 hours after the last Cetrotide™ dose. Additionally, patient #23/5 was reported to have been non-compliant; since she was never exposed to Cetrotide™, she was not considered in any study population.

All patients on buserelin were reported to have been fully compliant with the regimen.

6.7 Protocol violations

The following protocol violations were noted:

- Interval between Cetrotide™ injections > 36 hours (one patient-Glasgow)
- Interval between Cetrotide™ and hCG > 38 hours (one patient)
- First Cetrotide™ injection after HMG day 6 (one patient)
- Progesterone at HMG day 1 > 2ng/mL (5 patients)

Reviewer's comments: These protocol violations should not impede the efficacy analysis, especially since including patients with increased progesterone might work against efficacy success.

6.8 Efficacy analysis

6.8.1 Demographics

The demograpahic and infertility background of the Cetrotide™ and buserelin treated arms showed no significant differences.

6.8.2 Ovarian stimulation

HMG was administered in all patients for a minimum of 5 and a maximum of 24 days; on average 10 to 11 days. All patients started with two ampules of HMG per day and by far most remained on that dose during the whole controlled ovarian stimulation program. In some patients the dosage was increased to 3 to 4 ampules per day after the HMG day 6; in few patients the dosage was reduced towards the end of the controlled ovarian stimulation. The number of days on HMG was lower in the Cetrotide™ group; otherwise, there was no difference between the Cetrotide™ and the buserelin group with respect to usage of HMG. There was no apparent difference between the centers.

6.8.3 Cetrotide™ dosing

The mean exposure to Cetrotide™ was 4 days

6.8.4 Buserelin treatment duration

The mean exposure to buserelin was 26 days

6.8.5 LH surge and cycle cancellation

The sponsor reported that the success of reaching the day of hCG was 96.1% Cetrotide™ treated arm and 90.6% in the buserelin arm. According to local laboratory data LH surges were prevented in 95.2% of Cetrotide™ patients and 97.6% of buserelin patients. The cancellation rate reported by the sponsor for this study was 5.3%

The following table illustrates the numbers of patients with LH surge and / or cancellations in Study 3010 excluding the Glasgow site:

Table 5: LH surges and cancellations (excluding Glasgow)

Safety evaluable	188
Cetrotide™ treated pts excluding Glasgow	159
LH surge, hCG given (cycle not cancelled)	**3** (includes pt. 21/32 also listed below, 21/20, 27/21)
Cancellation of controlled ovarian stimulation, no hCG	**6**
--follicle size insufficient	0
--premature LH surge	1
--too many follicles	3
--too few follicles	2
hCG given but oocyte retrieval failure	**3**
--estradiol too low	0
--follicles collapsed	2
--too few follicles	1

Three Cetrotide™ treated patients had a premature LH surge (by central lab data) after Cetrotide™ treatment initiation, but received hCG:

- Patient #32 at site 21(Brussels) was 35 years of age with a weight of 66kg. She exhibited a low response to HMG. Laboratory criteria for LH surge occurring on Cetrotide™ treatment day 4 was documented in both the local and central laboratory. Five mature oocytes were retrieved, three were normalized fertilized, but no cleavage resulted. Cetrotide™ serum concentrations were above LOQ.

- Patient #20 at site 21 (Brussels) was 37 years of age with a weight of 83kg. She exhibited a low response to HMG for 10 days. An LH surge was documented by the central lab on Cetrotide™ treatment day 8. Six mature oocytes were obtained. Three fair quality embryos were transferred, but no pregnancy occurred. Cetrotide™ serum concentrations never rose above LOQ.

- Patient #21 at site 27 (Denmark) was 30 years of age with a weight of 90kg. She had 7 previous unsuccessful infertility treatments. She exhibited a low response to HMG. An LH surge was confirmed by the central lab on the 6th day of Cetrotide™ treatment. One mature oocyte was obtained. One embryo was transferred.

Six Cetrotide™ treated patients had cancellation of controlled ovarian stimulation cycle with no hCG given. Of these six patients, two had too few follicles, three had too many follicles, and one had a premature LH surge. The patient with the premature LH surge is described subsequently:

- Patient # 34 at site 27 (Denmark) was 29 years of age and weighed 63kg. She exhibited a low response to HMG for 9 days with the development of one small follicle. Laboratory criteria for LH surge occurred at the local lab but not central lab on Cetrotide™ treatment day 7. Cetrotide™ serum concentrations above LOQ were noted.

Three Cetrotide™ treated patients received hCG but failed to have oocytes retreived.

Reviewer's comments:

The sponsor discusses a cycle failure rate (cycle cancellation rate) for Cetrotide™ of 5.3% (10/188, including Glasgow) to compare to the historical cycle cancellation rate derived from the Society of Assisted Reproductive Technology (SART) data. The historical cancellation rate data presented by SART represent those patients who got to oocyte retrieval. The sponsor's cycle cancellation rate for Cetrotide™ included seven subjects who did not reach the day of hCG administration and three subjects who failed oocyte retrieval.

However, as previously commented upon, the sponsor allowed hCG to be given to subjects (3 in this study) who had clearly demonstrated an LH surge. Therefore, it is the opinion of this reviewer that these subjects should be included as cycle failures despite getting to hCG and oocyte retrieval. In the historical control these subjects would have been treated as cycle failures.

The cancellation rate obtained when including these additional 3 subjects and excluding subjects contributed by the Glasgow site equals 7.5% (12/159). Even with using this "stricter" criteria for cycle failure the rate of 7.5% compares favorable to the historical SART data as will be discussed later in the review.

6.8.6 Follicular development/ hCG/ oocyte retrieval

On HMG day 6 there were more small follicles in the Cetrotide™ patients than in the buserelin patients. This was reversed on the day of hCG, when the number of small (11-14 mm) follicles was lower in the Cetrotide™ than in the buserelin group. There was no difference with regard to the medium size and large follicles (20 mm) on the day of hCG.

Reviewer's comment: This may be a manifestation of the agonist activity.

A total of 181 patients in the Cetrotide™ group (96.3% of ITT), and 77 patients of the buserelin group (90.6% of ITT) reached the day of hCG. If Glasgow is excluded 155/159 patients in the Cetrotide™ group (97% of ITT) and 67/74 patients in the buserelin group (91% of ITT) reached the day of hCG.

Reviewer's comment: See previous section (section 6.8.5) and final comments (section 13.0) in regard to "reaching day of hCG"

Cumulus/oocyte complexes (COC) were obtained from 175 of the 178 patients in the Cetrotide™ group (Glasgow included).

6.8.7 Fertilization/embryo transfer/ luteal phase support (Glasgow included)

Sixteen Cetrotide™ treated patients had fertilization or cleavage failures (8.5%). Seven buserelin treated patients had fertilization or cleavage failures (8.2%)

In the total study (Cetrotide™ and buserelin) there were 184 IVF procedures and 73 ICSI procedures. The fertilisation rate was equal in both groups.

6.8.8 Pregnancy results

42 in cycle pregnancies were reported for the Cetrotide™ treatment arm (pregnancy rate=22%, 27% per embryo transfer) One of the pregnancies

resulted after intrauterine insemination. There were 33 deliveries resulting in 41 live births.

The pregnancy rate for the buserelin treatment arm was 26% (33% per embro transfer)

Reviewer's comments: If Glasgow is excluded there is a pregnancy rate of 20.7% in the Cetrotide™ treatment arm and 23.5% in the buserelin arm. The Glasgow site contributed 16/41 live births. The live birth rate excluding Glasgow is 25/159 is 16%.

6.9 Safety analysis

6.9.1 Total adverse events

28 total adverse events were reported from the patients with exposure to Cetrotide™ including seven with OHSS (5 grade I, 2 grade II). Pregnancy and newborn adverse events are listed separately.

6.9.2 Serious adverse events

Seventeen OHSS were reported during the course of the study. Seven cases were considered as being serious. All cases could be controlled by the investigators and in no case were any long-term sequelae reported. The incidence of the OHSS without respect to severity was considerably more frequent (p >0.015, Fisher's exact test) after buserelin (10 of 85 ITT patients = 11.8%) than after Cetrotide™ (7/188 = 3.7%), similarly, the OHSS of WHO grade II-III requiring hospitalisation (i.e. serious cases) were more frequent in the buserelin group (4.7%) than in the Cetrotide™ group (1.6%). The amount of hMG ampoules used in patients with OHSS was similar to that used in all patients.

Additionally, in three (1.6%) of the Cetrotide™ patients and five (5.9%) of the buserelin patients the COS-cycle was cancelled and hCG was not administered because of too many follicles (12 with a diameter =15 mm) or too high or too rapidly rising E2 levels; these criteria were defined in the protocol in order to prevent cases of OHSS.

Reviewer's comments: Though it would appear that there is less OHSS with Cetrotide™, the variability of patient responsiveness and the variability of stimulatory "aggressiveness" between different fertility centers makes it difficult to apply a statistical test to the numbers alone.

6.9.3 Pregnancy and newborn adverse events

One stillbirth (causality not certain, but there was maternal hypertension and velamentous cord insertion, no fetal anomalies), six spontaneous abortions, and one ectopic pregnancy were reported in the Cetrotide™ treated patients. Patient #21/27 had intrauterine growth retardation diagnosed at 34 weeks gestation. This patient was also hospitalized for OHSS. One was a healthy male, while the other was an anencephalic male who died after 4 days.

6.9.4 Other adverse events

Injection site reactions were reported in 6 patients. Headache was reported in 3 patients. There were two reports of fever. The following events had just one report: back pain, dizziness, endometriosis, coughing, rhinitis, sinusitis, flu-like symptom, lymphadenopathy, and nausea.

6.9.5 Laboratory parameters

Liver enzymes were changes were reported in twelve patients (9 with Cetrotide™, 3 with buserelin). See Table 6.

Table 6: Enzyme elevation in study 3010

Pt. #	Pre-existing elevation at screening	Enzyme abnormality
21/02 Cet	No	
21/27	No	
21/29	Yes (OT, PT, GGT)	
22/305	Yes (Alk phos)	
23/18	Yes (PT, GGT)	
25/313	No	
27/14	No	
27/40	No	
27/56	No	
21/15 Bus	Yes (LDH)	
21/16 Bus	No	
24/19 Bus	No	

Reviewer's comments: Table 6 documents the enzyme changes observed in study 3010. The highest enzyme levels are included in the table. The levels are derived from either the day of oocyte pick-up or 6-8 days after embryo transfer. After excluding cases with pre-existing elevation, cases with creatine kinase elevation, and cases of OHSS there are 5/188 (2.6%) cases in the Cetrotide™ group and 1/86 (1.1%) cases in the buserelin group.

The difference in the Cetrotide™ and buserelin treatment arms in regard to enzyme analysis is not statistically significant (p= 0.733)

No significant changes were noted in the other biochemical and hematologic safety laboratory determinations.

6.10 Summary of study

A total of 181 patients in the Cetrotide™ group (96.3% of ITT), and 77 patients of the buserelin group (90.6% of ITT) reached the day of hCG. With Glasgow excluded 155/159 patients in the Cetrotide™ group (97% of ITT) and 67/74 patients in the buserelin group (91% of ITT) reached the day of hCG.

According to local laboratory data LH surges were prevented in 95.2% of Cetrotide™ patients and 97.6% of buserelin patients. The number of mature and metaphase II oocytes was similar in both groups. The number and quality of embryos retrieved and transferred was similar in both groups. The pregnancy rate was slightly higher in the buserelin treatment group.

Seventeen cases of OHSS were reported in this study with seven regarded as serious. The most common minor adverse event was injection site reaction. Enzyme elevations were reported in nine patients in the Cetrotide™ treatment arm and three in the buserelin treatment arm.

6.11 Reviewer's summary of safety and efficacy

Safety

The total number of OHSS cases and serious OHSS cases is higher than expected. This appears to be related to the level of controlled ovarian stimulation rather than treatment with Cetrotide™.

The etiology for the hepatic enzyme elevation is undetermined. It may relate in some way to controlled ovarian stimulation. Though not statistically significant, it occurred in a slightly higher percentage in the Cetrotide™ treatment arm.

The most common minor adverse event is injection site reaction.

Efficacy

This reviewer considers study 3010 as the primary study supporting the efficacy of Cetrotide™ 0.25mg multidose regimen in the inhibition of premature LH surges (which result in cycle cancellation). The agency agreed to look at cycle cancellation as the endpoint supporting this indication and to use an historical control for comparison.

The sponsor calculated a cycle cancellation rate of 5.3%. Inclusions of those subjects who received hCG despite having an LH surge and exclusion of subjects from the Glasgow site results in a cancellation rate of 7.5% for the Cetrotide™ treatment arm. This cancellation rate and that presented by the sponsor are both greater than 10% better (the pre-specified clinically meaningful difference) than the historical cycle cancellation rate derived from SART data. Therefore this study demonstrates the efficacy of the 0.25mg multidose regimen of Cetrotide™. The secondary parameters of LH surge data, oocyte retrieval, and pregnancy rates are acceptable and support efficacy.

7.0 Clinical Study 3020 (phase III, uncontrolled)

7.1 Objective

The study objective was to investigate the safety and efficacy of once daily subcutaneous injections of 0.25mg Cetrotide™ in patients undergoing COS/ART.

7.2 Design

The trial design for study 3020 is the same as that of 3010 except that there is no active comparator. This phase III study was to be conducted in 14 centers in 7 European countries and Israel and was designed as a prospective, non-controlled and open-label trial. Cetrotide™ was planned to be administered in a dose of 0.25 mg daily for COS/ART patients, starting from the 5th or 6th day of the administration of HMG until and including the day of ovulation induction.

7.3 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.
- 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 COS treatment.
- PAP smear of III or higher within 2 years prior to or at screening.
- Arterial hypertension: systolic blood pressure >150 mm Hg or diastolic blood pressure >90 mm Hg.
- Any significant cardiovascular, pulmonary, neurologic, allergic, hepatic, or renal disease at present or in the past, if recurrence of sequel is possible.
- History of alcohol or drug abuse.
- Any laboratory parameter (e.g. clinical chemistry, haematology) clinically relevant outside the normal range.
- Administration of investigational drugs within 60 days prior to screening.

7.4 Efficacy endpoints

Responders were defined as patients who reached the day of hCG.

Secondary parameters:

- Follicular development (by sonography)
- Number and quality of oocytes
- Fertilization results
- Cycle outcome (embryos, pregnancy rate, children follow-up)

7.5 Patient disposition

The center sites and patient distribution are shown in Table 7. Center # 09 did not start the trial due to internal reasons in regard to an ethics committee. Center number 01's data is being evaluated for safety only due to an internal audit which discovered data management problems at this site. This audit discovery was conveyed the FDA by the sponsor and was the subject of a pre-filing meeting.

Table 7: Patient disposition in study 3020

Country	Center #	Patients treated
Germany	01- Lubeck (excluded for efficacy)	43
Germany	02- Freiburg	11
Germany	03- Bonn	24
Germany	04-Erlangen	11
Austria	05-Vienna	30
Austria	06-Graz	24
France	07-Paris	27
Greece	08-Tessaloniki	47
Italy	09-Palermo	Not started
Italy	10- Milan	24
Italy	11-Bologna	17
Israel	12-Zerefin	40
Spain	13-Barcelona	19
Norway	14-Trondheim	29

7.6 Compliance and withdrawals

No dose of Cetrotide™ was missed in any patient.

7.7 Protocol violations

Twenty-four Cetrotide™ treated patients were listed as major protocol violators. The reasons listed were as follows

- Interval between last Cetrotide™ and hCG injection >38 hours = 4 patients
- First Cetrotide™ injection after HMG day 6 = 1 patient
- Progesterone at HMG day 1 exceeded 2ng/mL = 9 patients
- FSH at HMG day 1 exceeded 12 U/L = 10 patients

Reviewer's comments: These protocol violations should not impede the efficacy analysis, especially since including patients with increased progesterone and FSH might work against efficacy success.

7.8 Efficacy analysis

7.8.1 Ovarian stimulation

HMG was administered in all patients for a minimum of 6 and a maximum of 19 days; on average 10 days. All patients started with two ampules of HMG per day and almost all remained on that dose for five days as advised in the study protocol. (Exceptions: Patient #07/06 and #14/02 received only 1 ampoule on HMG day 5). Thereafter the stimulation procedure with respect to the amount of HMG administered per day was handled variably in the different centers. In some centers the daily dose of 2 ampules per day was given during the whole controlled ovarian stimulation program to nearly all patients. Otherwise in many centers the dosage was increased to 3 ampules or more, with a maximum of 8 ampules per day.

7.8.2 Cetrotide™ dosing

The mean exposure to Cetrotide™ was 4 days. All but six of 303 patients started 0.25mg of Cetrotide™ on HMG day 6.

7.8.3 HCG Administration

The hCG dose was 10000 IU in most of the patients; twelve patients received 5000 IU.

7.8.4 Luteal phase support

All patients with embryo transfer received luteal phase support, administered for a median of 13 days (between 2 and 35 days) after ET in

non-pregnant patients and for a median of 16 days (between 3 and 121 days) after ET in pregnant patients. Most centers prescribed progesterone suppositories in the majority of the cases. In some centers injections of between 1500 IU and 5000 IU hCG were given at one to four occasions.

7.8.5 Cycle cancellation and LH surge

Table 8: Cycle cancellation and LH surge in study 3020

Safety evaluable	346
# of pts with Lubeck excluded	303
LH surge (central lab), hCG given (no cancellation)	**3** = 03/07, 08/12, 08/19
Cancellation of controlled ovarian stimulation, no hCG	**12**
-- estradiol too low	7 (includes pt 12/23 listed below)
--follicle size insufficient	2 (includes pt 12/23)
--premature LH surge	2 08/04, 12/23
--too many follicles, estradiol too high	1
--too high FSH, recognized late	1
--non compliance	1
hCG given but oocyte retrieval failed	**5**
--estradiol too low	1
--IUI done instead of ART	1
--follicles collapsed	2
--no embryo transfer, risk of OHSS	1

The patients who had a central lab confirmed LH surge (or evidence of a surge locally, where central lab was not done) after starting Cetrotide™ and who received hCG are listed below:

Patient #03/07 was a 37 year old overweight woman (111kg) who demonstrated a low response to HMG for 12 days with the development of only 5 small (11-14 mm) follicles. An LH surge (LH 19.0/11.3 U/l, P 1.6/1.2 ng/ml; [local/central lab) was observed on the morning of Cetrotide™ day 13. After retrieval of one mature oocyte and one immature oocyte, IVF and ET procedure were done resulting in 2 excellent embryos but no pregnancy occurred. Cetrotide™ serum concentrations were never above LOQ.

Patient #08/04 who did not receive an hCG injection experienced an LH surge (LH: 20 U/l; progesterone: 1 ng/ml,-according to local lab; central lab not available) on Cetrotide™ day 2. This patient was considered one of

the major protocol violators since FSH at HMG day 1 exceeded 12 U/l. Apart from this she started HMG on cycle day 4 instead of cycle day 2 or 3 as stipulated in the study protocol. Finally the cycle was cancelled on HMG day 9 as the woman refused to continue ovarian stimulation.

Patient #08/12 was a 35 year old woman weighing 76 kg who showed low response to HMG after 12 days of stimulation with an estradiol level of 870 pg/ml (local lab) and 445 pg/ml (central lab), respectively. Six small follicles and 2 follicles of >15 mm were observed at this day. On the following day (day 8 of Cetrotide™ and scheduled for hCG), an LH surge (LH 15.5/10.8 U/l, P 2.0/1.5 ng/ml {local/central}) Eight mature oocytes resulted in 4 normally fertilised oocytes following IVF. No pregnancy was obtained after transfer of all 4 "good" embryos. Cetrotide™ serum levels were never above LOQ

Patient #08/19 was a 33 year old woman weighing 65kg who showed elevated P levels in the central lab analysis from the beginning (menstrual cycle day 3) (P 1.5 to 2.1 ng/ml; LH 2.8 to 12.8 U/l). On Cetrotide™ treatment day 5 an LH surge was seen at local lab (LH 12.1 U/l, P 2.8 ng/ml) confirmed by central lab (LH 12.8 U/l, P 2.1 ng/ml). On HMG day 12, hCG was mistakenly self-injected by the patient and stimulation procedure was stopped on the next day. Intrauterine insemination was undertaken two days later. No pregnancy was observed. Cetrotide™ serum concentrations were never above LOQ.

Reviewer's comments:

The sponsor discusses a cycle failure rate (cycle cancellation rate) for Cetrotide™ of 6.9% (21/303) to compare to the historical cycle cancellation rate derived from the Society of Assisted Reproductive Technology (SART) data. The historical cancellation rate data presented by SART represent those patients who got to oocyte retrieval. The sponsor's cycle cancellation rate for Cetrotide™ included twelve subjects who did not reach the day of hCG administration and nine subjects who failed oocyte retrieval.

However, as previously commented upon, the sponsor allowed hCG to be given to subjects (3 in this study) who had clearly demonstrated an LH surge. Therefore, it is the opinion of this reviewer that these subjects should be included as cycle failures despite getting to hCG and oocyte retrieval since this would have occurred in the historical controls.

The cancellation rate obtained when including these additional 3 subjects and excluding subjects contributed by the Glasgow site equals 7.9% (24/303). Even with using this "stricter" criteria for cycle failure the rate of 7.9% compares favorable to the historical SART data as will be discussed later in the review.

7.8.6 Pregnancy results

60 pregnancies were reported in the 303 treated patients (Lubeck excluded). This represents a pregnancy rate of 19.8%. Of these 60 pregnancies there were 16 sets of twins and one set of triplets. Patient #10/8 had an embryo reduction of a triplet to a twin pregnancy. In 57 deliveries there were 77 live births (live birth rate 77/303 = 25.4%)

7.9 Safety analysis

7.9.1 Total adverse events

A total of 78 adverse events were reported from the Cetrotide™ exposed patients. This includes 46 cases of OHSS and 32 other events listed below. The pregnancy and newborn adverse events are listed separately.

Reviewer's comments: 26 grade I cases of OHSS were recorded and 20 grade II-III cases of OHSS were recorded. Two study sites (#6 and #11) had OHSS rates of 75% and 59% respectively which is markedly disproproportional to rest of the COS/ART studies in this application. The data from these two sites is questionable with little correlation to either clinical findings or hormonal levels.

7.9.2 Serious adverse events

Five OHSS cases required hospitalization (patient #1/01, #1/37, #5/20, #6/23, and #8/10)

Reviewer's comments: These 5 cases required hospitalization. The total number of grade II-III cases of OHSS from this study is 20. There were 16 cases categorized as grade II and 4 cases categorized as grade III. Center #6 had a disproportionately high level of OHSS (75%). Of 24 patients, they reported one grade III, ten grade II and 7 grade I cases of OHSS. Only one of the cases from this center required hospitalization. Only one of the grade II-III patients from center #6 had an estradiol that exceeded 3,000pg/mL.

7.9.3 Pregnancy and newborn adverse events

Patient #35 from the Lubeck site had vaginal bleeding at 28 weeks along with findings of oligohydramnios and placental insufficiency.

Twelve spontaneous abortions were reported in 3020 study. There was one reported stillbirth caused by placental abruption in a subject with hypertension. There were no ectopic pregnancies. Patient 13/17 had an induced abortion because of the diagnosis of fetal diaphragmatic hernia.The remaining two infants from the embryo reduction were both found to have long QT syndrome.

Reviewer's comment: Long QT syndrome without deafness has been described as autosomal dominant and isolation of specific genetic loci have been reported. This result is not considered to be drug related.

No significant problems have been reported in the baby follow-up data received in the four month safety update.

7.9.4 Other adverse events

Non-serious adverse events included headache (3), nausea (3), and injection site reaction (6)

7.9.5 Laboratory abnormalities

Enzyme elevations were reported in twelve patients. See Table 9.

Table 9: Enzyme elevation in study 3020

Pt. #	Pre-existing elevation at screening	Enzyme abnormality
01/01	No	
01/10	No	
01/23	No	
01/32	No	
01/42	No	
05/01	No	
05/05	No	
06/23	No	
08/02	No	
08/05	Yes, but minimal SGPT=37 (9-36)	
12/03	No	
12/25	No	

Reviewer's Comment: When OHSS and pre-existing elevation are excluded the number of cases of enzyme elevation following Cetrotide™ initiation is 8/346 (2.3%) in study 3020.

There are no other significant laboratory abnormalities in the biochemical and hematologic safety laboratory determinations.

7.10 Summary of study

Three hundred and three (303) patients, undergoing ovarian stimulation received daily injections of 0.25 mg of Cetrotide™ starting on day 5 or 6 of stimulation . With respect to the primary endpoint, reaching the day of hCG and injection of hCG for final follicular maturation, a success rate of 96.0% (with 93.7% as one-sided 95%-lower confidence limit) was obtained. In 4% of patients a premature

LH surge occurred with respect to local (central) laboratory hormone determinations and in 2% of patients according to central laboratory. Only in three of the patients (1%) did this event result in the cancellation of the ovarian stimulation procedure. In all other patients, the number of mature (used for IVF) or metaphase II (for ICSI) oocytes retrieved was excellent. The same holds true for the number and quality of embryos retrieved and transferred.

60 pregnancies were reported in the 303 treated patients (Lubeck excluded). This represents a treatment cycle pregnancy rate of 19.8%.

5 cases of OHSS occurred requiring hospitalization (1.4%). Enzyme elevations were reported in 12 patients.

7.11 Reviewer's summary of safety and efficacy

Safety

20 grade II-III OHSS cases were reported in this study. Five required hospitalization. One center (#6) contributed 11 of these cases, none of which required hospitalizaton.

A similar percentage of enzyme elevation is reported in this study as found in 2997 and 3010. The most common minor adverse event is injection site reaction.

Efficacy

Study 3020 was the second study to look at the efficacy of the Cetrotide™ 0.25mg multidose regimen in the inhibition of premature LH surges. The reviewer considers this as secondary to the previous study because this was an uncontrolled study. As previously stated the Agency agreed to compare Cetrotide™ to an historical control for efficacy considerations. The sponsor's cancellation rate was 6.9%. Inclusions of those subjects who received hCG despite having an LH surge results in a cycle cancellation rate of 7.9%. This cycle cancellation rate and that presented by the sponsor are both greater than 10% better (the pre-specified clinically meaningful difference) than the historical cycle cancellation rate derived from SART data. This study is supportive of the efficacy of the 0.25mg multidose regimen of Cetrotide™. The secondary parameters of LH surge data, oocyte retrieval, and pregnancy rates are acceptable and support efficacy.

8.0 Clinical Study 3030 (phase III, controlled)

8.1 Objective

Investigate the efficacy and safety of a single SC injection of 3 mg Cetrotide™ in patients undergoing COS/ART in comparison to a single intramuscular injection of GnRH-agonist triptorelin.

8.2 Design

8.2.1 Overall design

This study was a prospective, randomised, open-label, 2 parallel-group design comparing a single Cetrotide™ subcutaneous dose of 3mg on HMG day 7 of a controlled ovarian stimulation versus a single 3.75mg intramuscular dose of triptorelin (a GnRH-agonist) given during the preceding mid-luteal phase. The randomization was 3:1 (Cetrotide™:triptorelin). The study was carried out in 8 sites in France.

The cancellation criteria, initiation of medication criteria, hormonal lab assessment, and safety evaluations were the same as study 3010.

8.2.2 Ovarian stimulation

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. HMG was given for the ovarian stimulation.

- Cetrotide™ patients: HMG should be started on day 2 of the menstrual cycle with the two ampules (150 IU each of FSH and LH) per day for the first four days; thereafter the HMG dosage could be adjusted by the investigator according to the individual needs. The protocol recommended to give one additional HMG ampoule the day of the 3 mg Cetrotide injection.

- Triptorelin patients: HMG should be started 15 days after the triptorelin injection with 2 to 3 ampules (150 to 225 UI each of FSH and LH). After the first four days the dosage could be adjusted by the investigator according to the individual needs.

8.2.3 Cetrotide™ treatment

Cetrotide™ was to be injected on day 8 of the cycle, i.e. day 7 of the HMG treatment. The morning of that day all assessments of the proceeding HMG day 5 should have been available. The original protocol stipulated that Cetrotide™ was to be administered on HMG day 7, and that this injection could be postponed, if the patient showed insufficient response to the HMG stimulation signified by estradiol levels still being below 400 pg/ml. This rule was changed by Amendment No. 2. Accordingly, Cetrotide™ should be injected any day the estradiol levels were above 400 pg/ml. Cycle cancellation would occur if the estradiol remained low.

The 3 mg dose of Cetrotide™ was to be administered once only after taking a blood sample for endocrine assessments. If triggering of the ovulation had not been done within 4 days after the 3 mg injection, daily subcutaneous injections were to be done using 0.25 mg Cetrotide™ from the fifth day onwards until the day of triggering (hCG injection).

8.2.4 Triptorelin treatment

Decapeptyl LP® 3.75 mg depot formulation for injection (containing triptorelin) was purchased from [redacted]

The day of administration of triptorelin (Decapeptyl LP® 3.75 mg) should be between day 18 and 22 (i.e. the midluteal phase) of the previous cycle. Triptorelin was to be administered intramuscular into the buttocks.

8.2.5 HCG administration

Human chorionic gonadotropin (hCG) was given in a single dose 10,000 IU for the induction of the ovulation and for the final maturation of the dominant follicles. It was to be administered as soon as at least 1 follicle with a diameter of >18 mm was observed by ultrasound, or the estradiol levels were >1,200 pg/ml. However, in case of 12 or more follicles with a mean diameter of >14 mm or an estradiol level >4,000 pg/ml, no hCG was to be administered and the cycle was to be cancelled. 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.

8.2.6 Oocyte retrieval, fertilization, embryo transfer

Follicles were to be punctured 30-36 hours after hCG administraton. IVF and ICSI fertilization procedures were to be performed and embryo transfer was to occur 48 hours following oocyte retrieval. A maximum of three embryos will be transferred per patient.

8.2.7 Luteal phase support

Luteal phase support was to be given by daily intravaginal administration of micronised progesterone (Utrogestan®). The start of luteal phase support was not specified.

8.3 Inclusion and exclusion criteria

The inclusion criteria are the same as the other phase III studies.

The exclusion criteria are the same as the other phase III studies, except that the abnormal pap smear exclusion was listed for three years instead of two years.

8.4 Efficacy endpoints

The primary parameter was defined as prevention of premature LH surge, signified by serum levels of LH ≥10 U/L together with progesterone ≥1ng/mL.

The secondary parameters included:

- Follicular development (by sonography)
- Number and quality of oocytes
- Cycle outcome (embryos, pregnancy rate, children follow-up)

8.5 Patient disposition

The study population and its distribution is listed in Table 10

Table 10: Patient disposition in study 3030

Country	Center #	Cetrotide™ pts	Triptorelin pts
France	1-Clamart	23	7
France	2-Sevres	17	6
France	3-Schiltigheim	10	5
France	4-Bordeaux	19	4
France	5-Montpellier	16	6
France	6-Bron	9	3
France	7-Paris (Salat-Barous	17	3
France	7-Paris (Zorn)	4	2

The total ITT population was 115 in the Cetrotide™ treatment arm and 36 in the triptorelin treatment arm.

8.6 Compliance and withdrawals

All patient received study medication at the appropriate time. Three triptorelin patients dropped out before HMG administration.

8.7 Protocol deviations

Ten Cetrotide™ treated patients were considered as major protocol violators for the following reasons:

- Cetrotide™ administration >24 hours after an estradiol level above 400pg/mL = 6 patients
- Progesterone level at HMG day 1 exceeded 2 ng/mL= 1 patient
- FSH at HMG day 1 exceeded 12U/L = 3 patients
- Last HMG administration > 2 days prior to hCG = 1 patient

Reviewer's comments: These protocol violations should not introdce a bias in favor of Cetrotide™ for efficacy, especially since including patients with increased progesterone and FSH might work against efficacy success.

8.8 Efficacy analysis

8.8.1 Demographics

No demographic differences appeared in the two treatment arms.

8.8.2 Ovarian stimulation

HMG was administered in all patients for a minimum of 7 and a maximum of 14 days (in most patients for 9 to 11 days). All Cetrotide patients started with two ampules of HMG per day; the HMG dose was increased to 3 or 4 ampules the day of the Cetrotide™ injection; most patients received again 2 ampules thereafter, while in the rest the HMG dosage remained at a level of 3 to 4 ampules then. Most triptorelin patients started with 3 ampules HMG per day. The number of days on HMG was lower in the Cetrotide™ group; this difference was statistically significant ($p < 0.001$, explorative testing, t-test). Moreover, the number of ampules used was clearly lower in the Cetrotide™ group than in the triptorelin group; this difference may not be explained by the longer duration of

stimulation in the triptorelin group.

8.8.3 Cetrotide™ treatment

One hundred fifteen patients received the initial "single dose" injection of 3 mg Cetrotide™. Nine of these patients (9.6%) also received one additional dose of 0.25mg Cetrotide™. Two patients (1.7%) receive two doses of 0.25 mg Cetrotide™ in addition to the 3.0mg dose.

The 3 mg Cetrotide™ injection was administered in most patients (41.7%) on the HMG day 7, and in 27% of the patients on HMG day 8. The range was 5 to 12 days.

Reviewer's comment: There was a range in the cycle day that Cetrotide™ was injected based on estradiol levels. This should be reflected in the label.

8.8.4 Triptorelin treatment

Thirty-nine patients received the scheduled 3.75mg depot form of triptorelin.

8.8.5 Cycle Cancellation and LH surge

The cycle cancellations and ART failures are listed in Table 11. There were no cases of LH surge occurring after Cetrotide™ administration. All the cases of LH surge occurred prior to Cetrotide™ treatment.

Cetrotide™ treated patients in study 3030

Table 11: Cycle cancellation in study 3030

Safety evaluable and ITT	115
LH surge (central lab), hCG given	0
Cancellation of controlled ovarian stimulation, no hCG	2
-- estradiol too low	1
--progesterone too high	1 (pt. 07/01)
Failed oocyte retrieval	0

Reviewer's comments: The sponsor discusses a cycle failure rate (cycle cancellation rate) for Cetrotide™ of 1.7% (2/115) in the

integrated summary of effectiveness (ISE). This is comprised of two cancellations where no hCG was given. The stricter criteria mentioned in the reviewer's comment from study 3010 and 3020 are not required in this analysis because there were no patients exhibiting an LH surge where hCG was given. The 1.7% cycle failure rate compares very favorably to the historical SART data as will be discussed later in the review.

8.8.6 Follicular development / hCG / oocyte retrieval

On HMG day 7 there were more small follicles (11-14 mm) in the Cetrotide™ patients than in the triptorelin patients. On the day of hCG, however, the number of small follicles was equal in both groups and the number of medium size follicles (15-17 mm) was somewhat larger in the triptorelin group. There was no difference with regard to the large follicles (18 mm) on the day of hCG.

Reaching the day of hCG was fulfilled in 98% of the Cetrotide™ ITT population and in all of the triptorelin population.

The mean number of mature oocytes obtained in the Cetrotide™ treated group was 7.3 per patient.

8.8.7 Fertilization

The fertilization rate was equal in both the Cetrotide™ and triptorelin treatment arms. IVF accounted for 90% of the Cetrotide™ treated arm with ICSI making up 10%.

8.3.8 Pregnancy results

The pregnancy rates for the Cetrotide™ treated arm are as follows:

- Per treatment cycle – 23%
- Per oocyte pick-up 23%
- Per embryo transfer – 26%

The pregnancy rate variation in the eight centers for the Cetrotide™ treated patients was 10-30%. There were 21 deliveries of 27 live births in the Cetrotide™ treatment arm (live birth rate is 27/115 = 23.4%)

The pregnancy rates for the triptorelin treated arm are as follows:

- Per treatment cycle – 31%
- Per oocyte pick-up – 31%

- Per embryo transfer – 33%

The pregnancy rate variation in the eight centers for the triptorelin treated patients was 0-67%

Reviewer's comment: The pregnancy rate variation (especially for triptorelin) can be explained by the low number of patients in some of the sites.

8.9 Safety analysis

8.9.1 Total adverse events

A total of 40 adverse events were reported including 4 OHSS, 29 injections site reactions and other minor adverse events listed below. The pregnancy and newborn adverse events are listed separately.

8.9.2 Serious adverse events

Eight cases of OHSS were reported in the study with four considered to be serious in nature. Two of the severe cases were in the Cetrotide™ treatment arm (1.7%) and two were in the triptorelin treatment arm (5.6%)

One case of serious abdominal infection occurred a day following oocyte retrieval. The patient was treated with analgesics, anti-inflammatory agents, and antibiotics.

None of these adverse events were considered to be directly related to Cetrotide™.

Reviewer's comments: The percentage rates for OHSS are: total (8/151= 5.2%) and serious (4/151 = 2.6%) Again for this study as in studies 2997 and 3010, the rates for OHSS exceeded those reported prior to clinical use of GnRH agonists.

8.9.3 Pregnancy and newborn adverse events

Three spontaneous and one induced abortion were reported. There were no stillbirths. Two ectopic pregnancies were reported.

8.9.4 Other adverse events

Injection site reaction is the only significant non-serious adverse event. Twenty-nine cases were reported in this study. One event each was reported for the following: abdominal pain, diarrhea, nausea, ovarian disorder, uterine inflammation, fever, and menstrual disorder.

Reviewer's comment: The proportionally higher number of injection site reactions in this study compared to study 3020 may be related to the volume of injection (3ml compared to 1ml)

8.9.5 Laboratory parameters

Liver enzymes changes were reported in three patients in the Cetrotide™ treatment arm. No enzyme changes were reported in the 39 patients of the triptorelin treatmen arm. See Table 12.

Table 12: Enzyme elevation in study 3030

Pt. #	Pre-existing elevation at screening	Enzyme abnormality
1/27	Yes	
2/11	No	(10-78) (38-126)
4/03	No	(1-25)

Reviewer's Comment: Excluding the pre-existing elevation there are 2/115 (1.7%) of patients in study 3030 with elevated enzymes following Cetrotide initiation.

8.10 Summary of study

This study confirms that co-treatment with a single dose of 3 mg Cetrotide™ during COS prevents LH surges in more than 95% of the cases. While 18 cases of LH levels above 10 U/l were observed in the Cetrotide™ group (local lab data) and three of them were to be classified as LH surge according to the protocol criteria, all these cases occurred just before the Cetrotide™ administration and two cases because of a delayed administration of CET. The average success rate of the COS, e.g. if assessed as number of patients in whom mature or metaphase II oocytes could be obtained, is 93% The respective success rate for triptorelin was slightly better at 94.4%

Eight cases of OHSS occurred. The incidence of OHSS was higher in the triptorelin group (11%; 5.6% being serious) than in the Cetrotide™ group (3.5%; 1.7% being serious). Enzyme elevations were reported in three patients in the

Cetrotide™ treatment arm and in no patient in the triptorelin treatment arm. Injection site reactions were the most common minor adverse event.

8.11 Reviewer's summary of safety and efficacy

Safety

The percentage of OHSS in this study is higher than the usual reported incidence. A lower percentage of enzyme elevation was seen in this study compared to 2997, 3010, and 3020.

Efficacy

The reviewer considers study 3030 as the primary study supporting the efficacy of Cetrotide™ 3.0mg single dose regimen in the inhibition of premature LH surges (which result in cycle cancellation). The primary endpoint listed for this study was absence of LH surge. There were no cases of LH surge after Cetrotide™ administration. Both the sponsor and the reviewer calculate a cycle cancellation rate of 1.7% This rate is greater than 10% better (the pre-specified clinically meaningful difference) than the historical cycle cancellation rate derived from SART data. This study is supportive of the efficacy of the 3.0mg single dose regimen of Cetrotide™. The secondary parameters of oocyte retrieval and pregnancy rates are acceptable and support efficacy.

9.0 Summary of DSI audit:

The final DSI report was not complete at the completion date of this review. It will be added as an attachment.

10.0 Four month safety update

Data in the four month report from additional ongoing studies did not indicate any additional safety concerns.

11.0 Postmarketing adverse events

Since its marketing in Europe, only one adverse event has been reported to the agency. This case is one of approximately 13,000 patients treated with Cetrotide™ outside clinical trials. Only limited information is available on this spontaneous report at this time and in May /June 2000 when this case was reported. Dyspnea and tachycardia were reported after the self-injection of the first dose of 0.25 mg Cetrotide™ by a patient (161 cm, 110 kg) with a history of asthma.

12.0 Labeling review

The following clinical points were emphasized in the labeling discussions:

- The determination of OHSS risk based on recording up to the time of pregnancy confirmation rather than the time of embryo transfer
- The presence of liver enzyme elevations
- The timing of the single dose regimen
- The inclusion of the case of anaphylaxis reported in the ovarian cancer study

The final suggested labeling is attached.

13.0 Reviewer's assessment of safety and efficacy

Safety

OHSS

The most serious safety concern in controlled ovarian stimulation protocols is ovarian hyperstimulation syndrome (OHSS). It is a potentially fatal complication. Capillary hyperpermeability underlies the varied clinical manifestations of ascites, pleural effusion, pericardial effusion, oliguria/renal failure, hemoconcentration, liver dysfunction and thomboembolic disease.

The WHO criteria for OHSS separates this syndrome into three grades. Grade I is characterized by excessive steroid secretion and ovarian enlargement (5-7cm) with mild degrees of abdominal discomfort. Grade II is characterized by distinct ovarian cysts (ovary size 8-10cm) accompanied by abdominal pain and tension, nausea, vomiting, and diarrhea. Grade III is characterized by ovary size greater than 10cm accompanied by ascites and occasional hydrothorax. Abdominal tension and pain may be severe in grade III cases. Hydrothorax may cause severe breathing difficulties. Fluid shifts result in hemoconcentration and increased blood viscosity.

The clinically important grades are II and III and these may result in hospitalization. The following table presents the numbers of moderate and severe cases of OHSS found in the 10 COS/ART studies submitted in the application.

Table 13: Moderate to severe OHSS in the COS/ART studies

Study #	# Exposed	WHO II or moderate intensity	WHO III or severe intensity	OHSS, not classified
0008	20	0	0	1 – No hCG given, not serious
0012	24	1	1	0
0009	21	0	0	0
93005	18	0	1	0
2986	65	0	0	0
2997	90	1	5	0
3097	62	0	0	0
3010	188	2	0	0
3020	346	16	4	0
3030	115	1	1	0
Totals	**949**	**21**	**12**	1

Though study 3020 had more patients exposed, there is a disproportionately high number of OHSS cases represented. Further analysis reveals that study center six from study 3020 had eleven of the twenty cases of moderate to severe OHSS presented in the table. The data from this center may be questioned due to lack of correlation with either clinical manifestations or estradiol levels. Only one patient was reported to be hospitalized. The estradiol levels from these eleven cases were not in ranges that correlate with OHSS. If center six is included, the rate of moderate to severe OHSS in the ten studies is 33/949 (3.5%). If data from center six (aside from the hospitalized patient) is excluded the rate is 23/949 (2.4%)

There is no evidence from this study that Cetrotide™ was directly related to OHSS. In fact, there was a suggestion in the comparative studies that OHSS was seen less often in the Cetrotide™ arm. This may have some relationship to the amount of stimulation required with agonist therapy. These comparative studies however were not powered or appropriately designed to assess superiority of Cetrotide™ over agonist in this regard.

The sponsor discussed use of additional Cetrotide™ if hCG is not given to reduce the risk factors for OHSS and also included this idea in the labeling. Though there may be some theoretical basis for this suggestion, it has not been demonstrated in an appropriately controlled prospective trial.

Enzyme changes

A separate report was submitted by the sponsor on the evaluation of liver enzyme elevations noted in studies of Cetrotide™. The numbers in Table 14 reflect all 10 COS/ART studies. In these 10 studies, 37/949 (3.8%) subjects were found to have one or more elevated enzymes. 34 of these 37 subjects received Cetrotide™ and 3

received buserelin. In some cases there was only a minimal elevation of one enzyme. The elevations ranged from 1.5-3 times the upper limit of normal. There was no evidence of hyperbilirubinemia or long term hepatic toxicity.

Table 14: Enzyme elevations in 10 COS/Art studies of Cetrotide™

Subjects in 10 COS/ART studies	949
Subjects with enzyme changes	37
Subjects taking buserelin	3/37
Cetrotide™ treated subjects in COS/ART trials who developed enzyme changes within 2 months of treatment (excluding pre-existing elevation at screening, OHSS, and creatine kinase elevation)	18/37

The sponsor lists some of these cases as "not assessable" due to the timing of the analysis in relation to the treatment. Though ideally, it would best to have more frequent analyses to more accurately look at the relationship to Cetrotide™ treatment, the causal effect of the drug in certain individual cannot be totally excluded and warrants mentioning in the drug label.

The effect of controlled ovarian stimulation is listed by the sponsor as a probable explanation of the enzyme elevations. This proposal does have merit because of the known relationship of abnormal liver enzyme in cases of ovarian hyperstimulation syndrome (OHSS). Though the etiology for this relationship is not known, it is certainly possible that lesser degrees of stimulation could cause the same effect.

The sponsor implicates that an elevated estradiol level may be responsible for the enzyme elevation. There is not a strong correlation with estradiol levels in all of these cases. In fact some of the estradiol levels are low in these cases. Perhaps some other substance (cytokines etc.) is responsible for the enzyme alteration. The effect also may not necessarily be entirely related to the liver. One published research paper recently found evidence of ovarian production of SGOT and SGPT in a controlled ovarian stimulation study.

After exclusions for pre-existing enzyme elevation, concurrent creatine kinase elevation and OHSS, enzyme elevations were found in 18 of the 949 patients in the ten submitted COS/ART studies for a rate of 1.9%.

It is reassuring to see that there was no evidence of bilirubin alteration in these patients. In some of the cases there was only one enzyme elevated. The highest elevation did not exceed three times the upper limit of normal. The cases that demonstrated pre-existing enzyme elevation only showed mild elevations and no

severe adverse events developed after Cetrotide™ treatment. Severe hepatic adverse events were not reported in the four month safety update.

Congenital Anomalies/ Chromosomal abnormalities

The following table lists the congenital and chromosomal abnormalities detected in the Cetrotide™ treated groups. The case of trisomy 18 resulted from a later study of unstimulated women undergoing ICSI (study 3046) This data was submitted by the sponsor after labeling discussions had begun.

Table 15: Congenital anomalies and chromosomal abnormalities in the Cetrotide™ COS/ART studies.

Study	Center	Pt	Fertiliz	Finding/Result
				major
2997	1	108	ICSI	Ventricular septal defect (liveborn)
2997	1	218	ICSI	Trisomy 21, +Klinefelter- TAB
2997	1	225	ICSI	Polymalformation-TAB
3010	22	16	IVF	Anencephalic male twin dies at 4 days, other male twin is healthy
3010	21	17	ICSI	Congenital glaucoma (liveborn)
3020	13	17	ICSI	Diaphragmatic hernia - TAB
3046			IVF	Trisomy 18 - TAB
				minor
2997	1	117	ICSI	Supernumerary nipple
3020	10	8	IVF	Prolonged Q-T in each twin (liveborn) Autosomal dominant inheritance
2997	1	122	ICSI	Congenital nevus
2997	1	125	ICSI	Hemangioma
2997	1	129	IVF	Bilateral strabismus
2997	1	220	ICSI	Congenital nevus, hemangioma
3010	24	20	ICSI	Imperforate hymen

Between 3-5% of all newborns have a recognizable birth defect. The percentage increases with detection of additional problems as the infant ages (to about 6-7%). Holmes documented that 2% of newborns have a serious malformation. The incidence of chromosomal abnormalities in newborn infants is approximately 1 in 150.

The percentage of severe newborn/infant malformations in the Cetrotide™ clinical trials is 1.3 % (3/223 liveborn) Inclusion of minor malformations increases the percentage to approximately 5.3% (12/223) The number of congenital malformations and chromosomal abnormalities does not exceed that of the general population.

The malformations and chromosomal abnormalities found prenatally and which resulted in therapeutic abortion are listed as TAB (therapeutic abortion) in the above table.

Aside from congenital nevi and hemangiomata all of the reported abnormalities were single events. The agonist control arm also had a twin pregnancy in which one of the twins was anencephalic and the other twin normal. The agonist control arm had a case of prenatally diagnosed fragile X syndrome.

Pregnancy complications

The overall abortion rate listed in the phase II and phase III studies of Cetrotide™ indicate an abortion rate of 15%. This compares to a 15% rate found in the German IVF registry of 1996 and a 19% rate found in the SART registry in 1994.

The 3.0% ectopic rate found in the phase II and phase III Cetrotide™ trials compares to the 2.4% ectopic rate in the German 1996 registry and the 4.0% rate found in the SART 1994 registry.

Minor Adverse Events

Injection site reaction was the most common minor adverse event. It was primarily manifested by erythema and occasionally associated with itching. The reaction was transient lasting minutes to hours. No nodular formation or long term skin effects were demonstrated. The reaction was noted far more commonly in the phase I studies than in the phase II and III studies. Some of this difference may be related to the volumetric amounts and some related to the fact that individual researchers may not have recorded minor amounts of erythema. Other rarely reported minor adverse events include nausea and headache.

Efficacy

There are four major efficacy analysis issues in regard to Cetrotide™.

First there was no approved antagonist at the time of Cetrotide™ clinical trials to allow for a blinded study with a comparable drug. Ganirelix (Antagon) was approved in the summer of 1999.

Second, [redacted] This use developed off-label and is presently employed in the majority of infertility clinics. In the late 1980's and early 1990's the use of [redacted] was reevaluated. Some researchers felt that the agonists had practical (scheduling) advantages but no significant medical advantages over non-GnRH agonist protocols. The bulk of the comparative studies plus a 1992 meta-analysis; however, indicated that agonist use not only leads to a lower cancellation rate but also provided a greater number of oocytes and a higher pregnancy rate. The impact of scheduling benefits should not be downplayed. Protocols and medications that allow some predictability in infertility management theoretically provide emotional benefits to infertile patients in addition to allowing the clinic to run more efficiently.

Third, the use of historical controls to aid in efficacy analysis has definite weaknesses. It depends on non-study report data dating back 15 years. Cycle cancellation rates were probably higher particularly in the early to mid- 1980's due not only to poor response and prematue ovulation but also to an individual site's lack of experience, less exact sonographic and hormonal testing, and the influence of more laparoscopic oocyte retrievals affecting decisions.

Fourth, there are problems with the sponsor's selecting "reaching the day of hCG" as the primary endpoint. Although this was initially accepted by the agency in addition to confirmatory secondary endpoints (ie, pregnancy rates etc.) this endpoint analysis has the potential for making any COS medication appear better than it really is. Even if patients have poor follicular development and/or LH surges, but go on to receive hCG anyway they would end up qualifying for efficacy. Additionally "reaching the day of hCG" cannot be compared to SART historical data because SART did not record this data. Following further discussion the, use of cancellation rates (no oocyte retrieval) were accepted for comparison to SART historical data.

Despite these four major issues, the sponsor has demonstrated efficacy for Cetrotide™ throughout its phase III trials in regard to the cancellation rates compared to historical controls. All showed results that were 10% better than historical controls. Depending on the years evaluated the cycle cancellation rates in the historical controls varied from 22-28%. The lower figure represents data from 1989-90 when more GnRH agonists were used in the protocols. The cycle cancellation rates for the Cetrotide™ 0.25mg multidose regimen (studies 3010 & 3020) using the reviewer's strict analysis were 7.5% and 7.9% respectively. The cycle cancellation rate for Cetrotide™ 3.0 single dose regimen was 1.7%

Additional support for the efficacy of Cetrotide™ is derived from the assessment of daily LH and progesterone levels throughout the study. These laboratory values confirmed Cetrotide's™ ability to prevent and suppress LH surges that occur during controlled ovarian stimulation protocols. The pattern of premature ovulation, luteinization, and poor oocyte quality that was found in the 1980's did not occur in the patients receiving Cetrotide™. Therefore, premature ovulation which accounted for a large component of cycle cancellation in the past becomes negligible with antagonist therapy. The other secondary parameters of oocyte retrieval, fertilization data, and pregnancy rates also support efficacy.

Rare LH surges occurred (6/462, 1.3%) after the initiation of the 0.25mg daily dose, but even then most patients still have appropriate follicular development and can still reach the point of hCG injection and oocyte pick-up. Analysis of case report data in the phase III studies does not clearly establish why the 0.25mg dose rarely allows an LH surge to develop. Some of the patients were markedly obese and others had a recent increase in the level of HMG provided. Because the surge only rarely happens and because oocyte pick-up is not significantly affected with the surge, the 0.25mg dose is the appropriate level to use for the daily multidose regimen.

The phase III studies indicated that an LH surge is sometimes already underway before Cetrotide™ is given. Most of the patients were started on stimulation day 6. It was found that initiation of the Cetrotide™ at this point would usually correct the surging process and allow for hCG and oocyte pick-up. Alternatively as suggested by the sponsor labeling, Cetrotide™ could be initiated on stimulation day 5. The controlled ovarian stimulation protocols by necessity require a lot of individual assessment and adjustments in medication timing and dosage.

14. 0 Recommended regulatory action

The 3.0mg and 0.25mg dosage regimens for Cetrotide™ are recommended for approval for inhibition of premature LH surges in women undergoing controlled ovarian stimulation/assisted reproductive technology.

/S/

Gerald D. Willett, MD
Medical Officer 7/27/00

/S/

Shelley R. Slaughter, MD, PhD
Concurrence
Team Leader 7/28/00

cc: Division File NDA 21-197
Susan Allen, MD
Marianne Mann, MD
Daniel Shames, MD
Shelley R. Slaughter MD, Ph.D
Lisa Kammerman, Ph.D
Jeanine Best

NDA 21-197
Cetrotide™ (cetrorelix acetate for injection)
ASTA Medica, Inc.

Safety Update Review, See Medical officer Review, P. 65

APPEARS THIS WAY
ON ORIGINAL