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A Non-interventional Study of postoperative treatment with Goserelin acetate (Zoladex) in moderate to severe endometriosis patients

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NIS REPORT SYNOPSIS

A Non-interventional Study of post-operative treatment with Goserelin acetate (Zoladex) in moderate to severe endometriosis patients

Study Centres:

This study was conducted in 15 centers in China.

Publications:

None at the time of writing this report

Objectives

Primary:

- To assess the efficacy of post-operative treatment with Zoladex in moderate to severe endometriosis patients in terms of pelvic symptom recurrence rate and total recurrence rate(including pelvic symptom and physical findings) after 18 months since operation.

Secondary:

- To assess the pregnancy rate of infertile subjects receiving post-operative Zoladex treatment after 18 months since operation.
- To collect the information of the administration of Zoladex after operation for the subjects with moderate to severe endometriosis.
- To collect the information of add-back therapy for the subjects with moderate to severe endometriosis and used Zoladex after operation.

Study Design

This was a multi-centre, open-label, non-interventional study to evaluate the efficacy of post-operative treatment with Zoladex in moderate to severe endometriosis patients, which enrolled 426 subjects and was conducted in 15 centers in China.

The patient must sign the Informed Consent Form before any study related activity (e.g., filling out evaluation form) will be performed.

Before the patient recruitment, the investigator has decided to prescribe Zoladex as adjuvant treatment to the patient, which is separated from the patient recruitment. Patient who will fulfil all inclusion/exclusion criteria at visit 1 will enter this study, and the patients symptom

score and pregnant need also be recorded at visit 1. visit 2 (3 months post operation), visit 3 (6 months post operation), visit 4 (12 months post operation) and visit 5 (18 months post operation. The definition of last visit is Visit 5 or the time with confirmed disease relapse or pregnancy. Based on locally clinical practice, approximately 60-80% of patients are treated with GnRHa for 3 months. (Please refer the relative paragraph in local or national guideline on endometriosis diagnosis and treatment).

During Visit 1~5, symptom score will be collected according to physician's judgement and recorded in Out-patient medical records.

Target Subject Population and Sample Size

The target subject population were moderate to severe endometriosis confirmed histologically (r-AFS score III-IV) with laparoscopy or laparotomy.

The primary endpoints for this study were the pelvic symptom recurrence rate and the total recurrence rate at the last visit. No tests were conducted and the results primarily presented those rates and their 95% confidence intervals (CI). Assuming the rate is about 15%, to guarantee the width of half 95% CI is less or equal to 3.9% we needed almost 320 evaluable subjects by the formula $1.96 \times \sqrt{\frac{\pi(1-\pi)}{n}} = 3.9\%$. The total enrolled subjects should achieve 400 under the assumption of 20% drop out. If the rate is lower than 15%, the sample size would be even smaller to achieve the same accuracy.

Investigational Product Dosage Form and Strength and Manufacturer

No drug was supplied from AstraZeneca for this non-interventional study. Any drug that needed to be used would be decided and prescribed by investigator.

Zoladex depot 3.6mg, administered subcutaneously every 4weeks for 3-6months, AstraZeneca. (Recommended by the guideline and clinical practice).

Duration of Treatment

Duration of the treatment ranged from 1 to 6 months depending on the number of vials of Zoladex that each subject had been administered, as Zoladex was administered every 4 weeks.

Criteria for Evaluation

Efficacy

- Primary variable: The symptom recurrence rate and the total recurrence (including total pelvic symptoms and physical findings) rate at the last visit (visit 5 or the visit with confirmed endometriosis recurrence).

- Secondary variables:

  - Pregnancy rate of four subgroup subjects after operation at visit 5(or last visit)

- The information of Zoladex administration: time from surgery to Zoladex prescription date; the proportion of subjects who prescriped Zoladex by menstrual cycle or not; total doses of Zoladex;

- The information of add-back therapy: the proportion of subjects who had add-back therapy; the proportion of subjects who used add-back therapy concomitant with Zoladex; the category of add-back therapy and the proportion of subjects in each category.

Safety

No safety variables were analyzed since this study did not evaluate the safety of Zoladex.

Statistical Method

The primary and secondary variables were summarized for both FAS (Full Analysis Set) and PPS (Per Protocol Set) subjects associated with 2-sided 95% confidence intervals of the rates. No test was performed and efficacy variables were presented with the number and percentage of subjects who had confirmed recurrence.

The administration of Zoladex and the information of add-back therapy were summarized descriptively.

FAS subjects were all subjects who enrolled in this study and took at least one vial of Zoladex. PPS subjects were those in FAS without major protocol violations or deviations.

Subject Population and Disposition

The subject population and disposition were summarized in Table S1(please see the next page). The study planned to enroll 400 subjects and actually enrolled 426 subjects, among whom 414 subjects were included in FAS and 410 subjects in PPS.

Table S1. Subject Population and Disposition (all enrolled subjects)

	Enrolled patients *(N=426)*
Enrolled patients	426(100.0%)
FAS	414(97.2%)
Patients removed from FAS	12 (2.8%)
Violated incl. criterion 1：Advanced endometriosis confirmed histologically (r-AFS score III-IV) with conservative laparoscopy or laparotomy	1 (0.2%)
Violated incl. criterion 2：Patient who has the indication of Zoladex and has been prescribed Zoladex according to physician's judgement, irrespective of the inclusion in the study	3 (0.7%)
Study drug use unknown	8 (1.9%)
PPS	410(96.2%)
Patients removed from PPS	16 (3.8%)
Missing visits	4 (0.9%)
Violated incl. criterion 1：Advanced endometriosis confirmed histologically (r-AFS score III-IV) with conservative laparoscopy or laparotomy	1 (0.2%)
Violated incl. criterion 2：Patient who has the indication of Zoladex and has been prescribed Zoladex according to physician's judgement, irrespective of the inclusion in the study	3 (0.7%)
Study drug use unknown	8 (1.9%)

Notes: Denominator of percentage is the number of patients in the analysis set. Patients who missed data of all the visits after drug distribution were categorized into Study drug use unknown.

	Enrolled patients

Demographics and Baseline Characteristics

The demographics and baseline characteristics of FAS subjects were summarized in Table S2. With regard to endometriosis severity score, 213 patients （51.4%） were r-AFS III, and 201 （48.6%）were r-AFS IV, all in the category of moderate to severe endometriosis. The mean of baseline VAS score was 4.8 with range from 0 to 10. This fact showed the most FAS subjects suffered from obvious pain at the start of study.

Table S2. Demographics and Baseline Characteristics (FAS)

		FAS (N=414)
Age （years）	Mean (S.D)	32.5 (6.27)
	Min ~ Max	19 ~ 53
Pregnancy need (n and % of subjects)	No	248 (59.9%)
	Yes	166 (40.1%)
rAFS score of endometriosis (n and % of subjects)	Ⅲ	213 (51.4%)
	Ⅳ	201 (48.6%)
Infertility history (n and % of subjects)	No	351 (84.8%)
	Yes	63 (15.2%)
VAS score	Mean (S.D)	4.8 (3.00)
	Min ~ Max	0 ~ 10

Efficacy Results

Primary Variables

The primary endpoints, the symptom recurrence rate and the total recurrence rate at the last visit, were presented below for both FAS and PPS subjects in Table S3. After 18 months study 34 cases were reported with endometriosis recurrence accounting for 8.2% of FAS subjects. Among the 34 recurrence cases, 23 were confirmed by pelvic symptom which accounted for 5.6% of FAS subjects. Little difference was demonstrated between the results of PPS and FAS subjects.

Table S3. Symptom Recurrence Rate and Total Recurrence Rate at the Last Visit (FAS/PPS)

	FAS (N=414)		*PPS(N=410)*	
	n(%)	*95%CI*	*n(%)*	*95%CI*
Pelvic symptom recurrence rate (n and % of subjects)	23 (5.6%)	3.6% , 8.2%	23(5.6%)	3.6% , 8.3%
Total recurrence rate (n and % of subjects)	34 (8.2%)	5.8% , 11.3%	34(8.3%)	5.8% , 11.4%

Secondary Variables

In terms of secondary objectives, the pregnancy rates were summarized considering the classification of infertility histories and pregnancy need in Table S4. Subjects were categorized into 4 subgroups by their answers to the infertility history and pregnancy need in CRF. The highest pregnancy rate of 33.3% was observed in the subgroup consisting of subjects with both infertility history and pregnancy need.

Table S4. Pregnancy Rates at Last Visit (FAS/PPS)

	FAS (N=414)		*PPS (N=410)*	
	n(%)	*95 %CI*	*n(%)*	*95 %CI*
Pregnancy rate [1] (n and % of subjects)	18(33.3%)	21.1% , 47.5%	18(33.3%)	21.1% , 47.5%
Pregnancy rate [2] (n and % of subjects)	1(11.1%)	0.3% , 48.2%	1(11.1%)	0.3% , 48.2%
Pregnancy rate [3] (n and % of subjects)	26(23.2%)	15.8% , 32.1%	26(23.4%)	15.9% , 32.4%
Pregnancy rate [4] (n and % of subjects)	4(1.7%)	0.5% , 4.2%	4(1.7%)	0.5% , 4.3%

Denominators for each item：
Pregnancy rate 1: Patients with infertility history and with pregnancy need, the denominators of FAS and PPS are both 54；
Pregnancy rate 2: Patients with infertility history and without pregnancy need, the denominators of FAS and PPS are both 9；
Pregnancy rate 3: Patients without infertility history and with pregnancy need, the denominator of FAS is 112 and the denominator of PPS is 111；
Pregnancy rate 4: Patients without infertility history and without pregnancy need, the denominator of FAS is 239 and the denominator of PPS is 236； Every patient in FAS and PPS has pregnant status at the last visit.

The information of administration of Zoladex included several aspects. The accordance of medication with menstrual cycle and the total doses used were both presented descriptively in Table S5. Slightly more subjects were administered Zoladex based on their menstrual cycle than those who were not. Most subjects (96.9% of FAS subjects) took no less than 3 vials Zoladex.

Table S5. Administration of Zoladex (FAS/PPS)

		FAS (N=414)	*PPS (N=410)*
Medication by menstrual cycle (n and % of subjects)	No	190 (45.9%)	188 (45.9%)
	Yes	224 (54.1%)	222 (54.1%)
Total dose (vials)	Mean (S.D)	4.0 (1.28)	4.0 (1.28)
Total dose (n and % of subjects)	1	5 (1.2%)	5 (1.2%)
	2	8 (1.9%)	8 (2.0%)
	3	195 (47.1%)	193 (47.1%)
	4	93 (22.5%)	92 (22.4%)
	5	16 (3.9%)	15 (3.7%)
	6	97 (23.4%)	97 (23.7%)

The add-back therapy were summarized in Table S6, including both the number of subjects with add-back therapy and its relation with Zoladex administration. There are 114 subjects (27.5% of FAS subjects) who had add-back therapy and 27 of them (23.7% of subjects with add-back therapy) had their therapy concomitant with Zoladex administration.

Table S6. Summary of Add-back Therapy

		FAS (N=414)	*PPS (N=410)*
Proportion of add-back treatment (n and % of subjects)	No	300 (72.5%)	297 (72.4%)
	Yes	114 (27.5%)	113 (27.6%)
Concomitant with Zoladex (n and % of subjects)	No	87 (76.3%)	86 (76.1%)
	Yes	27 (23.7%)	27 (23.9%)
	Total	114 (100.0%)	113 (100.0%)

Safety

No safety variables were presented because the safety of Zoladex was not evaluated in this study. No SAE was reported during the study phase.