2. SYNOPSIS

Title of the study	Randomized, open label, multicenter, phase II study on pharmacokinetics, pharmacodynamics, efficacy and safety of Goserelin 3M implant HEXAL in patients with advanced prostatic cancer in comparison to Zoladex® 10.8 mg
Investigators	• Coordinating Investigator : [redacted] • Center 11 ([redacted]) : • Center 12 ([redacted]) : • Center 13 ([redacted]) : • Center 14 ([redacted]) : • Center 15 ([redacted]) : • Center 16 ([redacted]) : • Center 17 ([redacted]) : • Center 18 ([redacted]) : • Center 21 ([redacted]) : • Center 22 ([redacted]) : • Center 23 ([redacted]) : • Center 24 ([redacted]) : • Center 31 ([redacted]) : • Center 32 ([redacted]) : • Center 41 ([redacted]) : • Center 42 ([redacted]) : • Center 43 ([redacted]) :
Study centers	17 centers in Bulgaria (8), Lithuania (4), Ukraine (2), and Serbia and Montenegro (3)
Publication (reference)	–
Study period	Date of first patient enrolled : 30/08/2005 Date of last patient completed : 16/05/2006
Phase of development	II
Objectives	The aim of the study is to compare pharmacodynamics, pharmacokinetics, efficacy and safety of Goserelin 3M implant HEXAL, newly developed by HEXAL, with the approved drug Zoladex® 10.8 mg, AstraZeneca GmbH, in the palliative treatment of advanced prostatic cancer.
Methodology	Open label, controlled, multiple dose study versus an approved drug involving patients with advanced prostatic cancer treated with two consecutive applications every 12 weeks.
Number of patients	• Planned : N= 90 (2x45), N=80 evaluable (2x40) • Screened : N=146 • Treated : N=115 (59/56)[1] • Completers : N= 56 (5/51). On December 19th, 2005, the study was stopped in the GOS group due to inadequate response to treatment (sponsor's decision). Only 5 GOS patients received a second application.
Diagnosis and main criteria for inclusion	Histologically confirmed advanced adenocarcinoma of the prostate stage $T_{3-4}N_0M_0$, $T_{1-4}N_1M_0$ or $T_{1-4}N_{0-1}M_1$, newly diagnosed or recurrent. Morning testosterone level $\geq$ 2.3 ng/mL at screening.

[1] 1st number: Goserelin 3M implant HEXAL / 2nd number: Zoladex® 10.8 mg

Test product	Goserelin 3M implant HEXAL
Dose	11.3 mg goserelin acetate (corresponding to 10.8 mg goserelin)
Mode of administration	Depot implant for s.c. injection
Batch no.	50304/1, 50304/3
Duration of treatment	24 weeks, 2 administrations at weeks 0 (day 1) and 12 (day 85).
Reference therapy	Zoladex® 10.8 mg
Dose	11.3 mg goserelin acetate (corresponding to 10.8 mg goserelin)
Mode of administration	Depot implant for s.c. injection
Batch no.	CE683/1, CG483/1
Criteria for evaluation	
Efficacy	**Primary endpoint** Testosterone suppression after goserelin application: • Proportion of patients whose testosterone levels were successfully suppressed within 8 weeks after first administration and whose testosterone levels remained below or equal 0.50 ng/mL until week 12 (except for escapes). **Secondary endpoints** • Proportion of patients whose testosterone levels were successfully suppressed within 8 weeks after first administration and whose testosterone levels remained below or equal 0.50 ng/mL until week 24 (except for escapes) • Weekly testosterone levels • Time to onset of castrate level • Proportion of patients with relevant escapes of testosterone levels • Change in prostatic status (digital rectal examination) at weeks 12 and 24 as compared to screening visit • Change in serum PSA and PAP levels at weeks 4, 8, 12, 16, 20, and 24 as compared to week 0 • Subjective response on the basis of ECOG performance scale • Subjective clinical symptoms attributable to prostate cancer (dysuria, nycturia, bone pain) • Overall efficacy as judged by the investigator. *Definitions:* • *Defining a successful testosterone suppression 'until week W' as at least 2 consecutive testosterone values ≤ 0.50 ng/mL within the first 8 weeks **and** levels ≤ 0.50 ng/mL until week W, the primary endpoint is defined as proportion of patients whose testosterone values were successfully suppressed until week 12 (except for escapes)* • *Suppression: at least 2 consecutive testosterone values ≤ 0.50 ng/mL* • *Escape: testosterone level > 0.50 ng/mL for one or maximum two consecutive samples after achieving suppression, followed by at least one value again ≤ 0.50 ng/mL* • *Relevant escape: testosterone level > 0.50 ng/mL for **two** consecutive samples after achieving suppression, followed by at least one value again ≤ 0.50 ng/mL* • *Time to onset of castrate level: time from 1st administration of goserelin to the first suppressed testosterone value.*

Criteria for evaluation *[cont.]*	
Pharmacodynamics	• Pharmacodynamic profile of testosterone within 7 days after first administration.
Pharmacokinetics	• Pharmacokinetic profile of goserelin over 6 hours after administration • Pharmacokinetic profile of goserelin within 7 days after administration • Development of goserelin concentration over the course of study.
Safety	• Incidence and severity of all and of all drug-related adverse events (including the analysis of adverse events by body system: number of patients / number of patients involved / percentage) • Incidence and severity of local reactions at the injection site • Incidence of serious adverse events • Changes in safety laboratory at week 24 compared to screening visit • Number of patients who needed antiandrogens because of flare symptoms • Changes in vital signs up to week 24 compared to week 0 • Changes in concomitant medication up to week 24 compared to week 0 • Change in ECG at week 24 compared to screening visit • Overall tolerability as judged by the investigator and patient.
Statistical methods	• Descriptive statistics for continuous variables • Frequency distributions for categorial variables • Shift tables for changes from baseline in categorial variables • Kaplan-Meier-plots for time to onset of castrate level. Due to study cessation in the Goserelin 3M implant HEXAL trial group, it is not indicated to perform analytical statistics. All analyses were carried out in the Intention-To-Treat set (ITT). This population represents at the same time the All-Patients-Randomized set, the All-Patients-Treated set, and the Safety-Evaluable set.
Efficacy results	➢ Successful testosterone suppression until week 12 – *ITT, primary endpoint* • Goserelin 3M implant HEXAL : 37/59 (62.7%) • Zoladex® 10.8 mg : 55/56 (98.2%). ➢ All patients achieved suppression, i.e. at least two consecutive testosterone values ≤ 0.50 ng/mL, except for sc.no./pat.no. 4104/14 who was identified as treatment failure. ➢ The time to onset of castrate level ranged between 2 and 4 weeks, except for 1 belated suppression upon GOS at week 6. ➢ After suppression was achieved, the rates of relevant escapes were • Goserelin 3M implant HEXAL : 3/58 (5.2%) • Zoladex® 10.8 mg : 1/56 (1.8%). ➢ At week 24, 3/5 GOS-treated patients showed successfully suppressed testosterone levels (60.0%). In the REF group the rate amounted to 48/52 (92.3%).

Efficacy results *[cont.]*

➢ The digital rectal examination yielded normalized findings in the following proportion of patients with abnormal pre-treatment values:

DRE parameter	GOS	REF
Smooth surface of the prostate	18/49 (36.7%)	18/44 (40.9%)
Mobile rectum over the prostate	11/27 (40.7%)	9/21 (42.9%)
Normal size of the prostate	15/51 (29.4%)	13/48 (27.1%)

Changes from normal to abnormal occurred in both groups in isolated cases only.

➢ In patients with positive diameter of the tumor lesion in the TRUS examination, the improvement rates were

- Goserelin 3M implant HEXAL : 43/51 (84.3%)
- Zoladex® 10.8 mg : 38/46 (82.6%).

Seven patients of each group showed increased diameters.

➢ The prostatic status showed the following development:

Judgment of tumor remission	GOS [N=58]	REF [N=56]
returned to normal	4 (6.9%)	3 (5.4%)
> 50% improved	29 (50.0%)	37 (66.1%)
similar to baseline	25 (43.1%)	16 (28.6%)
> 25% worsened	–	–

No relevant deteriorations were detected.

➢ The ECOG performance status showed only isolated changes from baseline.

➢ In the majority of patients the subjective symptoms remained unchanged or improved in patients affected. Isolated deteriorations were seen in comparable frequencies in both trial groups.

➢ Twelve weeks after the first application the mean changes from baseline in PSA and PAP were determined as follows:

Parameter		Goserelin 3M implant HEXAL			Zoladex® 10.8 mg		
		N	mean	SD	N	mean	SD
PSA	[ng/mL]	56	–31.76	66.76	56	–20.03	111.56
PAP	[ng/mL]	56	–3.91	12.11	56	–17.25	93.18

[PSA: Prostate Specific Antigen
PAP: Prostatic Acid Phosphatase].

➢ With regard to endocrine profile and SHBG similar courses were observed in both groups except for

- LH : 7 increased values only in the GOS group
- estradiol : 9 increased values only in the GOS group.

Pharmacodynamics	The pharmacodynamic estimates of testosterone within 7 days after application of Goserelin 3M implant HEXAL and Zoladex® 10.8 mg showed no relevant differences between both trial groups.
Pharmacokinetics	The course of goserelin over 7 days after application of GOS and REF yielded markedly higher levels of AUC and C_{max} upon GOS.
Safety results	➢ 32 (54.2%) patients treated with Goserelin 3M implant HEXAL and 26 (46.4%) patients treated with Zoladex® 10.8 mg experienced adverse events. ➢ In 16 patients (27.1%) 17 adverse events were suspected to be caused by Goserelin 3M implant HEXAL. The following MedDRA[2] Preferred Terms were involved: • Hot flush : N=10 • Dysuria : N= 2 • Flushing : N= 2 • Androgen deficiency : N= 1 • Anxiety : N= 1 • Hypertension : N= 1. ➢ In the reference group, 18 patients (32.1%) experienced 20 adverse events suspected to be related to Zoladex® 10.8 mg: • Hot flush : N=15 • Flushing : N= 2 • Injection site hemorrhage : N= 2 • Dysuria : N= 1. ➢ One patient (GOS) died caused by sudden dyspnea after previous hospitalization due to fractura colli femoris. Two further patients (GOS) experienced serious adverse events in form of hospitalizations, too. The SAEs were not suspected to be related to the study medication. ➢ Regarding the profile of lab changes in both trial groups as well as the changes in vital signs, body weight, ECG, and physical findings, no relevant differences were detected except for hemoglobin, erythrocytes, and hematocrit which showed stronger decreases upon Zoladex® 10.8 mg.

[2] MedDRA: Medical Dictionary for Drug Regulatory Activities

Safety results *[cont.]*

➢ The tolerability was judged by the patient as follows:

Judgment	GOS [N=59]	REF [N=56]
very good	36 (62.1%)	35 (63.6%)
good	20 (34.5%)	19 (34.5%)
indifferent	2 (3.4%)	1 (1.8%)
bad	–	–
very bad	–	–
missing values	1	1

➢ The tolerability was judged by the investigator as follows:

Judgment	GOS [N=59]	REF [N=56]
very good	35 (60.3%)	37 (67.3%)
good	22 (37.9%)	17 (30.9%)
indifferent	1 (1.7%)	1 (1.8%)
bad	–	–
very bad	–	–
missing values	1	1

➢ Overall, there was no substantial difference in safety profile between Goserelin 3M implant HEXAL and Zoladex® 10.8 mg.

Conclusions

Testosterone suppression, defined as occurrence of two consecutive levels lower than or equal to 0.50 ng/mL, was achieved in all patients except for sc.no./pat.no. 4104/14 who was identified as treatment failure. But the testosterone-lowering effect of GOS was not stable in an unacceptably high number of patients. Therefore, it was decided to discontinue the administration of Goserelin 3M implant HEXAL. Only 5 patients received the 2nd application at week 12.

In the Goserelin 3M implant HEXAL study group the rate of successful suppression until week 12 amounted to 37/59 (62.7%). The corresponding result upon Zoladex® 10.8 mg was 55/56 (98.2%).

In 5 patients who received two applications of Goserelin 3M implant HEXAL the rate of successful testosterone suppression until week 24 was 3/5. Summarizing, the study 2005-01-IMP-2 established the efficacy of Goserelin 3M implant HEXAL in approximately 60% of the patients only.

Regarding the safety profile, no substantial differences between Goserelin 3M implant HEXAL and Zoladex® 10.8 mg were revealed.