2. Synopsis of Study Report

NAME OF COMPANY **HEXAL AG** **NAME OF FINISHED PRODUCT:** **Goserelin 10.8 mg Implant HEXAL** **NAME OF ACTIVE INGREDIENT(S):** **goserelin acetate**	**INDIVIDUAL STUDY TABLE REFERRING TO CLINICAL DOCUMENTATION OF THE DOSSIER:** **Volume:** **Page:**	*(FOR NATIONAL AUTHORITY USE ONLY)*

Title of the study:

Open Label, Multicenter Study on Pharmacokinetics, Pharmacodynamics, Efficacy and Safety of Goserelin 10.8 mg Implant HEXAL in Patients with Advanced Hormone Dependent Prostate Cancer

Investigator(s):

Coordinating investigator: [redacted]

Principal investigators:
Centre 1: [redacted]
Centre 2:
Centre 3:
Centre 4:
Centre 5:
Centre 6:

Study centers:

n=6 in Bulgaria

Publication (reference):

the results are not yet published

Studied period:		**Phase of development:**
date of first enrolment:	19-Jan-2009	Phase III
date of last completion:	29-Jun-2009	

Objectives:

The primary objective of this trial was the evaluation of efficacy in terms of testosterone suppression after goserelin application.

Study design:

- Multicentric
- Open label
- Randomized
- Single dose
- Phase III
- 50 patients planned for randomization
- s.c. injection

Subjects (planned and analyzed):	planned for completion:	45
	screened:	67
	randomized:	48
	drop-outs after randomization:	3
	evaluated:	
	– safety population:	48
	– full analysis set:	47

Diagnosis and criteria for selection:

Inclusion criteria:

- Age ≥ 18 and ≤ 85 years
- Histologically confirmed diagnosis of advanced hormone dependent adenocarcinoma of the prostate stage $T_{3\text{-}4}N_0M_0$, $T_{1\text{-}4}N_1M_0$ or $T_{1\text{-}4}N_{0\text{-}1}M_1$ and for which a curative treatment by surgery or radiotherapy is not possible
  - either as newly diagnosed adenocarcinoma of the prostate
  - or recurrence of adenocarcinoma of the prostate after previous prostatectomy and/or radiotherapy and/or brachytherapy
- Life expectancy > 12 months
- ECOG Performance status 0-2

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	• Testosterone level ≥ 2.3 ng/ml at screening • Patients with ability to follow study instructions and likely to attend and complete all required visits • Written informed consent of the patient	
Diagnosis and criteria for selection:	**Exclusion:** • Patients expected to require additional anti-neoplastic treatment during the entire study period • Patients with previous hormonal treatment of prostate cancer • Patients with previous chemotherapy, antibody therapy, gene therapy, immunmodulating therapy (e.g. somatostatin) • Patients with previous orchiectomy and other treatments disturbing the hypothalamic-pituitary-gonadal axis (hypophysectomy, adrenalectomy) • Patients at particular risk of spinal cord compression • Patients with known hormone-refractory prostate cancer • Severe hepatic dysfunction (ALT and/or AST above 2 x upper limit of normal range; or gamma-GT above 3 x upper limit of normal range) and/or renal dysfunction (creatinine > 1.8 mg/dl) • History of blood coagulation disease • Evidence of any uncontrolled medical illness other than prostate cancer precluding study treatment or patient survival • Any other concurrent malignancy except squamous and/or basal cell carcinoma of the skin • Primary central nervous system disease with or without brain metastases • History of severe drug related allergy • Patients with a known allergy to one of the ingredients of the test product • Patients who participate simultaneously in another clinical study or who have participated in any clinical study involving an investigational drug within 1 month prior to start of this study with visit 0 • Patients with a physical or psychiatric condition which at the investigator's discretion may put the patient at risk, may confound the study results, or may interfere with the patient's participation in the study	
Test product, dose and mode of administration, batch number:	name: active ingredient: dosage form: strength: route / regimen: manufacturer: batch no. and expiry date:	Goserelin 10.8 mg Implant HEXAL goserelin acetate implant 10.8 mg s.c. injection HEXAL AG 80201/1, 08/2010
Duration of treatment: One single application of Goserelin 10.8 mg Implant HEXAL which corresponds to a treatment period of 13-17 weeks.		

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Criteria for evaluation:

Efficacy:

Primary endpoint:

- proportion of patients who were successfully suppressed within 8 weeks after administration and whose testosterone levels remained ≤ 0.5 ng/ml until week 13, except for escapes from suppression

Secondary endpoints:

- proportion of patients who were successfully suppressed within 8 weeks after administration and whose testosterone levels remained ≤ 0.5 ng/ml until week 17, except for escapes
- proportion of patients with escapes from testosterone suppression
- time to onset of serum testosterone castrate level
- weekly testosterone levels
- change in serum PSA and PAP levels over time
- subjective clinical symptoms attributable to prostate cancer (dysuria, nycturia, bone pain)
- clinical prostate status judged by investigator
- overall efficacy as judged by the investigator

Safety:

Safety endpoints:

- incidence and severity of all and of all drug related adverse events
- incidence and severity of local reactions at the injection site
- laboratory safety parameters (hematology, clinical chemistry, urinalysis)
- need of antiandrogenic medication because of flare symptoms
- vital signs (blood pressure, pulse rate)
- ECG
- overall tolerability as judged by the investigator and patient
- concomitant medication

Pharmacokinetics/ Pharmacodynamics:

- testosterone and goserelin profile within seven days after application
- plasma levels of goserelin and testosterone over time

Statistical methods:

The statistical analysis was performed on two different patient data sets:
The data set for safety was defined as all patients who started treatment with Goserelin 10.8 mg Implant HEXAL.
The full data set for efficacy (full analysis set, FAS) consists of all patients with a successful administration of the study drug and for whom at least the post-baseline testosterone value at week 13 is available (primary outcome).

RESULTS

Disposition of patients:

A total number of 67 patients were screened. Nineteen patients failed screening. 48 subjects were randomized. To all of them the implant was successful applied and thus all 48 patients are included into the safety population. In 47 patients the testosterone level at week 13 (visit 18) was available (FAS population).Three patients dropped out, and 45 patients completed the trial.

Efficacy:

In 40 patients (85.1 %) a successful testosterone suppression within 8 weeks after goserelin application was observed. In these patients the testosterone levels remained ≤ 0.5 ng/ml until week 13, whereas in one patient an escape from suppression was observed.

Considering the patients whose testosterone levels remained ≤ 0.5 ng/ml until week 17 a successful supression could be seen for 34 patients (72.3 %).

The serum testosterone castrate level (≤ 0.5 ng/ml) was achieved in a mean of 19.2 (± 4) days.

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Severe cases of subjective clinical symptoms attributable to prostate cancer were reported only at baseline for 3 patients concerning nycturia.

The application of the goserelin implant caused a clear decrease of serum concentrations of PAP and PSA after the first 4 weeks, that remained roughly constant in the course of the trial.

Safety:

A total number of 25 adverse events were registered in 20 patients. In 4 patients 4 events were regarded serious.
13 AEs were judged as having a relationship to the intake of the study drug. In all cases hot flushes are concerned.
In none of the patients a local skin reaction at injection site occurred.
No clinically important laboratory changes or trends were observed during the present trial.

CONCLUSIONS:

The evaluation of the efficacy endpoints shows positive results in view of a testosterone suppression after goserelin application for 85.1 % (13 weeks) and 72.3 % of patients (17 weeks) respectively.
This suppression rate is unexpected low considering a rate of 95-100% published for Zoladex. Therefore the planned follow-up study IMP-4 is cancelled and the development of the current product is stopped.

The majority of adverse events are expected in this kind of study population as seen with other hormonal therapies due to the expected physiological effects from decreased testosterone levels. In none of the patients any problems related to the application of the implant was reported.

The results of this study do not indicate any safety concerns. The extend and kind of adverse events correspond to published data in view of the study population and the application of Goserelin. The assessed efficacy parameter related to testosterone suppression did not met the results expected.

Date of Study Report (Final Version): 16-Dec-2009