2. SYNOPSIS

Title of the study	Randomized, open label, multicenter, phase III study on pharmacokinetics, pharmacodynamics, efficacy and safety of Goserelin 1M implant HEXAL in patients with advanced prostatic cancer in comparison to Zoladex 3.6® mg
Investigators	• Coordinating Investigator : • Center 11 : • Center 12 : • Center 13 : • Center 14 : • Center 16 : • Center 17 : • Center 18 : • Center 19 : • Center 20 : • Center 21 : • Center 22 : • Center 31 : • Center 32 : • Center 41 :
Study centers	14 centers in Bulgaria, Lithuania, and Ukraine
Publication (reference)	–
Study period	Date of first patient enrolled : 21/09/2004 Date of last patient completed : 13/07/2005
Phase of development	III
Objectives	The aim of the study was to compare pharmacokinetics, pharmacodynamics, efficacy and safety of Goserelin 1M implant HEXAL and Zoladex® 3.6 mg in patients with prostatic cancer.
Methodology	Open label, multiple dose, multicenter, phase III study on pharmacokinetics, pharmacodynamics, efficacy and safety of Goserelin 1M implant HEXAL involving patients with advanced prostatic cancer in comparison to Zoladex 3.6® mg
Number of patients	• Planned : N= 90 / 76 evaluable (2x45 / 2x38) • Screened : N=134 • Randomized: N=104 (2x52) • Completers : N=104 (2x52) --- • Primary analysis population (= Per protocol set PP) : N= 91 (Goserelin 1M implant HEXAL: 42; Zoladex® 3.6 mg: 49) • Intention-to-treat set (ITT) : N=104 (Goserelin 1M implant HEXAL: 52; Zoladex® 3.6 mg: 52)
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 ≥ 2.30 ng/mL at screening.

Test product	Goserelin 1M implant HEXAL
Dose	3.8 mg goserelin acetate (corresponding to 3.6 mg goserelin)
Mode of administration	Depot implant for s.c. injection
Batch no.	40601/1, 41104/1
Duration of treatment	16 weeks, 4 administrations at weeks 0, 4, 8, 12 (days 1, 29, 57, 85)
Reference product	Zoladex® 3.6 mg
Dose	3.8 mg goserelin acetate (1:1) (corresponding to 3.6 mg goserelin)
Mode of administration	Depot implant for s.c. injection
Batch no.	BR872/1, RA211B/1, BX820/1

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 16 (except for escapes).

Secondary endpoints

- Testosterone levels at weeks 4, 8, 12, and 16
- Proportion of patients with testosterone levels below or equal 0.50 ng/mL at weeks 4, 8, 12, and 16
- Time to onset of castrate level
- Proportion of patients with relevant escapes of testosterone level after achieving suppression
- Change in prostatic status (digital rectal examination) at week 16 compared to screening visit
- Change in serum PSA and PAP levels at weeks 4, 8, 12, and 16 as compared to week 0
- Subjective response on the basis of ECOG performance status
- Change in subjective clinical symptoms attributable to prostatic 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 16 (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*
- *Castrate level: testosterone 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.]*

Pharmacokinetics: Pharmacokinetic profiles of goserelin and testosterone.

Safety:
- Incidence and severity of all and of all drug-related adverse events
- Incidence and severity of local reactions at the injection site
- Incidence of serious adverse events
- Changes in safety laboratory at week 16 compared to screening visit
- Number of patients who needed antiandrogens because of flare symptoms
- Changes in vital signs up to week 16 compared to week 0
- Changes in concomitant diseases up to week 16 compared to week 0
- Change in ECG at week 16 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
- Exact one-sided 95% confidence intervals for rates of successfully suppressed testosterone levels and rates of relevant escapes
- Exact two-sided 95% confidence intervals based on the binomial distribution.

Efficacy results

Primary analysis population (PP)

➢ Successful testosterone suppression until week 16: – *primary endpoint*
- Goserelin 1M implant HEXAL : 38/42 (90.5%)
- Zoladex® 3.6 mg : 45/49 (91.8%).

➢ Exact lower 95% confidence limits of the suppression rates were determined as follows:
- Goserelin 1M implant HEXAL : 79.5%
- Zoladex® 3.6 mg : 82.3%

lower limits for the estimate of suppression rates

➢ The time to onset of castrate level was
- Goserelin 1M implant HEXAL : 3 weeks
- Zoladex® 3.6 mg : 4 weeks.

In the majority of patients, the time to onset of castrate level was 3 or 4 weeks:
- Goserelin 1M implant HEXAL : 36/42 (85.7%)
- Zoladex® 3.6 mg : 41/49 (83.7%).

➢ After suppression was achieved, the rates of relevant escapes were
- Goserelin 1M implant HEXAL : 0/42 (0.0%)
- Zoladex® 3.6 mg : 1/49 (2.0%).

➢ In patients successfully suppressed until week 16, the rates of relevant escapes were
- Goserelin 1M implant HEXAL : 0/38 (0.0%)
- Zoladex® 3.6 mg : 0/45 (0.0%).

Efficacy results *[cont.]*

Intention to treat population (ITT)

➢ Successful testosterone suppression until week 16:

- Goserelin 1M implant HEXAL : 44/52 (84.6%)
- Zoladex® 3.6 mg : 46/52 (88.5%).

➢ Exact lower 95% confidence limits of the suppression rates were determined as follows:

- Goserelin 1M implant HEXAL : 74.0%
- Zoladex® 3.6 mg : 78.5%

lower limits for the estimate of suppression rates

➢ After suppression was achieved, the rates of relevant escapes were

- Goserelin 1M implant HEXAL : 1/50 (2.0%)
- Zoladex® 3.6 mg : 2/52 (3.8%).

➢ In patients successfully suppressed until week 16, the rates of relevant escapes were

- Goserelin 1M implant HEXAL : 1/44 (2.3%)
- Zoladex® 3.6 mg : 0/46 (0.0%).

Further efficacy results

With regard to further efficacy parameters (digital rectal examination, transrectal ultrasound, TNM, ECOG performance status, subjective symptoms, PSA, PAP) as well as endocrine profile and SHBG, no marked differences between the trial groups Goserelin 1M implant HEXAL and Zoladex® 3.6 mg were determined. The prostatic status showed the following course upon both study medications:

Table 2.1: Prostatic status after 16 study weeks (PP)

Prostatic status	Goserelin 1M implant HEXAL	Zoladex® 3.6 mg
N	42	49
returned to normal	2 (4.8%)	2 (4.1%)
> 50% improved	24 (57.1%)	25 (51.0%)
similar to baseline	16 (38.1%)	21 (42.9%)
> 25% worsened	–	1 (2.0%)

Overall, the following treatment results were obtained:

Table 2.2: Overall efficacy as judged by the investigator (PP)

Judgment	Goserelin 1M implant HEXAL	Zoladex® 3.6 mg
N	42	49
very good	24 (57.1%)	22 (44.9%)
good	17 (40.5%)	22 (44.9%)
indifferent	1 (2.4%)	4 (8.2%)
bad	–	1 (2.0%)
very bad	–	–

Goserelin concentration – *SCOPE International AG* –	No accumulation of trough levels was seen. The total rate and extent of exposure was lower after Goserelin 1M implant HEXAL than after Zoladex® 3.6 mg. Under safety considerations the lower rate and extent of goserelin exposure under the new formulation appears to be favorable.
Safety results	➢ 28 (53.8%) patients treated with Goserelin 1M implant HEXAL and 29 (55.8%) patients treated with Zoladex® 3.6 mg experienced adverse events. ➢ In 16 patients (30.8%) 20 adverse events (frequenting 18 SOCs due to multiple ratings) were suspected to be caused by Goserelin 1M implant HEXAL: • General disorders and administration site conditions : N= 2 • Musculoskeletal and connective tissue disorders : N= 1 • Psychiatric disorders : N= 2 • Vascular disorders (predominantly 'hot flushes') : N=13. In the Zoladex® 3.6 mg trial group, 15 patients (28.8%) experienced 16 adverse events (frequenting 16 SOCs) suspected to be related to the study drug: • Psychiatric disorders : N= 1 • Reproductive system and breast disorders : N= 1 • Vascular disorders (predominantly 'hot flushes') : N=14. ➢ Three serious adverse events in the Goserelin 1M implant HEXAL trial group in form of hospitalizations 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. ➢ The tolerability was judged by the patient as follows: **Table 2.3: Overall tolerability as judged by the patient** ➢ The tolerability was judged by the investigator as follows: **Table 2.4: Overall tolerability as judged by the investigator** ➢ Overall, there was no relevant difference in safety profile.

Judgment	Goserelin 1M implant HEXAL	Zoladex® 3.6 mg
N	52	52
very good	29 (55.8%)	29 (55.8%)
good	22 (42.3%)	21 (40.4%)
indifferent	1 (1.9%)	2 (3.8%)
bad	–	–
very bad	–	–

Judgment	Goserelin 1M implant HEXAL	Zoladex® 3.6 mg
N	52	52
very good	32 (61.5%)	29 (55.8%)
good	17 (32.7%)	19 (36.5%)
indifferent	3 (5.8%)	4 (7.7%)
bad	–	–
very bad	–	–

Conclusions	The testosterone-suppressive efficacy of Goserelin 1M implant HEXAL was confirmed with a 'successful suppression' rate of 38/42 (90.5%) at week 16 in the primary analysis population. The lower one-sided 95% confidence limit of this rate was 79.5%. These results were very similar to those of the reference product. With Zoladex® 3.6 mg, the 'successful suppression' rate at week 16 amounted to 45/49 (91.8%), and the lower limit of the one-sided 95% confidence interval was 82.3%. The endocrine profile showed parallel developments upon Goserelin 1M implant HEXAL and Zoladex® 3.6 mg. The pharmacokinetic results yielded no accumulation of trough levels. The total rate and extent of exposure was lower after Goserelin 1M implant HEXAL than after Zoladex® 3.6 mg. Under safety considerations the lower rate appears to be favorable. No relevant differences were observed between Goserelin 1M implant HEXAL and Zoladex® 3.6 mg regarding the main efficacy and safety results. Therefore, the study 2004-27-IMP-2 established the comparable efficacy and tolerability of Goserelin 1M implant HEXAL and Zoladex® 3.6 mg after 4 subsequent administrations in 4-weekly intervals in patients with advanced prostatic cancer.