2. SYNOPSIS

Title of the study	Randomized, open label, multicenter, phase II study on pharmacokinetics, pharmacodynamics, efficacy and safety of Buserelin 3M implant HEXAL in patients with advanced prostatic cancer in comparison to Profact® Depot 9.45 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 19 ([redacted]) : • Center 21 ([redacted]) : • Center 22 ([redacted]) : • Center 23 ([redacted]) : • Center 24 ([redacted]) : • Center 31 ([redacted]) : • Center 32 ([redacted]) : • Center 61 ([redacted]) : • Center 62 ([redacted]) : • Center 63 ([redacted]) :
Study centers	18 centers in Bulgaria (9), Lithuania (4), Ukraine (2), and the Czech Republic (3)
Publication (reference)	–
Study period	Date of first patient enrolled : 14/02/2006 Date of last patient completed : 17/10/2006
Phase of development	II
Objectives	The aim of the study is to compare pharmacodynamics, pharmacokinetics, efficacy and safety of Buserelin 3M implant HEXAL, newly developed by HEXAL, with the approved drug Profact® Depot 9.45 mg, Aventis Pharma, 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=2x45 (2x40 evaluable) • Screened : N=146 • Randomized : N=126 (1 randomization failure not treated) • All patients treated : N=125 (64/61[1] = Intention-To-Treat population • Completers week 12 : N=103 (44/59) • Completers week 24 : N= 62 (5/57). On May 24th, 2006, the study was stopped in the BUS group due to inadequate response to treatment (sponsor's decision). Only 6 BUS-treated 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 ≥ 2.3 ng/mL at screening.

[1] 1st number: Buserelin 3M implant HEXAL / 2nd number: Profact®Depot 9.45 mg

Test product	Buserelin 3M implant HEXAL
Dose	9.9 mg Buserelin acetate (corresponding to 9.45 mg buserelin)
Mode of administration	Depot implant for s.c. injection
Batch no.	50801/1, 50801/3, 50801/5
Duration of treatment	24 weeks, 2 administrations at weeks 0 (day 1) and 12 (day 85).
Reference therapy	Profact® Depot 9.45 mg
Dose	9.9 mg Buserelin acetate (corresponding to 9.45 mg buserelin)
Mode of administration	Depot implant for s.c. injection
Batch no.	40D344/1
Criteria for evaluation	
Efficacy	**Primary endpoint** Testosterone suppression after buserelin 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 • Duration of suppression • 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.

Criteria for evaluation *[cont.]*	
	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 buserelin to the first suppressed testosterone value* • *Duration of suppression: the duration of suppression is defined as the time from onset of suppression until the first of more than two consecutive measurements above the castrate level.*
Pharmacodynamics	• Pharmacodynamic profile of testosterone within 7 days after first administration.
Pharmacokinetics	• Pharmacokinetic profile of buserelin over 6 hours after administration • Pharmacokinetic profile of buserelin within 7 days after administration • Development of buserelin 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 Due to study cessation in the Buserelin 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* • Buserelin 3M implant HEXAL : 18/64 (28.1%) • Profact®Depot 9.45 mg : 58/61 (95.1%). ➢ All patients achieved suppression, i.e. at least two consecutive testosterone values ≤ 0.50 ng/mL, except for 5 BUS-treated and 1 REF-treated patients. Two of the BUS-treated patients were identified as implantation failures. ➢ The time to onset of castrate level ranged between 2 and 4 weeks, except for 2 BUS-treated and 3 REF-treated patients who achieved suppression after 5 or 6 weeks. ➢ After suppression was achieved, the rates of relevant escapes were • Buserelin 3M implant HEXAL : –/59 (0.0%) • Profact® Depot 9.45 mg : 1/60 (1.7%). ➢ In patients who achieved castrate level, the median duration of suppression was determined as follows: • Buserelin 3M implant HEXAL : 7 weeks • Profact® Depot 9.45 mg : 21 weeks. ➢ Six patients received a second BUS implantation, one of them stopped the trial for administrative reasons. Four of the remaining 5 cases were successfully suppressed until week 24, resulting in a total rate of successes at week 24 of 4/64 (6.3%). In the REF group, the corresponding rate amounted to 56/61 (91.8%). ➢ In the Buserelin 3M implant HEXAL group, deteriorations of clinical findings, PAP, or PSA were seen in • 10/37 (27.0%) patients with violated castrate level • 3/27 (11.1%) patients with suppressed testosterone level at study discontinuation. The difference between both rates was not significant, and furthermore, the proportion of deteriorations in patients with suppressed testosterone levels in the reference group was higher than both rates shown above (18/59 = 30.5%). Therefore one may conclude that the higher rate of deteriorations in treatment failures upon BUS was **not** caused by the inadequate response to treatment in this group.
Pharmacodynamics	The pharmacodynamic estimates of testosterone within 7 days after application of Buserelin 3M implant HEXAL and Profact®Depot 9.45 mg showed no marked differences between both trial groups.
Pharmacokinetics	The course of buserelin over 7 days after application of Buserelin 3M implant HEXAL and Profact® Depot 9.45 mg yielded markedly higher levels of AUC and C_{max} upon Profact® Depot 9.45 mg.
Safety results	➢ One patient (REF) died caused by heart failure (possibly due to a myocardial infarction). ➢ 28/64 (43.8%) patients treated with Buserelin 3M implant HEXAL and 31/61 (50.8%) patients treated with Profact® Depot 9.45 mg experienced adverse events.

Safety results *[cont.]*

➢ In 16 patients (25.0%) 18 adverse events were suspected to be caused by Buserelin 3M implant HEXAL. The following MedDRA[2] Preferred Terms were involved:

- Hot flush : N=12 (18.8%)
- Flushing : N= 2 (3.1%)
- Erectile dysfunction : N= 1 (1.6%)
- Headache : N= 1 (1.6%)
- Injection site erythema : N= 1 (1.6%)
- Vertigo : N= 1 (1.6%).

➢ In the reference group, 21 patients (34.4%) experienced 22 adverse events suspected to be related to Profact® Depot 9.45 mg:

- Hot flush : N=14 (23.0%)
- Flushing : N= 6 (9.8%)
- Dysuria : N= 1 (1.6%)
- Erectile dysfunction : N= 1 (1.6%).

➢ Injection site reactions were observed in two BUS-treated patients.

➢ No clinically significant changes in laboratory findings, ECG, vital signs, and physical examinations were judged to be related to the trial medication.

➢ The tolerability was judged by the patient as follows:

Judgment	BUS [N=64]	REF [N=61]
very good	29 (46.8%)	32 (54.2%)
good	28 (45.2%)	26 (44.1%)
indifferent	5 (8.1%)	1 (1.7%)
bad	–	–
very bad	–	–
missing values	2	2

➢ The tolerability was judged by the investigator as follows:

Judgment	BUS [N=64]	REF [N=61]
very good	26 (41.9%)	35 (59.3%)
good	33 (53.2%)	23 (39.0%)
indifferent	3 (4.8%)	1 (1.7%)
bad	–	–
very bad	–	–
missing values	2	2

➢ Overall, there was no substantial difference in safety profile between Buserelin 3M implant HEXAL and Profact® Depot 9.45 mg.

2 MedDRA: Medical Dictionary for Drug Regulatory Activities

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 5 BUS-treated patients, 2 of them being identified as implantation failures, and 1 REF-treated patient. But the testosterone-lowering effect of BUS was not stable in an unacceptably high number of patients. Therefore, it was decided to discontinue the administration of Buserelin 3M implant HEXAL. Only 6 patients received the 2nd application at week 12. In the Buserelin 3M implant HEXAL study group the rate of successful suppression until week 12 amounted to 18/64 (28.1%). The corresponding result upon Profact® Depot 9.45 mg was 58/61 (95.1%). Among 6 patients who received two applications of Buserelin 3M implant HEXAL, 1 case discontinued the study for administrative reasons. The rate of successful testosterone suppression until week 24 was 4/5 in the remaining patients. Summarizing, the study 2005-34-IMP-2 established the efficacy of Buserelin 3M implant HEXAL in approximately 30% of the patients only. Regarding the safety profile, no substantial differences between Buserelin 3M implant HEXAL and Profact® Depot 9.45 mg were revealed.