



European Medicines Agency  
*Evaluation of Medicines for Human Use*

Doc.Ref: EMEA/CHMP/635761/2008

**ASSESSMENT REPORT**

**FOR**

**FIRMAGON**

International Nonproprietary Name: **degarelix (as acetate)**

**Procedure No. EMEA/H/C/000986**

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# 1. BACKGROUND INFORMATION ON THE PROCEDURE

## 1.1 Submission of the dossier

The applicant Ferring Pharmaceuticals A/S submitted on 27 February 2008 an application for Marketing Authorisation to the European Medicines Agency (EMA) for FIRMAGON, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 July 2007.

The legal basis for this application refers to:

A - Centralised / Article 8(3) / New active substance.

The application submitted is a complete dossier: composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

The applicant applied for the following indication:

FIRMAGON is a GnRH receptor blocker indicated for treatment of patients with prostate cancer in whom androgen deprivation is warranted. This includes patients with rising PSA after having undergone prostatectomy or radiotherapy.

### Scientific Advice

The applicant received Scientific Advice from the CHMP on 17 September 2004. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

### Licensing status:

A new application was filed in the following countries: USA.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: **Pierre Demolis** Co-Rapporteur: **Eva Skovlund**

## 1.2 Steps taken for the assessment of the product

- The application was received by the EMA on 27 February 2008.
- The procedure started on 26 March 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 16 June 2008. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 16 June 2008.
- During the meeting on 21-24 July 2008 the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 July 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 September 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 5 November 2008.
- During the CHMP meeting on 17-20 November 2008 the CHMP agreed on a list of outstanding issues to be addressed by the applicant.
- The applicant submitted the responses to the CHMP list of outstanding issues on 26 November 2008 and 3 December 2008.
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 8 December 2008.

- During the meeting on 15-18 December 2008 the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to FIRMAGON on 18 December 2008. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 18 December 2008 and an additional commitment to be fulfilled post-authorisation was received on 21 January 2009.

## SCIENTIFIC DISCUSSION

### 2.1 Introduction

#### Prostate Cancer

Prostate cancer is a leading cause of morbidity and mortality for men in the industrialised world. It increases steadily with age and the median age at diagnosis is slightly above 70 years. Worldwide more than 670,000 men are diagnosed with prostate cancer each year and the number of new cases is rising due to increasing life expectancy. In 2006 in Europe there were 345,900 cases of prostate cancer diagnosed. The 2007 estimate of new cases in the USA was 218,890 with 27,050 deaths. The incidence varies widely between ethnic groups, regions and countries, with the highest rates in USA African-Americans and the lowest in Asian males.

Long-term disease-free intervals are commonly associated with surgical or radiotherapeutic treatment in more than 60% of subjects with localized disease (stages I and II). In contrast, such outcomes are uncommon for subjects with loco-regional (stage III) or distant (stage IV) disease.

Hormonal manipulations, such as luteinizing hormone-releasing hormone agonists (GnRH agonists) or surgical castration are effective for 90% of subjects with loco-regional or distant disease. Anti-androgens are commonly used during the first weeks of GnRH agonist therapy in order to prevent the sequelae of an initial and temporary rise in serum testosterone (flare up effect).

#### The Medicinal Product

Degarelix, a third generation GnRH receptor antagonist (a GnRH blocker), has been developed as a new therapy for prostate cancer patients in need of androgen ablation therapy. The aim of the degarelix development has been to achieve testosterone suppression in the same range as for GnRH agonist therapy without any increase in testosterone levels after the initial dose.

Degarelix binds to GnRH receptors in the anterior pituitary gland resulting in a decreased secretion of LH and FSH, and subsequently decreased production of testosterone by the Leydig cells in the testes. Testosterone suppression is achieved almost immediately after s.c. administration of degarelix. The degree and duration of testosterone suppression are related to plasma concentrations of degarelix. The formation of a depot following s.c. administration gives rise to sustained plasma concentrations of degarelix, resulting in prolonged GnRH receptor-mediated suppression of testosterone levels.

The claimed indication for Degarelix was initially “treatment of patients with prostate cancer in whom androgen deprivation is warranted, including patients with rising PSA after having undergone prostatectomy or radiotherapy”. However, the approved indication is treatment of advanced hormone-dependent prostate cancer. A dosing regimen consisting of a starting dose of 240 mg, followed by a monthly maintenance dose of 80 mg throughout the 12-month treatment period, has been proposed. The aim of the clinical study program has been to develop a safe and efficacious one-month dosing regimen, which achieves testosterone suppression in the same range as for GnRH agonist therapy without any increase in testosterone levels after the initial dose. As of the submission database cut-off date (September 28, 2007), 16 clinical safety and efficacy studies of degarelix in prostate cancer patients, including seven extension studies, were completed or are ongoing. Of these, 11 clinical studies were completed. Five studies (4 extension studies and one 3-month dosing regimen main study) are ongoing and safety data, as of the database cut-off date for these ongoing studies, were integrated for analysis.

The applicant requested scientific advice (article 57(1)(n) of Regulation (EC) 726/2004 ) from the European Medicines Agency (EMA) on 21 June 2004. Advice was sought primarily on the proposed Phase 3 clinical study program (originally two studies were planned), the anticipated safety database, and specific monitoring of hepatic liver enzymes and allergic reactions.

No pediatric development programme has been carried for this medical product since this is a non-existing indication in the paediatric population.

## 2.2 Quality aspects

### Introduction

FIRMAGON is presented as powder and solvent for solution for injection, containing 80 mg or 120 mg of degarelix (active substance) and is intended for subcutaneous use. The sterile powder is a freeze-dried product containing degarelix (as acetate) and mannitol. The solvent consists of sterile water for injection.

Powder is a white to off-white and the solvent is a clear, colourless solution. After reconstitution drug product forms a clear solution.

After administration, in contact with body fluids such as plasma, degarelix spontaneously forms a gel (naturally forming prolong-release form). The gelling process is mainly influenced by the concentration of degarelix, time, temperature, salt content and proteins (mannitol has no functionality for gel formation). Therefore, while the process does not take place visibly in the reconstituted suspension, the depot-formation occurs instantaneously following subcutaneous administration. The natural depot formation after subcutaneous administration results in sustained release of degarelix and a prolonged duration of pharmacological effect.

The powder is supplied in glass vials with bromobutyl rubber stoppers. The solvent is supplied in glass vials with chlorobutyl rubber stoppers with silicate filler.

### Active Substance

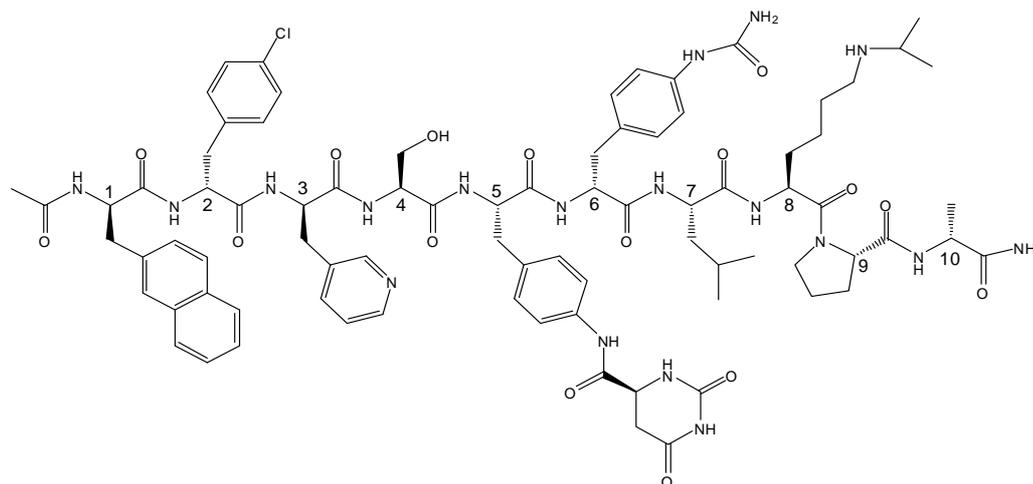
Degarelix (INN), which is a third generation gonadotropin releasing hormone (GnRH) antagonist (blocker), is a synthetic linear decapeptide containing seven unnatural amino acids, five of which are D-amino acids.

The drug substance is chemically designated as D-Alaninamide, *N*-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-4-[[[(4*S*)-hexahydro-2,6-dioxo-4-pyrimidinyl]carbonyl]amino]-L-phenylalanyl-4-[(aminocarbonyl)amino]-D-phenylalanyl-L-leucyl-*N*6-(1-methylethyl)-L-lysyl-L-prolyl-.

Its common names is: [Ac-D-2Nal<sup>1</sup>, D-4Cpa<sup>2</sup>, D-3Pal<sup>3</sup>, 4Aph(L-Hor)<sup>5</sup>, D-4Aph(Cbm)<sup>6</sup>, Lys(iPr)<sup>8</sup>, D-Ala<sup>10</sup>] GnRH

where: 2Nal is 2-Naphthylalanine, 4Cpa is 4-Chlorophenylalanine, 3Pal is 3-Pyridylalanine, Hor is hydroxyrotyl, Lys(iPr) is *N*6-Isopropyllysine, 4Aph is 4-Aminophenylalanine, and Cbm is the carbamoyl group.

Degarelix consists of ten chiral centers in the back bone of the molecule. The amino acid residue at position 5 in the sequence has an additional chiral center in the side-chain substitution giving eleven chiral centers in total. The N-terminal is acetylated. The C-terminal Ala<sup>10</sup> is present as its amide. It has an empirical formula of C<sub>82</sub>H<sub>103</sub>N<sub>18</sub>O<sub>16</sub>Cl and a molecular weight of 1632.3 Da, and the following structure:



Degarelix is a white to off-white amorphous powder of low density. It is obtained as the acetate salt in the form of a lyophilised powder after the final purification step. It is soluble in water and in aqueous solution containing mannitol. However, in concentrations ranging 0.1 – 10 mg/ml the solution tends to become turbid and forms gel after several hours or days, depending on concentration and temperature. The phenomenon is explained by the self-aggregation propensity of the drug substance.

Experimental pKa values for degarelix are 10.8 (side-chain of Lys(iPr)) and 4.4 (side-chain of D-3Pal). Specific optical rotation (in 30 % acetic acid) is  $-39^\circ \pm 1$ .

Degarelix is hygroscopic. Water is unspecifically bound to degarelix drug substance, and not present as crystal water.

- **Manufacture**

Degarelix is synthesised in a liquid phase peptide synthesis (LPPS) process. A detailed description of the manufacturing process, including process flow diagram and in-process controls was provided.

Initially degarelix was synthesised via solid phase peptide synthesis (SPPS). The SPPS route was employed for the majority of the batches used in pre-clinical and some clinical studies. However, with the SPPS route the production capacity was limited, and later on, when more drug substance was required, the larger scale LPPS process was developed. For the LPPS route also a more efficient purification procedure can be applied.

Adequate tests have been performed to provide evidence on the chemical structure, enantiomeric purity, amino acid sequence, the chemical impurities and residual solvents of the drug substance. The techniques used for structure elucidation include FT-IR spectroscopy, UV spectroscopy, mass spectrometry (MS) for determination of molecular mass, MS/MS (collision induced dissociation) for sequence of amino acids,  $^1\text{H}$  and  $^{13}\text{C}$ -NMR spectroscopy (one and two dimensional experiments) for structure elucidation, GC-FID for identity and ratios of individual amino acids, and chiral amino acid analysis by GC-MS and LC-UV for identity and chirality of individual amino acids. Identity of the acetic acid was tested by RP LC-UV.

The NMR experiments were also carried out on a batch manufactured by the (former) SPPS process in order to confirm that the structure of degarelix was not modified when changing from SPPS to LPPS. No structural differences were detected.

Synthetic impurities and degradation products are adequately characterised and the proposed limits for impurities are established taking into account levels found in the analysed batches. During development some impurities have been synthesised and used to control the purity of the drug substance. As the impurity profiles of peptides prepared by SPPS and LPPS may be different, peptides

obtained from both processes were analysed. It has been confirmed that different synthesis related impurity profiles do not affect degradation of degarelix.

- **Specification**

The drug substance specification includes tests for appearance, identification (electrospray MS and LC/UV), assay (LC), related substances (LC/UV and GC/MS), acetate content (LC/UV), (Karl-Fisher), trifluoroacetate content, palladium, bacterial endotoxins and total viable aerobic count.

Test for acetate content, trifluoroacetate content, water content, palladium bacterial endotoxins and total viable aerobic count are compendial tests performed according to relevant monographs.

For non-compendial analytical methods such as the LC method with UV detection for identity and assay, an appropriate validation studies were performed. The content of impurities is analysed using several LC methods with UV detection and GC/MS method. All methods have been validated with regards to specificity, linearity, accuracy, precision, range, limit of detection, limit of quantification and robustness.

In general analytical methods proposed are suitable to control the quality of the drug substance.

Batch analysis results were provided on 13 batches of degarelix. Two batches were of pilot scale and 11 of commercial scale batches. All results were within the specification limits and met requirements of the drug substance specification.

- **Stability**

Stability studies have been performed on five production scale batches of the drug substance. Degarelix was stored at long term ( $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ ) and accelerated conditions ( $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \text{ RH} \pm 5\% \text{ RH}$ ). Results generated during the studies (storage at  $5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ ) showed only minor degradation, and all results were within the specification limits.

A forced degradation studies (exposure to elevated temperature, humidity, oxidation, photolysis, alkaline and acidic conditions) have been performed to characterise the degradation pathways of degarelix. Degradation products were compared with synthesised related impurities in order to elucidate their structure. Main degradation products were identified but only some of the identified impurities have been observed during the long-term stability studies.

The stability data provided for the drug substance confirmed the proposed re-test period.

## **Medicinal Product**

- **Pharmaceutical Development**

Aqueous solutions of the drug substance have been used in pharmacological screening and clinical studies, and were found to have the potential to form a depot form leading to a long duration of action of degarelix. However solutions of degarelix are not chemically stable for long term storage and therefore a freeze-dried formulation was developed.

In early development of the drug product formulation containing drug substance synthesised in the solid phase peptide synthesis (SPPS) was used. Formulations containing drug substance synthesised in a liquid phase peptide synthesis (LPPS) were used in the phase 3 clinical study and are intended for market supply. Physicochemical properties of the drug substance obtained by two different routes of synthesis and of drug products, both laboratory scale and production scale, prepared from SPPS and LPPS drug substance were compared. It has been proven that physicochemical properties of the two substances were comparable. Initially three strengths have been developed but only two are intended for marketing (80 mg and 120 mg).

The fibrillation of degarelix has been investigated in detail. Although the solubility of degarelix in water is initially high (concentrations up to 100 mg/ml can be prepared), degarelix aqueous solutions

tend to turn turbid and/or viscous with time as an indication of gelation, and may then be described as “suspensions”. Degarelix gel-formation can be explained by intermolecular interactions (self-aggregation). Self-aggregation in aqueous solutions has been described for several GnRH analogues. The structure of the aggregates and the properties of the gels differ from one compound to another. In the case of degarelix, the gel formed in aqueous solution is based on a fibrillar network.

- Adventitious Agents

None of the excipients used in the formulation or during the manufacturing process are of animal or human origin.

- Manufacture of the Product

The freeze dried drug product is manufactured by a standard aseptic process which includes sterilisation by filtration of the formulated bulk, aseptic filling into sterile pyrogen free vials and freeze-drying under aseptic conditions.

Solvent (water for injections) is filled, and terminally sterilised by autoclaving (121 °C/ 15 minutes). No special development was necessary. Validation results for the filter and the terminal sterilisation, respectively, have been provided

A detailed description of the manufacturing process was provided. The process has been validated on three pilot scale batches of both strengths and validation is ongoing for the commercial scale batches. Critical steps of the manufacturing process have been identified and are sufficiently controlled by in-process control testing.

Batch analysis data on seven pilot scale and three commercial scale batches of the 80 mg strength and nine pilot scale and two commercial scale batches of the 120 mg strength have been provided. All results indicate satisfactory uniformity and compliance with the proposed specifications.

- Product Specification

The drug product specifications include test for appearance, identification (LC/UV), degarelix content (LC/UV), impurities (LC/UV), acetate content (LC/UV or capillary electrophoresis), water content (Karl Fisher), uniformity of dosage units, pH, sterility, bacterial endotoxins, particulate contamination – visible and subvisible particles, reconstitution time, optical density, viscosity and in vitro dissolution. The dissolution test is not performed routinely, but the result is predicated based on the results of the optical density and viscosity tests

The solvent complies with the Ph Eur monograph - Water for Injections. The compendial specification has been amended with additional tests for pH, calcium content and carbon dioxide content.

Adequate method descriptions have been provided for all methods. The LC/UV method for identification, degarelix content and impurities is identical with the method used for the drug substance (the main part of the method). The analytical methods and acceptance criteria have been established to confirm the identity, purity and the quality of the drug product and to ensure its suitability for their intended use.

- Stability of the Product

The stability data was provided on three pilot scale batches for each of the strength. A reduced test design (matrixing) according to ICH Q1D was conducted to follow the stability of these batches. The 80 mg strength was stored up to 18 months and the 120 mg strength was stored up to 24 months at 25°C/60% RH (normal conditions). For both strengths results from the accelerated conditions (40°C/75% RH), covering period up to 6 months, were provided. Parameters subject to statistical analysis, in particular specified impurities, as well as total degradation products, were found well within the shelf-life limits at the end of the shelf-life prediction.

Results from photostability studies, proving that the drug product is photostable, have also been provided.

The stability study will be further performed on the first three commercial scale batches of the drug product.

In-use stability of the reconstituted drug product was also investigated. The drug product must be administered within 1 hour after reconstitution however immediate administration after reconstitution is the preferable approach.

#### Solvent

Three pilot scale batches of the solvent have been stored at long term (25°C/60% RH) and accelerated stability studies (40°C/75% RH). 60 months long term- and 6 months accelerated stability data has been provided. First three production scale batches will be subjected to long term, intermediate and accelerated stability studies.

Based on the stability data the proposed shelf-life and storage conditions, as defined in the SPC, are acceptable.

- Compatibility Exercise for Medicinal Product

Compatibility of formulation with the proposed container closure system was demonstrated by the ongoing stability studies. After reconstitution an aqueous solution of degarelix becomes turbid and viscous with time as a result of fibrillation of the drug substance. However, it was concluded that the solution was stable in its primary packaging during the first hour after reconstitution.

There is no precipitation of the drug substance as the formulation is exempted from salt excipients.

The solvent for reconstitution (water for injections) is included in the product.

### **Discussion on chemical, pharmaceutical and biological aspects**

The drug substance and the drug product have been appropriately characterised and generally satisfactory documentation has been provided. The excipients used in the preparation of the drug product and manufacturing process selected are typical for injectable preparations. The results indicate that the drug substance and the drug product can be reproducibly manufactured.

At the time of the CHMP opinion, there were minor unresolved quality issues which have no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve it as a Follow-up Measures after the opinion, within an agreed time-frame.

## **2.3 Non-clinical aspects**

### **Introduction**

The non-clinical development programme of degarelix consisted of pharmacology studies (primary pharmacodynamics, secondary pharmacodynamics, and safety pharmacology), pharmacokinetic studies (absorption, distribution, metabolism, excretion and pharmacokinetic interactions), toxicology studies (single dose toxicity, repeat dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, and local tolerance studies) and an environmental risk assessment.

### **Pharmacology**

- Primary pharmacodynamics

*In vitro*, the binding of degarelix to cloned hGnRH receptor expressed in membranes from COS-I cells was measured in a radioligand binding assay. Degarelix showed a high affinity to the cloned human

GnRH receptor with  $K_i$  values of  $1,68 \pm 0,12$  nM. Degarelix demonstrated similar functional antagonism as three other GnRH peptide antagonists (azaline B, cetrorelix and ganirelix) when tested *in vitro* using HEK293 cells expressing a cloned human GnRH receptor and a luciferase reporter gene. No significant affinity towards 37 other receptors, mainly G-protein-coupled, was observed *in vitro* in radioligand binding assays.

*In vivo*, degarelix administered by s.c route in male Sprague Dawley rats induced a dose dependant reduction in testosterone levels. Long term suppression of testosterone levels was investigated in the intact male rats in comparison with surgical castration and three other GnRH antagonists (abarelix, ganirelix and azaline B). A single administration of 2 mg/kg of degarelix showed a significant longer duration of action than the other antagonists similarly administered with respect to dose and concentration.

*In vivo*, the effect of degarelix on prostate tumor size was investigated. Degarelix showed antitumoral activity in three experimental models of prostate hormone dependant tumors: androgen dependent human prostate tumour PAC120 in the nude mice and androgen-dependent rat prostate tumour Dunning R-3327H in rats when administered at the dose level of 2 mg/kg every two weeks and once a month respectively. At the tested doses, degarelix suppressed plasma testosterone levels and reduced tumour volume with efficacy similar to surgical castration. Degarelix had no effect on the growth of the androgen-independent human prostate tumour PC3.

- Secondary pharmacodynamics

No secondary pharmacodynamic studies have submitted.

- Safety pharmacology programme

The safety pharmacology program included the ICH S7 safety pharmacology battery in addition to tests on renal, autonomous nervous and gastrointestinal systems (see table 1 below). These studies raised no concerns, although effects on renal and gastrointestinal systems were studied at small exposure multiples. However, toxicity studies at higher doses have not indicated that these organs are target organs.

Table 1: Safety pharmacology programme

Organ Systems Evaluated/ Study ID/ GLP-status	Species/ Strain Number	Method of Administration/ Dose	Major findings
<b>Central nervous system</b>			
CNS Primary observation (Irwin test) PHA9801/ No GLP	Mouse NMRI 3M	S.C 0/ 0,3/ 1/ 3/ 10/ 30 mg/kg	<b>1-10 mg/kg:</b> increased reactivity to touch at 15 min <b>30 mg/kg:</b> increased reactivity to touch at 30 min & 24h; increased fear at 30 min; tremor in 1 animal at 30 min .
Primary Irwin PHA9814/ No GLP	Rat Wistar 4M	S.C 0/ 0,03/ 0,3/ 3/ 30 mg/kg	<b>0.3 mg/kg:</b> increased reactivity to touch at 30 min; decreased muscle tone in 2/4 at 15 min. <b>3 mg/kg:</b> increased reactivity to touch and fear at 30 min; sedation at 15 & 30 min; decreased muscle tone at 15 & 30 min. <b>30 mg/kg:</b> increased reactivity to touch at 15, 30, 60 min & 24 h; increased fear at 15 min; sedation at 30 min; decreased muscle tone in 2/4 at 30 min.
Activity meter PHA9814/ No GLP	Rat Wistar 10M	S.C 0/ 0,03/ 0,3/ 3 mg/kg (reference substances caffeine and chlorpromazine)	None.
Rotating rod PHA9814/ No GLP	Rat Wistar 10M	S.C 0/ 0,03/ 0,3/ 3 mg/kg (reference substance diazepam)	None.
Electro-convulsive shock threshold PHA9814/ No GLP	Rat Wistar 15M	S.C 0/ 0,03/ 0,3/ 3 mg/kg (reference substance diazepam)	<b>0.03 mg/kg:</b> statistically significant increase in threshold (23%); 1 death. <b>0.3 mg/kg:</b> no statistically significant effect. <b>3 mg/kg:</b> no statistically significant effect; 2 deaths
CNS Irwin profile 2372/ GLP	Rat Sprague Dawley 6M	S.C 0 (naive)/ 0 (vehicle)/ 0,5/ 5 / 50 mg/kg	No significant difference between any of the treated groups and naive or vehicle treated animals
<b>Cardiovascular system</b>			
hERG current PHA0204/ GLP	HEK293 cell transfected with hERG cDNA	<i>In vitro</i> / 0/ 20 µg/ml	No effect.
Action potential PHA0203/ GLP	Purkinje fibres	<i>In vitro</i> / 0/ 0,2/ 2/ 20 µg/ml	No effect.
Cardiovascular function PHA9904/ GLP	Anaesthetized Dog Beagle 3M and 3F	S.C 0,003/ 0,03/ 0,3/ 3 mg/kg	No effect at any of the dose levels.
<b>Cardiovascular and respiratory system</b>			
Cardiovascular and respiratory system PHA004/ GLP	Conscious Dog Beagle 1M and 1F	S.C 1/ 3 mg/kg	None.
Cardiovascular and respiratory system TOX0005/ GLP	Conscious Dog Beagle 2M and 2F	I.V 0/ 0,03/ 0,3 (all 4 dogs)/ 3 (1 dog)/ 1 mg/kg (the remaining 3 dogs)	<b>0.3 mg/kg:</b> Slight transient fall in heart rate (HR), 10 min after dose administration. <b>1 mg/kg:</b> Transient increases in HR & BP approx. 4 to 15 min after dose administration. No ECG changes. <b>3 mg/kg:</b> Marked hypotension in first animal treated – therefore all others treated at 1 mg/kg. Single premature QRS complex at 2.5h, and 2 premature ventricular contractions at 4 h after dosing.
Cardiovascular and respiratory system TOX0118/ GLP	Anaesthetized Dog Beagle 4M	I.V 1/ 3 mg/kg	<b>3 mg/kg:</b> moderate decrease in blood pressure for 30 min and transient increase in contractility index.
Cardiovascular and respiratory system TOX0402/ GLP	Cynomolgus monkeys 4M	0/ 20 mg/kg (3 doses or 3 consecutive days)	No effect was observed during the first 2 applications, however the arterial blood pressure and HR did not decline to the expected level during the dark (sleep) period after the 3 administration but stayed at levels observed at the light (wake) level.
<b>Respiratory system</b>			

<b>Organ Systems Evaluated/ Study ID/ GLP-status</b>	<b>Species/ Strain Number</b>	<b>Method of Administration/ Dose</b>	<b>Major findings</b>
Respiratory system PHA9906 GLP	Rat, Wistar 6M and 6F	S.C 0/ 0.03/ 0.3/ 3 (method control, clonidine)	None.
Respiratory system PHA0401 GLP	Rat, Sprague Dawley 8M	S.C 0/0,5/ 5/ 50 (reference substance morphine)	No effect at any of the dose levels, however a very weak but statistically significant effect on inspiratory time in 0.5 and 50 mg/kg group was observed.
<b>Renal function</b>			
Renal study with saline overload PHA9903/ GLP	Rat, Wistar 6M and 6F	S.C 0/ 0,03/ 0,3/ 3 (method control, furosemide)	None.
<b>Automatic nervous system</b>			
Autonomic nervous system PHA9905/ GLP	Rat Wistar 6M and 6F	S.C 0/ 0,03/ 0,3/ 3 (method control, guanethidine)	None.
<b>Intestinal transit</b>			
Intestinal transit PHA9902 GLP	Rat Wistar 6M and 6F	S.C 0/ 0,03/ 0,3/ 3 (method control, atropine)	None.

*HEK – Human Embryonic Kidney / HR = heart rate*

Histamine releasing properties of degarelix have been investigated *in vitro* in rat peritoneal cells and human skin in comparison with other GnRH antagonists (abarelix, cetrorelix and ganirelix). Histamine-releasing activity was weak and similar or lower than other GnRH antagonists tested.

Degarelix induced no statistically significant effect on cutaneous vascular permeability following single intradermal administration in female rats. In a tolerance study in dogs prior to a cardiovascular study, dogs developed clinical signs consistent with a histamine reaction following three consecutive daily s.c doses of 20 mg/kg/day and higher.

- Pharmacodynamic drug interactions

No specific pharmacodynamic drug interaction studies have been submitted.

### **Pharmacokinetics**

The following methods of analysis were used to determine the pharmacokinetic profile of degarelix in animal models: radiommunoassay, liquid chromatography with tandem mass spectrometry detection (LC\_MS/MS), and scintillation counting of total radioactivity. The pharmacokinetics of degarelix was primarily obtained from the toxicology studies.

#### *Absorption*

After subcutaneous administration, degarelix forms a local depot at the injection site, leading to retarded and extended release of the active drug. The release from the depot is dependent on the concentration in the dose formulation and the dose volume. Furthermore, in repeat dose studies, increasing concentrations in the dose formulation resulted in sub-proportional increases in maximum plasma concentration ( $C_{max}$ ) and area under plasma concentration vs time in the dosing interval ( $AUC_{\tau}$ ), an increase in trough plasma concentration ( $C_{trough}$ ), an increase in terminal half-life ( $t_{1/2}$ ), thus increasing the time to reach steady state, and a tendency of increase in time to maximum plasma concentration ( $T_{max}$ ).

#### *Distribution*

The protein binding in plasma of mouse, rat, dog, monkey, and humans was measured using the <sup>3</sup>H-degarelix and the ultracentrifugation technique. The plasma binding was approximately 90% in

animals and humans. Distribution of radioactivity following administration of 3H-degarelix was studied in rats, dogs and monkeys, doses were respectively 0.03 mg/kg, 0.003 mg/kg and 0.0082 mg/kg. Radioactivity of tissues was measured after sacrifice and necropsy of the animals. High concentrations were mainly seen at the s.c. injection site and in organs of excretion. Lower concentrations, but still higher than those in plasma were generally seen in some organs of the endocrine and reproductive systems most of which contain specific receptors for LHRH, and organs rich in reticuloendothelial cells during the elimination phase. There was no indication of tissue retention.

### *Metabolism*

The stability of degarelix was studied in liver microsomes from males in rat, guinea pig, rabbit, dog, monkey, and human, for up to 60 min. No degradation of degarelix was detected in liver microsomes from rabbit, dog, monkey, and human. Tendency to minor degradation of degarelix was seen in liver microsomes from guinea pig and rat. The *in vitro* metabolism of degarelix was further investigated in human liver microsomes for up to 60 min. The metabolism pattern of degarelix was reported to be similar in humans and animals. Degarelix was virtually no substrate for oxidative metabolism, but was degraded by peptidases with generation of various truncated peptides. Only low concentration of one metabolite was seen in human plasma, and this metabolite was also seen in rats, dogs and monkeys. The metabolism data support the use of rats and monkeys for evaluation of toxicity.

### *Excretion*

Balance of the radioactivity following SC administration of 3H-degarelix was studied in rats, dogs and monkeys. Degarelix was mainly excreted unchanged via the urine and was subject to sequential peptidic degradation during its elimination via the hepato-biliary pathway in both animals and man.

### *Pharmacokinetic interactions*

*In vitro* studies have been conducted to assess the effect of degarelix on hepatic isoenzymes and also on protein transporters (efflux and influx). No inhibition or induction effects were seen. No studies were carried out in animal biomaterials or *in vivo*.

## **Toxicology**

- Single dose toxicity

Single dose toxicity studies have been conducted using subcutaneous and intravenous routes in mice, rats and monkeys. The acute toxicity studies indicate a rather low toxicity of degarelix after s.c. dosing, which is the intended route of administration in humans. No deaths occurred, and no clinical signs were observed, except for a local reaction at the injection site and the expected pharmacological effect. With i.v. dosing, the lowest lethal dose in rats was 12.5 mg/kg. Deaths occurred within minutes after dosing. Findings in decedents were non-specific, with congestion of internal organs.

- Repeat dose toxicity (with toxicokinetics)

Studies have been performed with s.c and i.v administration. By subcutaneous route, rats and monkeys were treated up to 6 and 12 months respectively. Moreover, a 13-week study was carried out in mice, primarily as a dose range finding study for a carcinogenicity study. By intravenous route, treatment was administered for up to 4 weeks in rats and monkeys. A summary of the pivotal repeat dose toxicity studies is presented below:

Following s.c administration, the predominant effects were related to the pharmacological properties of degarelix. Complete chemical castration was obtained at all dose levels, hence those effects that are related to the pharmacological effect were not clearly dose-related. They included atrophy of reproductive organs, effects on body weight, haematology, and clinical chemistry. Similar changes were observed in the rat study comparing surgical castration with degarelix treatment. The maximum

tolerated dose was governed by the local reaction at the injection sites. There were dose-related increases in the local reactions at injections sites, which in mice and rats caused signs of systemic toxicity in some studies. These were decrease in body weight, decrease in red blood cell parameters, elevated neutrophil counts, and in mice extramedullary haemopoiesis, granulopoiesis in bone marrow and lymphoid hyperplasia. These systemic reactions have on occasion been the reason for pre-term euthanasia. In monkeys there was a dose-related increase in reactions at the injection site, which in the 12 month study led to sacrifice of one high dose male after 8 months. Disregarding the pharmacological effects or local reaction, no target organ was identified. Disregarding the systemic effects levels related to the local reaction, the NOAEL were 100 mg/kg/ 2weeks in mice and rats and 50 mg/kg/ 4 weeks in monkeys.

By intravenous route, disregarding the pharmacological effects, the findings with toxicological significance were transient effects on the blood pressure and heart parameters in both species and systemic toxicity in the lungs, kidneys, and liver in the rat, and the kidneys and liver in monkeys, with evidence of uptake of degarelix in cells of the reticuloendothelial system (RES) in lungs, liver and spleen.

The pharmacokinetic profile comparison amongst species is presented in the table 2 below:

Table 2: Pharmacokinetic profile comparison amongst species

Species	Dosage mg/kg/ (dose interval)	C <sub>max</sub>		C <sub>trough</sub>		C <sub>mean</sub> =AUC <sub>0-τ</sub> /τ	
		ng/ml	Ratio	ng/ml	Ratio	ng/mL	Ratio
Man	1.03	70	1.0	10.9	1.0	23.7	1.0
Mouse 13 week [TOX0111]	1.0 (2weeks)	261	3.7	0.46	0.04	8.9	0.4
	10 (2weeks)	403	5.8	29	2.7	53	2.3
	100 (2weeks)	2268	32	95	8.7	354	14.9
Rat 13 week [TOX0112]	0.5 (2weeks)	87	1.2	0.49	0.04	5.3	0.2
	5.0 (2weeks)	131	1.9	25	2.3	34	1.5
	50 (2weeks)	261	3.7	127	11.7	122	5.2
Rat 26 week [TOX0401]	10 (2weeks)	253	3.6	52	4.8	82	3.5
	50 (2weeks)	447	6.4	158	14.5	221	9.3
	100 (2weeks)	506	7.2	206	18.9	294	12.4
Monkey 12 month [TOX0126]	0.5 (4weeks)	63	0.9	3.5	0.3	10.2	0.4
	5 (4weeks)	165	2.4	27	2.5	55	2.3
	50 (4weeks)	1204	17	124	11.4	315	13.3
Mouse 104 week [CAR0102]	2.0 (2weeks)	398	5.7	3.8	0.3	24	1.0
	10 (2weeks)	557	8.0	58	5.3	110	4.7
	50 (2weeks)	1217	17	148	13.6	404	17.0
Rat 104 week [CAR0101]	2.0 (2weeks)	155	2.2	21	1.9	43	1.8
	10 (2weeks)	301	4.3	113	10.4	148	6.2
	25 (2weeks)	534	7.6	234	21.5	294	12.4

- Genotoxicity

The genotoxicity of degarelix has been studied with respect to gene mutations in bacteria, mutations in TK locus *in vitro* in mouse lymphoma L5178Y cells and *in vivo* in the rat micronucleus test in bone marrow. The *in vitro* program including 6 Ames test and 6 TK locus assay in murine lymphoma was carried out as part of programmes to qualify changes of production methods. No genotoxic potential was evident in any test system.

- Carcinogenicity

Long-term (104-week) carcinogenicity studies have been performed in mice and rats following s.c administration. There was a dose-related increase in severity of reactions at the injection site in both species.

In mice, degarelix was administered at 2, 10 and 50 mg/kg/2 weeks. In males, statistical significant increase in the incidence of focal hyperplasia of the intermediate lobe of the pituitary was observed from the lowest dose tested. In the liver, hepatocellular adenoma was increase in incidence in all female groups and to a lesser extent in male. In the lung, bronchio-alveolar adenoma was increased in incidence in all female groups. There was an increased incidence of sarcoma at the injection site.

In rats, degarelix was administered at 2, 10 and 25 mg/kg/ 2 weeks. In female rats the incidence of hemangiosarcomas in the mesenteric lymph node was increased, however, the incidence was low, and there was no concurrent increase in treated males.

- Reproduction Toxicity

In agreement with the pharmacological effect, treatment with degarelix resulted in infertility in male rats, which was reversible following termination of treatment. There was a good agreement between the persistence of degarelix in serum/plasma and the persistence of decreased testosterone levels.

Disruption of hormonal balance in female rats and rabbits led to a dose-dependent prolongation of the time to mating and pregnancy, a reduced number of corpora lutea, increased number of pre- and post-implantation loss, and increased number of abortions, and increased number of early embryo/foetal deaths, an increased number of premature delivery and an increased duration of parturition. The dams were more sensitive to the effect of degarelix in the early part of the gestation period. No teratogenic effects were observed in rats or rabbits. No adverse effects during lactation or on pup growth and development were observed

- Toxicokinetic data

The ratios between the mean plasma concentrations at the highest dose level and plasma concentrations in humans at the recommended human dose were 17 and 12,4 in mice and rats respectively. This data was obtained from 104-week carcinogenicity studies in rats and mice with subcutaneous administration of degarelix.

The effect of degarelix on fertility was examined in male rats and showed infertility.

To support possible indications in women, the effects of degarelix in embryo-foetal development were studied in rats and rabbits, and the effects of degarelix in prenatal and postnatal development were evaluated in rats. Degarelix did not reveal any teratogenic potential in rats and rabbits. There were no adverse effects on pup growth and development. Studies in juvenile animals were not performed.

- Local tolerance

Local tolerance has been examined following subcutaneous, intramuscular or intravenous administration in mice, rats and monkeys and in specific local tolerance in rabbits. The subcutaneous administration was associated with a dose dependent localised inflammatory response, resulting in the formation of a foreign body giant cell granuloma.

- Other toxicity studies

Studies were conducted to examine the long term fate of a subcutaneous depot, to examine the acute distribution after a single lethal dose by intravenous administration and to evaluate target organs (the time to develop and the efficacy of clinical chemical markers of treatment-related hepatic and renal effects) in response to single and repeated intravenous administration of degarelix in rats. There was a tendency for a decrease in availability when the viscosity in the dosing solution increased. The potential for antigenicity and passive cutaneous anaphylaxis were studied in guinea pigs. There was no indication of degarelix stimulating an acute anaphylactic response in guinea pigs after subcutaneous induction followed by either intravenous or subcutaneous challenge. The potential for inducing phototoxicity was also assayed. A neutral red uptake phototoxicity assay in Balb/C 3T3 mouse fibroblasts indicated no potential for phototoxicity.

### **Ecotoxicity/environmental risk assessment**

An environmental risk assessment was performed with reference to the Guideline on the environmental risk assessment (EMA/CHMP/SWP/4447/00).

### **Discussion on the non-clinical aspects**

The following non-clinical issues were identified in this application:

Regarding the environmental risk assessment, given the pharmacological activity of the drug, the CHMP considered that an endocrine disruptor activity could be suspected. As outlined in the guideline on the environmental risk assessment, some drug substances as potential endocrine disruptors need a Phase II environmental risk assessment irrespective of the quantity release into the environment. Therefore, the applicant agreed to perform a phase II environmental risk assessment with an investigation of the endocrine disruptor activity as a follow-up measure, as requested by the CHMP. The studies (readily biodegradability, adsorption to sewage sludge and the fish screening assay for endocrine active substances) were considered an appropriate tailored risk assessment strategy, given that there are no international accepted test guidelines for establishing endocrine disrupting effects

Degarelix is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients (see SPC section 4.3).

No formal drug-drug interaction studies have been performed with degarelix, given the experience with GnRH analogues, and the little or no activity in the *in vitro* radioligand binding assays. Given that androgen deprivation treatment may prolong the QTc interval, the CHMP considered that the concomitant use of degarelix with drugs known to prolong the QTc interval or drugs able to induce torsades de pointes (e.g. class IA (quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, cisapride, moxifloxacin, antipsychotics, etc.) should be carefully evaluated. Degarelix was not a substrate for the human CYP450 system and had not been shown to induce or inhibit CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4/5 to any great extent *in vitro*. Therefore, clinically significant pharmacokinetic drug-drug interactions in metabolism related to these isoenzymes are considered unlikely (see SPC section 4.5).

There is no relevant indication for use of degarelix in women. However, in both reproductive toxicity and toxicokinetic studies, no adverse effects during lactation or on pup growth and development were observed with degarelix (see SPC section 4.6).

## 2.4 Clinical aspects

### Introduction

The clinical development programme of degarelix consisted of pharmacokinetic studies (absorption, bioavailability, distribution, excretion, metabolism, dose proportionality, special populations, drug-drug interactions and safety/interaction studies), pharmacodynamic studies, dose response studies and main clinical studies.

### GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

### Pharmacokinetics

The pharmacokinetic profile of degarelix has been investigated during the clinical development program in:

- three phase I studies in healthy subjects (CS01, CS05, CS08),
- five phase II studies in patients with prostate cancer (CS02, CS06, CS07, CS12, CS14, CS15),
- one phase III study in patients with prostate cancer (CS21),
- one study in Japanese patients (CS11),
- one study in subjects with mild or moderate hepatic impairment (CS23).

*In-vitro* studies investigated plasma protein binding, metabolism, the stability of degarelix in plasma drug-drug interactions, and interaction with drug transporters.

Table 3

Study ID and Indication	Design	Treatments <sup>1</sup>	Number of subjects treated with degarelix	Population
<b>Phase 1 studies in non-prostate cancer subjects</b>				
[CS01]	Randomised, placebo-controlled, double-blind dose escalation	Single s.c. dose 0.5@5 0.1mLx1 2@5 0.4mLx1 5@10 0.5mLx1 10@10 1 mLx1 20@20 1 mLx1 40@20 1 mLx2 40@10 2 mLx2 40@20 2 mLx1 30@15 2 mLx1 30@30 1 mLx1	6 6 6 6 6 6 6 6 6 6 6	Healthy men 19-69 years of age
[CS05]	Open label, dose escalation	15 or 45 min i.v. infusion 1.5, 6, 15, 30 µg/kg single s.c 20@5. single i.m. 20@5	24, 6/group 6 6	Healthy men 19-46 years of age
[CS08]	Open-label, randomised, placebo-controlled, dose-response	48 h i.v. infusion 0.864, 1.73, 3.70, 9.87, 24.7, 49.4 µg/kg	48	Healthy men ≥65 years of age
[CS23]	Open-label, parallel	1 h i.v. infusion 1 mg	24	16 subjects with mild or moderate hepatic impairment, 8 healthy subjects
<b>Phase 2 and Phase 3 studies in prostate cancer patients</b>				
[CS02]	Randomised, open label, parallel groups, uncontrolled	Once monthly, s.c.: 40/40/40@20 80/80/40@20 80@20/-/20@10	46 43 40	55-87 years of age
[CS06]	Open-label, dose escalation, uncontrolled	Single dose, s.c.: 40@10 80@20 120@30 160@40	10 24 24 24	59-88 years of age
[CS07]	Open-label, dose escalation, uncontrolled	Single dose, s.c.: 120@20 120@40 160@40 200@40 200@60 240@40 240@60 320@60	25 12 12 24 24 24 24 27	48-89 years of age
[CS11]	Open-label, dose escalation, uncontrolled	Single dose, s.c.: 160@40 200@40 240@40	6 6 6	Patients from Japan 56-74 years of age

[CS12]	Open-label, randomised, parallel, uncontrolled	Once monthly, s.c.: 200/80@40 200/120@40 200/160@40 240/80@40 240/120@40 240/160@40	30 32 32 30 33 30	52-93 years of age
[CS14]	Open-label, randomised, parallel groups, uncontrolled	Once monthly, s.c.: 200@40/60@20 200@40/80@20	63 64	47-93 years of age
[CS15]	Open-label, randomised, parallel groups, uncontrolled	Every 3 months, s.c.: 240@40/240@40 (Months 3-6-9) 240@40/240@60 (Months 3-6-9) 240@40/240@60 (Months 4-7-10)	150 150 147	49-90 years of age
[CS21]	Randomized parallel groups, open label, active controlled	Once monthly, s.c.: 240@40/80@20 240/160@40	207 202	50-98 years of age

During the degarelix clinical development programme, bioanalytical methods based on both radioimmunoassay (RIA) and liquid chromatography with tandem mass spectrometry detection (LC-MS/MS) were used for the quantification of degarelix in human biological samples (plasma, urine and plasma ultracentrifugate). The LC-MS/MS methods used to determine the degarelix concentrations in plasma were adequately validated with respect to precision, accuracy and stability. However, for some methods (0595/036 and 0595/046) employed in a total of 10 studies, high variability of the internal standard and low and variable recovery values were considered a problem.

The measurement and identification of metabolites in vitro in human biomaterial and in vivo in human plasma, urine, and faeces was also performed by LC-MS/MS. However, no validation reports were submitted for the analysis of metabolites in plasma, urine and faeces.

Two different methods were used to manufacture the drug substance: One formulation (SPPS) is used in all phase I and most phase II studies while the other formulation (LPPS) is used in only two phase II (CS15/15A and CS18) and one phase III (CS21/21A) study. The pharmacokinetics of the two formulations, when administered s.c., seems not to be identical. However, no bioequivalence study comparing these two types of formulations has been performed. Thus, the applied posology regarding dose, concentration and formulation has not been tested adequately in pharmacokinetic studies. A new, thorough PK study with the applied posology and formulation was requested to be performed to confirm the simulated data as a follow-up measure (see discussion on clinical pharmacology aspects).

- Absorption

The pharmacokinetics of degarelix were investigated in three studies (CS06, CS07 and CS11) after single dose administrations in prostate cancer patients. The mean terminal half-life was long (between 23 and 61 days) and markedly variable between subjects and studies.  $C_{max}$  (maximum observed serum concentration) and AUC (Area Under the Concentration) were influenced by several factors including dose, number of injections and the concentration of the delivered degarelix suspension.  $T_{max}$  ranged from 34 to 62 hours. Steady state occurred after 5-6 months with the 240/80 mg dosing regimen.

With regards to absorption, after subcutaneous administration of 240 mg degarelix at a concentration of 40 mg/ml to prostate cancer patients in the pivotal study CS21, the  $AUC_{0-28 \text{ days}}$  was 635 (602-668) day\*ng/ml,  $C_{max}$  was 66.0 (61.0-71.0) ng/ml and occurred at  $T_{max}$  at 40 (37-42) hours. Mean trough

values were approximately 11-12 ng/ml after the starting dose and 11-16 ng/ml after maintenance dosing of 80 mg at a concentration of 20 mg/ml.

- Bioavailability

The pharmacokinetic properties of degarelix after a subcutaneous or intramuscular injection to healthy men were investigated in studies CS01 and CS05. The bioavailability was calculated to 30-40% for both administration routes.

- Distribution

Degarelix was found to be released from the depot form in two phases: a first phase of fast release shortly after dosing followed by a slow release phase. Spontaneous formation of the gel-like depot only occurs after injection of degarelix suspension at concentrations  $\geq 5\text{mg/mL}$ . The distribution volume in healthy elderly men was approximately 1 l/kg and plasma protein binding is estimated to be approximately 90%.

Binding of degarelix was mainly on serum albumin and  $\alpha$ 1- and glycoprotein. Estimated Vd (volume of distribution) was high and close to 1L/Kg.

- Elimination

Approximately 20 % of degarelix appears to be excreted unchanged in the urine. Degarelix is eliminated in a biphasic fashion, with a median terminal half-life of approximately 43 days for the starting dose or 28 days for the maintenance dose, as estimated based on population pharmacokinetic modelling.

- Metabolism

Degarelix is subject to common peptidic degradation during the passage of the hepato-biliary system and is mainly excreted as peptide fragments in the faeces. No significant metabolites were detected in plasma samples after subcutaneous administration. In vitro studies showed that degarelix is not a substrate for the human CYP450 system. In healthy men, approximately 20-30% of a single intravenously administered dose was excreted in the urine, suggesting that 70-80% is excreted via the hepato-biliary system. The clearance of degarelix when administered as single intravenous doses (0.864-49.4 $\mu\text{g/kg}$ ) in healthy elderly men was found to be 35-50 ml/h/kg.

The data relative to drug metabolism through hepatic system are sparse and not part of the main clinical pharmacokinetic studies (CS01, CS06, CS07, CS23).

- **Pharmacokinetics of metabolites**

No active metabolites were identified and only one of the six identified metabolites were detected in plasma.

Two studies in human liver microsomes showed that degarelix is a very poor substrate for the CYP450 metabolism in vitro. Further, degarelix showed no propensity to form glucuronidated metabolites in vitro. In line with this, no oxidative metabolites or conjugated metabolites of degarelix have been detected in samples from clinical studies.

Small amounts (0-10%) of FE 200486(1-9) (2.7.2) were detected in plasma from CS11 and CS23. This is a known metabolite of degarelix and has previously been detected in human liver microsomes and in animal plasma and excreta. The presence of less than 10% of FE 200486(1-9) in plasma was not regarded to be of any clinical relevance.

- Dose proportionality and time dependencies

Global dose-proportionality for C<sub>max</sub> and AUC was established from single-dose studies in healthy subjects and prostate cancer patients. Pharmacokinetic follow-up during repeated administrations (up to 11-12 doses) showed no signs of drug accumulation (through levels).

- **Pharmacokinetics in target population**

Comparison of clearance and distribution volume between healthy subjects and prostate cancer patients are presented in table 4 below:

Table 4: Comparison of clearance and distribution volume of degarelix following a single subcutaneous dose of degarelix to prostate cancer patients and healthy subjects.

		Healthy subjects [CS01,] <sup>1</sup>						Prostate cancer patients [CS06,]		
		10@10 1mLx1 N=6	20@20 1mLx1 N=6	30@15 2mLx1 N=6	30@30 1mLx1 N=6	40@20 1mLx2 N=6	40@10 2mLx2 N=6	40@20 2mLx1 N=6	40@10 2mLx2 N=10	80@20 2mLx2 N=24
<b>Degarelix conc.</b> mg/mL		10	20	15	30	20	10	20	10	20
<b>CL/F</b> (L/h)	Mea n	5.45	8.18	6.10	7.91	5.84	5.67	6.08	12.3	7.3
	S.D.	0.87	2.50	0.73	1.94	1.14	1.23	1.21	5.3	2.5
<b>V<sub>z</sub>/F</b> (L·10 <sup>-3</sup> )	Mea n	6.8	11.6	8.4	18.7	9.2	7.9	10.4	9.4	10.7
	S.D.	1.7	2.3	2.4	8.8	2.3	1.9	3.3	3.0	3.6

Source: [CS01], [CS06]

<sup>1</sup>The denotation x@y, e.g. 30@15, translates into a dose of x (30) mg at a concentration of y (15) mg/mL

- Special populations

*Impaired renal function*

No specific study was conducted in patients with renal impairment (see discussion on clinical pharmacology aspects).

*Impaired hepatic function*

The study performed in subjects with mild or moderate hepatic impairment was conducted with a single i.v. dose (1.0mg) and not with a s.c. dose representative of the proposed schedule (CS23). Study CS23 was an open-label, single center, single-dose, controlled study conducted in three parallel groups of eight subjects each, two test groups of subjects with hepatic diseases (mild or moderate hepatic impairment) and a control group of healthy subjects. The study showed that there was no increased exposure to degarelix in hepatically impaired patients compared to healthy subjects. Actually, somewhat lower exposure was seen especially in patients with moderate hepatic dysfunction. Furthermore, a rapid decrease in the plasma levels of testosterone and LH in healthy as well as hepatically impaired subjects was seen subsequently to the degarelix administration.

*Gender*

Degarelix is not indicated in women. Therefore the impact of the gender on the degarelix PK profile was not studied.

*Race*

There is no evidence that the PK profile of degarelix is different between different races.

### *Weight and elderly:*

The impact of these factors on the PK profile of degarelix was assessed via a PK modelling analysis based on the pivotal study CS21. It would have been advisable to examine the impact of age and weight on degarelix pharmacokinetics by performing a comparative analysis with true observed data. Indeed, the PK modelling analysis shows a significant impact of weight and age on the PK parameters of degarelix. Weight and age were covariates in the FE200486 CS21 PK Modelling Report, and degarelix clearance was estimated to increase with weight at a rate of 0.7% per kg, and central volume of distribution (V1) to increase 4% per kg body weight. With increasing age, clearance of degarelix was estimated to decrease at a rate of 0.6% per year. These results are not mentioned in the SPC and no dose adjustment is proposed. This point needs some explanation.

### *Ethnic origin and tumour stage at enrolment*

Ethnic origin (Hispanic vs not Hispanic) and tumour stage at enrolment show to have significant effects on AUC<sub>0-28</sub> at the  $\alpha=0.05$  significance level. These findings are not confirmed at the end of one year treatment duration.

The PK modelling analysis based on the pivotal study CS21 shows that the maintenance dose had significant effects on degarelix trough levels on Days 308 and 336 ( $p \leq 0.05$ ). These results need to be commented in the frame of the selected maintenance dose in the SPC.

### *Children*

There is no paediatric development programme for this medicinal product.

- Pharmacokinetic interaction studies

### *Drug-drug interaction (DDI)*

The *in vitro* metabolism of degarelix was further investigated in human liver microsomes. The total amount of the oxidative metabolites formed was very low (<1% of the initial amount of degarelix in the incubation samples), indicating that degarelix is not a substrate for the human CYP450 system.

Data from the *in vitro* studies have not shown any inhibitory effects on hepatic isoenzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5 nor any induction potential on CYP1A2, CYP2C9 and CYP3A4/5 activity. In addition degarelix has been screened in cultured human cell-lines for interactions with various transporter proteins, efflux transporters (p-glycoprotein, MRP2, BCRP, BSEP) as well as uptake transporters (OATP1B1, OATP1B3, OATP2B1).

Therefore, the PK profile of degarelix is unlikely to be affected by concomitant medication, nor to have any effect on the metabolism or excretion of such medication. Moreover, no clinical PK drug-drug interaction studies were conducted.

The target population for degarelix treatment often presents with co-morbidities and consequently to comedications which might interact with degarelix. On a pharmacokinetic aspect, the Applicant has conducted *in vitro* studies to assess the effect of degarelix on hepatic isoenzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5 and also on protein transporters (efflux and influx). Results showed that degarelix has no inducing or inhibitory effect on these enzymes and transport proteins. As regards degarelix metabolites (free amino acids derived from peptidase cleavage), in the frame of a Scientific Advice in June 2004, the Applicant was encouraged to perform further *in vitro* studies assessing the effect of metabolites on cytochromes. However, considering the low circulating metabolite amount, this issue is not considered as needed excepted for CYP2C9. Indeed, in human liver microsomes a slight, dose-independent degarelix-induced increase of CYP2C9 activity was seen. Additional data on this possible effect and potential interactions with drugs metabolised by this pathway should be provided.

In addition, the lack of *in vitro* studies assessing the inhibition and induction potential of degarelix on CYP2C8 and CYP2B6, two isoenzymes potentially involved in clinically relevant interactions; needs to be explained.

Degarelix appears to have a mild pharmacokinetic interaction profile but this does not preclude to pharmacodynamic interactions.

#### *Pharmacodynamic interactions*

No formal drug-drug interaction studies have been performed.

#### *Safety / Interactions*

The only prohibited medications during these studies were other hormone manipulative drugs, and, in CS21, those which might prolong the QT interval as well as 5- $\alpha$  reductase inhibitors. Therefore, during the clinical study program, the use of concomitant medications in the study populations has been extensive without evidence of any impact on the therapeutic effect or safety of either degarelix or the concomitant treatment.

The Applicant claims that there is no evidence of interaction between degarelix and concomitant drugs and cross-referred to a table which shows the distribution of comedications in the different arms of the 2/3 phase studies.

However, no clear table of adverse events with and without degarelix in patients treated by other drugs, (specifying the name and dosage of the concomitant drug) has been displayed. The Rapporteur insists on the fact that even if degarelix is subject to mild pharmacokinetic interaction, pharmacodynamic one (other than QT prolonging-drugs because excluded from clinical studies) cannot be ruled out. The corresponding data should be provided as a follow-up measure.

- Pharmacokinetics using human biomaterials

No studies investigating the pharmacokinetics of degarelix using human biomaterials were submitted.

#### **Pharmacodynamics**

- Mechanism of action

Degarelix is a decapeptide that antagonizes pituitary gland GnRH receptors. This compound differs from GnRH agonists in that it is a selective and competitive blocker of GnRH receptors and not an GnRH agonists (with a reversible effect). The consequence is an absence of flare up at the beginning of the treatment as observed with GnRH agonists. In addition, it differs from previous generation of GnRH antagonists in that it has weak histamine releasing properties in vitro.

- Primary and Secondary pharmacology

The pharmacodynamic effect of degarelix in pre-clinical models is also confirmed by clinical studies. In clinical studies in both healthy subjects and patients with prostate cancer, the profile of rapid testosterone suppression following degarelix administration, without any surge has been observed. A dose-response relationship was observed with respect to both the degree of testosterone suppression and the duration, as illustrated by CS01 (healthy subjects), in which s.c. single doses of degarelix ranging from 10 mg to 40 mg were investigated. It was also noted that similar to the PK profile, the pharmacodynamic effect was also influenced by the concentration of the degarelix suspension.

Data from the studies CS06, CS07 and CS11 in patients with prostate cancer demonstrated that the duration of testosterone suppression was highly dependent on both the dose and concentration of degarelix administered. These studies showed that starting doses of 200 mg and 240 mg at a concentration of 40 mg/mL suggested an effective and sustained response during the first 28 days. Two multiple dose studies, CS12 and CS14, showed that doses of 160 mg (40 mg/mL) and 80 mg (20 mg/mL) could be effective maintenance doses for evaluation in the pivotal study.

- Safety related to drug-drug interactions and other interaction studies

During the clinical study program, the use of concomitant medication in the study populations has been evaluated without evidence of any impact on the therapeutic effect or safety of either degarelix or the concomitant treatment.

In the Phase 3 active control study, the treatment groups were comparable in the use of concomitant medications. Most of the concomitant medications were in the anatomic main groups of cardiovascular system (62%), alimentary tract and metabolism (39%), blood and blood forming organs (33%), nervous system (31%), and musculoskeletal system (30%). Particularly at the therapeutic subgroup level, most commonly used concomitant medications were agents acting on the renin-angiotensin system (38%), antithrombotic agents (29%), antiinflammatory and antirheumatic products (26%), lipid modifying agents (24%), antibacterials for systemic use (23%), analgesics (23%), beta-blocking agents (22%), calcium channel blockers (17%), urologicals (17%), diuretics (16%), cardiac therapy (14%), drugs for acid related disorders (12%), and drugs used in diabetes (11%). The most commonly used concomitant medications in both treatment groups (degarelix and placebo) in the Phase 1 studies were analgesics (25%).

However, the applicant was requested to provide a clear table of adverse events with and without degarelix in patients treated with other drugs, specifying the name and dosage of the concomitant drug.

### **Discussion on clinical pharmacology aspects**

The CHMP was of the opinion that the analytical methods 0595/36 and 0595/046 had not been adequately validated, and therefore the PK data obtained using these methods [0595/036 (in the studies CS02A, CS06/06A and CS07/07A) and 0595/046 (in the studies CS11/11A, CS12/12A, CS15/15A, CS18, CS21/21A and CS23)] was considered unreliable. In addition, PK data on the LPPS formulation was considered to be very limited, and the available data was only obtained from two phase II studies (CS15/CS15A and CS18) and one phase III study (CS21/21A), using the above-mentioned methods. Therefore the applicant was asked to provide a new PK study with the applied posology and formulation, using an adequately validated analytical method as a follow-up measure. The applicant subsequently committed to perform a dedicated single/multiple dose PK-study in patients with prostate cancer (n=30) using the applied posology and the applied formulation (LPPS) and provide the study protocol in the first quarter of 2009.

It is a weakness of the submitted Marketing Authorisation Application that individual conventional pharmacokinetic data were not obtained in the target population with the proposed degarelix administration schedule. None of the pharmacokinetic (PK) studies have used the same combination of doses and concentrations as the applied posology. Only pooled data were obtained from the different subjects.

Based on results from the study DCB-MAR-9, assessing in vitro effect of degarelix on CYP2C8, the CHMP did not expect that degarelix might inhibit this isoenzyme at therapeutic concentration. However, with regards to CYP2B6, the lack of degarelix inhibitory effect on CYP3A4, 1A2, 2D6, 2C9 or 2C19 does not preclude any effect on CYP2B6. Therefore the CHMP requested that the applicant investigate an in vitro study assessing the effect of degarelix on this isoenzyme, as a follow-up measure, to which the applicant committed

With regards to cytochromes induction, the CHMP requested that further in vitro studies be carried out in order to explore the induction effect of degarelix on CYP2C8, 2C19 and 2B6, as a follow-up measure to which the applicant committed.

The pharmacokinetics of degarelix are adequately reflected in the SPC (see section 5.2)

Degarelix is eliminated in a biphasic fashion, with a median terminal half-life of approximately 43 days for the starting dose or 28 days for the maintenance dose, as estimated based on population pharmacokinetic modelling. The long half-life after subcutaneous administration is a consequence of a very slow release of degarelix from the depot formed at the injection site(s). The pharmacokinetic behaviour of the drug is influenced by its concentration in the solution for injection. Thus, C<sub>max</sub> and

bioavailability tend to decrease with increasing dose concentration while the half-life is increased. Therefore, no other dose concentrations than the recommended should be used.

Two special populations were further discussed (patients with renal impairment and patients with hepatic impairment):

With regards to patients with renal impairment, no pharmacokinetic studies were conducted. Only about 20-30% of a given dose of degarelix was excreted unchanged by the kidneys. A population pharmacokinetics analysis of the data from the confirmatory Phase III study demonstrated that the clearance of degarelix in patients with mild to moderate renal impairment is reduced by approximately 23%; therefore dose adjustment in patients with mild or moderate renal impairment is not recommended. Data on patients with severe renal impairment was scarce and the CHMP warranted caution in this patient population.

Degarelix was also studied in a pharmacokinetic study in patients with mild to moderate hepatic impairment. No signs of increased exposure in the hepatically impaired subjects were observed compared to healthy subjects. Dose adjustment was not considered necessary in patients with mild or moderate hepatic impairment. However, patients with severe hepatic dysfunction were not studied and caution is therefore warranted in this group.

### Clinical efficacy

The efficacy of degarelix was evaluated in prostate cancer patients in eight Phase 2 studies and six Phase 2 extension studies, and in one Phase 3 study and its extension study. The status, design features, dosing regimens, and numbers of patients in these studies are summarized in table 5 below:

Table 5: Overview of Phase 2 and Phase 3 Clinical Studies

Study ID	Study start Study status	Design, blinding, type of control	Study drug frequency, route of administration: degarelix dose @ concentration (mg@mg/mL) for starting /maintenance dose	No. patients entered/completed	Study duration
<b>Phase 2 Studies in Prostate Cancer Patients</b>					
CS02,	21 March 2001 Completed	Randomized, parallel groups, open label, uncontrolled	Once monthly, s.c.: 40/40/40@20 80/80/40@20 80@20/-/20@10	46/30 43/32 40/26	6 months
CS02A	22 October 2001 Completed	Extension, open label, uncontrolled	Once monthly, s.c.: 40/40/40@20 80/80/40@20 80@20/-/20@10	30/2 32/7 26/3	Study stopped by sponsor due to inadequate doses
CS06	14 May 2002 Completed	Dose escalation, open label, uncontrolled	Single dose, s.c.: 40@10 80@20 120@30 160@40	10/10 24/19 24/20 24/17	Single dose with follow- up for at least 28 days
CS06A	01 August 2002/ Completed	Extension, open label, uncontrolled	Flexible, s.c.: 40@10 80@20 120@30 160@40	1/0 11/4 16/0 9/3	Study stopped by sponsor due to inadequate doses

Study ID	Study start Study status	Design, blinding, type of control	Study drug frequency, route of administration: degarelix dose @ concentration (mg@mg/mL) for starting /maintenance dose	No. patients entered/completed	Study duration
CS07	22 November 2002 Completed	Dose escalation, open label, uncontrolled	Single dose, s.c.: 120@20 120@40 160@40 200@40 200@60 240@40 240@60 320@60	25/24 12/8 12/9 24/19 24/23 24/21 24/23 27/26	Single dose with follow- up for at least 28 days
CS07A	21 October 2003 Completed	Extension, open label, uncontrolled	Flexible, s.c.: 120@20 120@40 160@40 200@40 200@60 240@40 240@60 320@60	20/4 6/1 7/2 24/6 17/4 20/4 14/4 23/11	Study stopped by sponsor due to inadequate doses
CS11	16 January 2004 Completed	Dose escalation, open label, uncontrolled	Single dose, s.c.: 160@40 200@40 240@40	6/5 6/6 6/4	Single dose with follow- up for at least 28 days
CS12	25 September 2003 Completed	Randomized, open label, uncontrolled	Once monthly, s.c.: 200/80@40 200/120@40 200/160@40 240/80@40 240/120@40 240/160@40	30/20 32/23 32/26 30/28 33/27 30/23	Thirteen 28- Day cycles (one year)
CS12A	22 February 2005 Ongoing  Dose shift effective 27 January 2006	Extension, open label, uncontrolled	Once monthly, s.c.: 80@40 120@40 160@40  After dose shift: 160@40	45 48 44  106	Until marketing approval granted in participating countries
CS14	23 February 2004 Completed	Randomized, parallel groups, open label, uncontrolled	Once monthly, s.c.: 200@40/60@20 200@40/80@20	63/42 64/45	Thirteen 28- Day cycles (one year)
CS14A	07 March 2005 Ongoing  Dose shift effective 24 July 2006	Extension, open label, uncontrolled	Once monthly, s.c.: 60@20 80@20  After dose shift: 160@40	30 27  33	Until marketing approval granted in participating countries

Study ID	Study start Study status	Design, blinding, type of control	Study drug frequency, route of administration: degarelix dose @ concentration (mg@mg/mL) for starting /maintenance dose	No. patients entered/completed	Study duration
CS15,	27 October 2004 Completed	Randomized, parallel groups, open label, uncontrolled	Every 3 months, s.c.: 240@40/240@40 (Months 3-6-9) 240@40/240@60 (Months 3-6-9) 240@40/240@60 (Months 4-7-10)	150/121  150/125  147/128	12 to 13 months
CS15A,	16 January 2006 Ongoing   Dose shift effective 11 September 2006	Extension, open label, uncontrolled	Every 3 months, s.c.: 240@40 (Months 3-6-9) 240@60 (Months 3-6-9) 240@60 (Months 4-7-10)  After dose shift: 360@60 480@60	87  89  80   99 103	Until marketing approval granted in participating countries
CS18,	23 March 2007 Ongoing	Randomized parallel groups, open label, uncontrolled	Every 3 months (Months 1, 4, 7, and 10), s.c.: 240@40/360@60 240@40/480@60	67 66	13 months
<b>Phase 3 Studies in Prostate Cancer Patients</b>					
CS21	07 February 2006 Completed	Randomized parallel groups, open label, active controlled	Once monthly, s.c.: 240@40/80@20 240/160@40 leuprolide 7.5 mg	207/169 202/163 201/172	One year
CS21A	12 March 2007/ Ongoing	Randomized parallel groups,	Once monthly, s.c.: Continue degarelix: 80@20 160@40  Switch to degarelix from leuprolide 7.5 mg: 240@40/80@20 240/160@40	120 123   67 65	Until marketing approval granted in participating countries

Sc = subcutaneous.

Cut off date: 28 September 2007.

Extension study numbers include an "A" after the CS number of the main study (e.g., CS21A is the extension study of the main study CS21).

The primary endpoint in all studies was the reduction of serum testosterone to castrate levels (i.e.,  $\leq 0.5$  ng/mL).

The primary prostate cancer inclusion criteria were similar throughout the Phase 2/3 program. Eligible patients were to have a histologically confirmed (Gleason graded) adenocarcinoma of the prostate (any stage). This included patients with a rising prostate specific antigen (PSA) level who had previously undergone prostatectomy or radiotherapy with curative intent. Patients had to have a PSA value of  $\geq 2$  ng/mL, except for the first study [FE200486 CS02, in which the PSA value had to be  $\geq 20$  ng/mL.

"A" following a study number indicates that the study is an extension of the main study. Also, "FE 200486" that precedes each study number is the sponsor's internal code for degarelix. Further citations of study numbers will be by CS number only.

- Dose response studies

#### *Starting dose*

According to the applicant, Study CS06 suggested that the dose of 120mg leads to the longest median

time to insufficient testosterone response and the highest proportion of patients with testosterone response in comparison with the other tested doses. However neither the 120mg nor the other doses reached a sufficient proportion of patients (i.e between 90% and 100%) with testosterone response. Study CS07 suggested that the doses/concentration combinations of 200 mg (40 mg/mL) and 240 mg (40 mg/mL) produce an effective and sustained response for at least 28 days and could be considered as acceptable starting regimens. The repeated dose study CS12 suggested that the doses/concentration combinations of 240 mg (40 mg/mL) as starting dose produced an effective response for at least 28 days. Indeed, the proportion of patients with testosterone suppression (testosterone  $\leq 0.5$  ng/mL) at Day 28 was higher (although not statistically significant) after the 240 mg than the 200 mg initiation dose. For the 240@40 pooled group the proportion of patients with testosterone  $\leq 0.5$  ng/mL was 95% (n=93, 5 failures) whereas for the 200@40 pooled group the proportion was 86% (n=94, 13 failures) (p=0.089).

#### *Maintenance monthly dose*

According to the applicant, Study CS12 suggested that maintenance doses of 160 mg (40mg/ml) or 120 mg (40mg/ml) produce sustained testosterone suppression. Study CS14 suggested that the maintenance dose of 80 mg (20mg/ml) produces a higher testosterone suppression out to day 364, than the 60 mg (20mg/ml).

- Main study

#### **Study FE 200486 CS21**

##### METHODS

CS21 an open-label study with different routes of administration for degarelix Subcutaneous (s.c) and leuprorelin 7.5 mg, Intramuscular (i.m.).

Patients were assessed for testosterone, PSA, LH and FSH on day 0, 1, 3, 7, 14 and 28, and then every 28 days for one year.

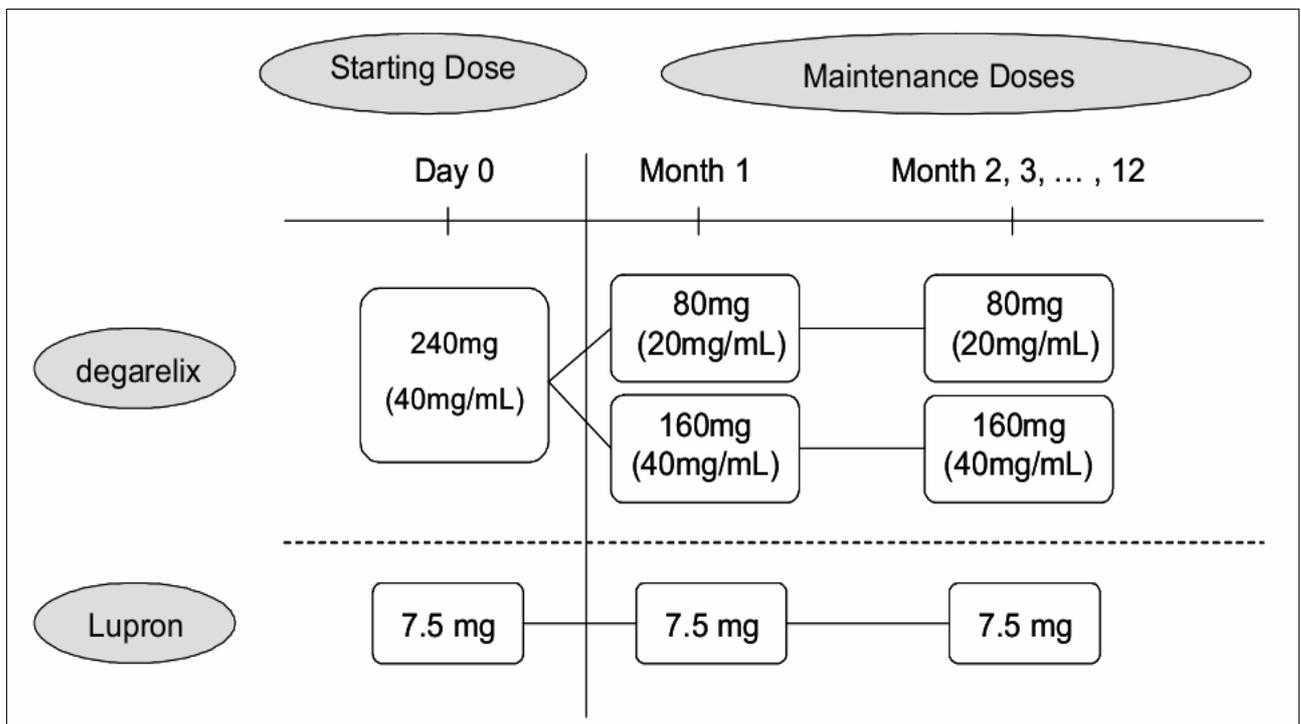
Patients who received degarelix were assessed for degarelix concentration before treatment on day 0, after starting dose on day 1, 3, 7 and 14, and before treatment on day 28, 308 and 336.

Some patients were included in a sub-study in France, Germany, Romania and Netherlands. An Magnetic Resonance Imaging (MRI) investigation was introduced at baseline, on day 28, 196 and day 364, in order to evaluation tumour size and infiltration into adjacent tissues.

Patients completed Quality of Life (QoL) questionnaires on day 0, 28, 84, 168 and at the end of study visit.

An external, independent Data Safety Monitoring Board (DSMB) was established to ensure the safety of the patients participating in the study, composed of three clinical experts and a statistician. There were no findings by the Ferring Safety Committee or the DSMB that had an impact on the study conduct and no safety concerns were identified.

A diagrammatic representation of the study design is provided below:



### Study Participants

The main inclusion criteria were:

- Histologically confirmed adenocarcinoma of the prostate, all stages, requiring androgen ablation treatment, including patients with rising PSA after having undergone curative prostatectomy or radiotherapy.
- Age  $\geq$  18 years old.
- Serum testosterone  $>$  1.5ng/mL.
- ECOG  $\leq$  2.
- PSA  $\geq$  2ng/mL.
- Life expectancy  $>$  12 months.

The main exclusion criteria were:

- Previous or concurrent hormonal management of prostate cancer (surgical or medicinal), apart from neoadjuvant/adjuvant hormonal therapy for a maximum duration of 6 months, and terminated at least 6 months before inclusion.
- Concurrent treatment with a 5- $\alpha$ -reductase inhibitor.
- Concurrent medications that may prolong the QT/QTcF interval
- Considered candidate for curative therapy (prostatectomy or radiotherapy).
- History of severe untreated asthma, anaphylactic reactions or severe urticaria and/or angioedema.
- Marked baseline prolongation of QT/QTcF interval, history of additional risk factors for Torsade de Pointes ventricular arrhythmias, use of concomitant medications that may prolong QT/QTcF (QTc interval using Fridericia's correction) interval.
- Adequate liver function.

### Treatments

- Degarelix 240/160: degarelix starting dose of 240mg (40mg/mL) on Day 0 administered as two equivalent s.c. injections of 120 mg each. Thereafter, patients received 12 additional single s.c. degarelix doses of 160mg (40mg/mL) every 28 days.
- Degarelix 240/160: degarelix starting dose of 240mg (40mg/mL) on Day 0 administered as two equivalent s.c. injections of 120 mg each. Thereafter, patients received 12 additional single s.c. degarelix doses of 160mg (40mg/mL) every 28 days.
- LUPRON: leuporelin 7.5 mg at Day 0 and every 28 days subsequently, administered as a single

## *Objectives*

This study investigated the efficacy and safety of two degarelix dosing regimens with a 240 mg starting dose and either 160 mg (40 mg/mL) or 80 mg (20 mg/mL) maintenance doses, and leuprorelin 7.5 mg administered at monthly intervals for up to 12 months in patients with prostate cancer. Both degarelix dosing regimens were compared against a threshold value for suppression of testosterone to castrate levels and to leuprorelin 7.5 mg.

## *Outcomes/endpoints*

### Primary endpoint

- Probability of testosterone  $\leq 0.5$  ng/mL from Day 28 through Day 364.

### Secondary endpoints

- Proportion of patients with testosterone surge during the first 2 weeks of treatment
- Proportion of patients with testosterone level  $\leq 0.5$  ng/mL at Day 3
- Percentage change in PSA from baseline to Day 28
- Probability of testosterone  $\leq 0.5$  ng/mL from Day 56 through Day 364
- Serum levels of testosterone, LH, FSH and PSA over time
- Time to PSA failure (two consecutive increases of 50%, and at least 5 ng/mL as compared to nadir)
- Degarelix concentration over the first month and trough levels at Day 308 and 336
- Frequency and size of testosterone increases at Day 255 and/or 259 compared to the testosterone level at Day 252
- Frequency and severity of AEs
- Clinically significant changes in laboratory values
- Change in ECGs and vital signs
- Quality of life on Days 0, 28, 84, 168 and End of Study Visit (EORTC Cancer Specific Questionnaire - EORTC QLQ-C30 and Short Form 12, version 2 Health Survey Scoring Demonstration- SF-12 ~2)
- Hot flush frequency and hot flush score daily from study start until End of Study Visit (endpoint assessed for all patients except those from Mexico, Romania, Russia and Ukraine)
- Probability of sufficient testosterone response from Day 28 through Day 364 (a patient was considered to have insufficient testosterone response if he had one testosterone value  $>1.0$  ng/mL or two consecutive testosterone values  $>0.5$  ng/mL at Day 28 onwards)
- Percentage change in PSA from baseline to Day 14.
- Serum testosterone levels were determined using a validated LC-MS/MS assay . For each timepoint, samples were analysed in triplicate and the median testosterone value was reported.

## *Sample size*

For the study to demonstrate with 90% power, that the lower limit of the 95% confidence interval was  $\geq 90\%$ , it was calculated that 200 patients would be needed for each degarelix treatment group, assuming a 96% testosterone response rate and a drop-out rate of 15%.

With 200 patients per treatment group, there would be  $>90\%$  power to demonstrate non-inferiority of degarelix versus leuprorelin 7.5 mg with respect to the probability of testosterone  $\leq 0.5$  ng/mL from Day 28 to Day 364, assuming a common response rate of 96%, a non-inferiority margin of -10%, a two-sided significance level of 2.5% and a drop-out rate of 15%.

In total, 600 patients (200 per treatment group) would need to be recruited.

## *Randomisation*

At screening, all potential participants in the study received a unique screening number which was entered into the Screening log. Patients who met the eligibility criteria were recruited into this study

and randomised in parallel to one of the three treatment groups. Randomisation lists were prepared centrally by the Department of Biometrics, Ferring Pharmaceuticals A/S using a validated computer program. These randomisation lists were stratified by geographic region (Central and Eastern Europe, Western Europe, The Americas) and body weight (<90 kg and ≥90 kg) and were prepared before the first patient was enrolled into the study.

#### Blinding (masking)

This was an open-label study as blinding was not possible due to different routes of administration for degarelix and the comparator (leuprorelin). However, the treatment was blinded for the central laboratory personnel. In addition, Ferring personnel were blinded to the hormone results (serum testosterone, PSA, LH and FSH) during the main part of the study after the last patient was recruited.

#### Statistical methods

For the primary endpoint, two hypotheses were tested:

1. The lower bound of the 95% confidence interval for the probability of testosterone ≤ 0.5 ng/ml from Day 28 through 364 is no lower than 90%

$$H_{01}: \pi_{\text{Degarelix}} < 90\% \text{ against the alternative } H_{A1}: \pi_{\text{Degarelix}} \geq 90\%$$

where  $\pi_{\text{Degarelix}}$  denotes the probability of testosterone ≤0.5 ng/ml from Day 28 through 364 after treatment with degarelix.

The null hypothesis ( $H_{01}$ ) was tested against the alternative ( $H_{A1}$ ) by constructing a 95% confidence interval for each treatment arm. For calculation of the 95% confidence interval, the standard error was calculated using the log-log transformation of the survivor function in order to yield plausible values.

2. Degarelix is non-inferior to LUPRON DEPOT 7.5 mg with respect to probability of testosterone ≤0.5 ng/ml from Day 28 through 364. The non-inferiority limit for the difference between treatments (degarelix versus LUPRON DEPOT 7.5 mg) was -10 percentage points

$$H_{02}: \pi_{\text{Degarelix}} - \pi_{\text{LUPRON DEPOT® 7.5 mg}} \leq -10 \text{ percentage points against the alternative } H_{A2}: \pi_{\text{Degarelix}} - \pi_{\text{LUPRON DEPOT® 7.5 mg}} > -10 \text{ percentage points,}$$

where  $\pi_{\text{Degarelix}}$  and  $\pi_{\text{LUPRON DEPOT® 7.5 mg}}$  denote the probability of testosterone ≤0.5 ng/ml from Day 28 through 364 after treatment with degarelix and LUPRON DEPOT 7.5 mg, respectively.

Two separate non-inferiority assessments were performed (degarelix 240/160 mg vs. LUPRON DEPOT 7.5 mg and degarelix 240/90 vs. LUPRON DEPOT 7.5 mg). In order to protect the overall type I error rate of 5%, this was corrected using the bonferroni-method, and therefore each assessment was performed on a significance level of 2.5%. The null hypothesis ( $H_{02}$ ) was tested against the alternative ( $H_{A2}$ ) by constructing a two-sided 97.5% confidence interval for the difference in probability of testosterone ≤0.5 ng/ml from Day 28 through 364. The 97.5% confidence interval for the difference between treatments was based on the pooled standard error.

#### Sensitivity analyses

A Cox-proportional hazards analysis was added as sensitivity analysis. Testosterone monitoring frequency (number of non-missing testosterone values /treatment months) was included as covariate. If a patient dropped out at month 8 with only 5 non-missing testosterone values then monitoring frequency was 5/8. Patients with no non-missing testosterone values had monitoring frequency =1, regardless of whether the patients completed the study (13/13=1) or not.

Only in the case of a statistically significant additive effect of monitoring frequency, was its impact discussed by providing 95% one year suppression probabilities (and 97.5% CI of the difference of each of the degarelix arms vs. LUPRON DEPOT 7.5 mg) of for those with no missing testosterone

values vs. those with at least one missing testosterone values. The 97.5% confidence interval for the difference between treatments was based on the pooled standard error, calculated similar as the primary analysis. Primary analyses were based on the analysis unadjusted for monitoring frequency in the case of no statistically significant effect of monitoring frequency.

This analysis was performed both for the ITT and the PP analysis set. The efficacy results are presented for the ITT analysis set.

#### *Insufficient testosterone response*

Testosterone was measured in triplicates and the median was used.

An extra efficacy endpoint was added:

- Probability of sufficient testosterone response from Day 28 through Day 364,

The same time-points as for the primary endpoint and the same statistical methodology and similar displays were used for this endpoint.

#### *Injection site reactions*

Crude incidences (n/N), incidence rates expressed as number of patients with at least one local tolerability reaction (reported as an AE) per 100 injections, were reported.

#### *Missing values and drop-outs*

Drop-outs were accounted for by the Kaplan-Meier approach.

For patients discontinued before Day 28, time to testosterone  $> 0.5$  ng/ml was censored at the time from dosing for the last available testosterone measurement. Patients discontinued between Day 28 and Day 364 (both inclusive) with all testosterone measurements  $\leq 0.5$  ng/ml were censored at the time from dosing for the last available testosterone measurement.

If a patient had a missing value after Day 28 with testosterone values  $\leq 0.5$  ng/ml before and after the specific time point it is reasonable to assume that the testosterone value at the missing visit was also  $\leq 0.5$  ng/ml, and therefore the missing value was set to ' $\leq 0.5$  ng/ml'. If one or both of the surrounding values was  $> 0.5$  ng/ml, the patient was considered a failure at the first visit where testosterone was  $> 0.5$  ng/ml. If the patient had completed the study, the Day 364 value was missing, and all previous values from Day 28 onwards were  $\leq 0.5$  ng/ml, the Day 364 value was also set to ' $\leq 0.5$  ng/ml'. If the Day 28 value was missing and the patient continued in the study to Day 28 or beyond, the last observation before Day 28 was carried forward.

#### *Secondary endpoints*

The number and percentage of patients with a testosterone surge during the first two weeks of treatment were presented by treatment group and for the pooled degarelix group together with p-values derived from Fisher's exact test.

The number and percentage of patients with testosterone  $\leq 0.5$  ng/ml at Day 3 were presented by treatment group and for the pooled degarelix group together with p-values derived from Fisher's exact test.

For the median percentage change in PSA from baseline to Day 28, each degarelix group as well as the pooled degarelix group was compared to LUPRON DEPOT 7.5 mg by a Wilcoxon test using the normal approximation.

Kaplan-Meier estimates of the probability of testosterone  $\leq 0.5$  ng/ml from Day 56 to 364 were presented by treatment group.

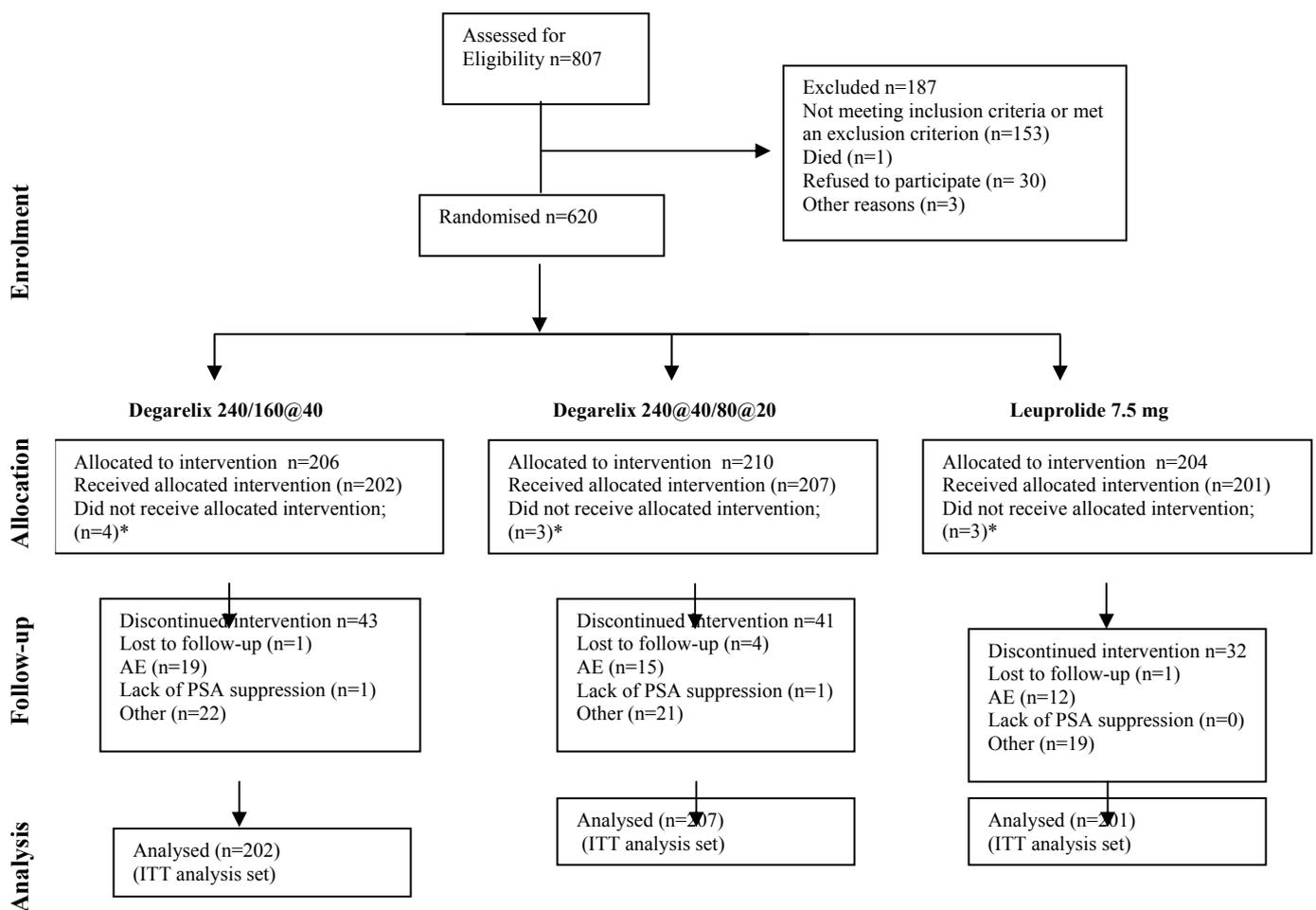
The time to PSA failure was defined as the days from first dosing (scheduled study days) where an increase in serum PSA of  $\geq 50\%$  from nadir and at least 5 ng/ml measured on two consecutive occasions at least two weeks apart was noted. That is, the two consecutive values must both represent:

- An absolute increase of  $\geq 5$  ng/ml above nadir and
- An increase of  $\geq 50\%$  of nadir

The probability of completing the study without experiencing PSA failure was estimated and presented for each treatment group using Kaplan-Meier methods.

## RESULTS

### Participant flow



### Patient withdrawals

Of the 620 patients randomised to this study, ten did not receive degarelix/leuprorelin treatment. These patients withdrew from the study for the following reasons: withdrew consent, taking prohibited medication, randomisation errors, language barriers, not satisfying inclusion criteria, drug delay which meant the patient would have to be re-screened.

There were 610 patients that received at least one dose of degarelix/ leuprorelin and which were included in the ITT analysis set. Of these, 504 (83%) patients completed the study with 163 (81%) patients in the degarelix 240/160 mg group, 169 (82%) patients in the degarelix 240/80 mg group and 172 (86%) patients in the leuprorelin group, thus more leuprorelin patients than degarelix patients completed the study.

AEs were the most common reason for withdrawal with 34 (8%) patients withdrawn in the degarelix groups and 12 (6%) in the leuprorelin group. Of these, 18 patients died while receiving treatment, five (2%) and four (2%) patients in the degarelix groups 240/80 mg and 240/160 mg, respectively, and nine (4%) in the leuprorelin group. Withdrawals due to non-fatal AEs were highest in the degarelix groups with 14 (7%) and 10 (5%) patients withdrawn from the 240/160 mg and 240/80 mg groups, respectively, and three (1%) patients in the leuprorelin group. Fifty-two patients withdrew due to 'other' reasons, mainly (>1 patient): withdrew consent (20 patients), taking prohibited medication (5), met exclusion criteria (4), missed study visit (4), unable to attend study visits (3), disease progression (2), patient relocated (2).

### Protocol Deviations

There were 39 (6%) patients in the ITT analysis set with at least one major protocol deviation including 30 (7%) who received degarelix and nine (4%) patients who received leuprorelin (Table 6).

Table 6: Major Protocol Deviations

	Treatment Group							
	Degarelix				Leuprolide		Total	
	240/160 mg		240/80 mg		7.5 mg			
N	(%)	N	(%)	N	(%)	N	(%)	
ITT analysis set	202	(100%)	207	(100%)	201	(100%)	610	(100%)
Any major protocol violation	18	( 9%)	12	( 6%)	9	( 4%)	39	( 6%)
Dosing	2	(<1%)	2	(<1%)	1	(<1%)	5	(<1%)
Exclusion criteria			2	(<1%)			2	(<1%)
PSA Criteria (SAP)	2	(<1%)	1	(<1%)	1	(<1%)	4	(<1%)
Prohibited Medication			1	(<1%)			1	(<1%)
Randomised, but treated according to another regimen	1	(<1%)					1	(<1%)
Testosterone Criteria (SAP)	13	( 6%)	5	( 2%)	6	( 3%)	24	( 4%)
Visit N/D			1	(<1%)	1	(<1%)	2	(<1%)

### Recruitment

First patient visit was on the 7. Feb. 2006. Last patient last visit was on the 8. Oct. 2007

### Conduct of the study

After finalisation of the CS21 protocol (01 December 2005) four protocol amendments were introduced, and the main changes are described below.

Protocol Amendment 1: 14 February 2006

Protocol Amendment 2: 14 February 2006

Protocol Amendment 3: 10 April 2006

Protocol Amendment 4: 25 September 2006

Protocol amendments 1, 2 and 4 were reviewed and approved by the IECs/ IRBs and regulatory authorities before implementation. Amendment 3 was reviewed by regulatory authorities only.

*Amendment 1*, 14 February 2006. The amendments were implemented before the first patient received their first dose of degarelix/leuprorelin.

The statistical analyses of the primary objective were changed, as recommended by the FDA and European authorities, to enable the efficacy of degarelix 240/160 mg and 240/80 mg treatment groups to be assessed separately. Thus, two formal analyses were performed, one assessing the degarelix response versus a pre-determined threshold of success and one non-inferiority analysis of degarelix versus leuprorelin. The primary objective was changed from:

- To demonstrate non-inferiority with respect to the proportion of patients achieving and maintaining testosterone suppression to castrate levels using a degarelix dosing regimen compared to leuprorelin during 12 months treatment.

to

- *To demonstrate that degarelix is effective with respect to achieving and maintaining testosterone to castrate levels, evaluated as the proportion of patients with testosterone suppression  $\leq 0.5$  ng/ml during 12 months treatment.*

The change in the statistical analysis meant that the number of patients to be screened was increased from 675 to 750 patients to provide 600 instead of 540 randomised patients. A 20% screening failure rate was expected.

The definition of the PP analysis set was modified to exclude patients who:

- Had a baseline PSA value  $< 2$  ng/ml for patients who had not undergone prostatectomy or radiotherapy with curative intention
- Did not have at least 28 days follow-up (testosterone measurements) after the first dose.

*Amendment 2*, also dated 14 February 2006.

This amendment introduced a MRI sub-study at seven sites in France, Germany, Romania and the Netherlands, in order to evaluate possible changes in tumour size and infiltration into adjacent tissues. This was in compliance with the requirements of the Japanese Society of Clinical Oncology. Patients participating in the MRI investigation had four MRI investigations performed (baseline, Day 28, Day 196 and Day 364) to assess the size of the tumour throughout the course of the study.

*Amendment 3*, dated 10 April 2006.

Data on the degarelix IMP were updated to include an extension of drug product shelf-life from 18 months to 24 months when stored below 25°C, and new stability data. In addition, the amendment included other changes to the analytical procedures.

*Amendment 4*, dated 25 September 2006.

As part of the assessment of ECG parameters, the list of suspected QT-prolonging drugs prohibited was updated. In addition, there was a change in the method used for recording images in the MRI sub-study, to accommodate patient well-being.

#### *Baseline data*

##### *Demographic profile*

The patient demography for the ITT analysis set was presented in a table. Overall, most patients in each treatment group were 65 years of age or older, white, with a body weight of  $< 90$  kg and a BMI  $< 30$  kg/m<sup>2</sup>.

##### *Disease baseline profile*

All patients entering the study had a histological proven adenocarcinoma of the prostate (all stages). Of the 610 patients in the ITT analysis set, 191 (31%) had localized cancer, 178 (29%) had locally advanced cancer, 125 (20%) had metastatic cancer and 116 (19%) had non-classifiable disease, at the time of enrolment (Table 7 below). Of the patients with non-classifiable disease at the time of enrolment, 35% had previous treatment with curative intent and the remaining could not be classified for other reasons (most of these cases were because the patient's metastatic status could not be precisely determined).

Table 7: Disease baseline profile - ITT analysis set

	Degarelix			
	240@40/80@20	240/160@40	Total	Leuprorelin 7.5 mg
Stage of PCa at Diagnosis	N=207	N=202	N=409	N=201
Localized	56 (27%)	43 (21%)	99 (24%)	40 (20%)
Locally advanced	27 (13%)	29 (14%)	56 (14%)	25 (12%)
Metastatic	10 ( 5%)	18 ( 9%)	28 ( 7%)	19 ( 9%)
Not classifiable	114 (55%)	112 (55%)	226 (55%)	117 (58%)
Stage of PCa at Enrollment	N=207	N=202	N=409	N=201
Localized	69 (33%)	59 (29%)	128 (31%)	63 (31%)
Locally advanced	64 (31%)	62 (31%)	126 (31%)	52 (26%)
Metastatic	37 (18%)	41 (20%)	78 (19%)	47 (23%)
Not classifiable	37 (18%)	40 (20%)	77 (19%)	39 (19%)
Curative Intent	N=207	N=202	N=409	N=201
Yes	30 (14%)	24 (12%)	54 (13%)	24 (12%)
No	177 (86%)	178 (88%)	355 (87%)	177 (88%)
No PCa Stage Classification	N=37	N=40	N=77	N=39
No curative intent	23 (62%)	27 (68%)	50 (65%)	25 (64%)
Curative intent	14 (38%)	13 (33%)	27 (35%)	14 (36%)
Gleason score	N=207	N=200	N=407	N=200
2-4	20 (10%)	21 (11%)	41 (10%)	24 (12%)
5-6	68 (33%)	67 (34%)	135 (33%)	63 (32%)
7-10	119 (57%)	112 (56%)	231 (57%)	113 (57%)
PC Duration since 1 <sup>st</sup> Diagnosis (year)	N=207	N=201	N=408	N=200
Mean (SD)	1.34 (2.72)	1.33 (3.04)	1.34 (2.88)	1.36 (2.98)
Range	0.038-14.3	0.033-16.2	0.033-16.2	0.030-18.0
ECOG Performance Score	N=207	N=202	N=409	N=201
Normal activity	158 (76%)	143 (71%)	301 (74%)	148 (74%)
Symptoms but ambulatory	37 (18%)	48 (24%)	85 (21%)	42 (21%)
Bedridden < 50%	12 ( 6%)	11 ( 5%)	23 ( 6%)	11 ( 5%)
Bedridden > 50%				
Bedridden 100%				

Source: Module 2, Summary of clinical efficacy.

PCa = prostate cancer.

#### *Duration of prostate cancer and previous cancer therapy*

For the ITT analysis set, the median duration of prostate cancer from diagnosis was 62 days (range: 11days to 18.1 years). In general, the history of previous cancer therapy was similar for all three treatment groups. Before enrolling in the study, 37 (6%) patients had undergone radical prostatectomy, 58 (10%) of patients received radiotherapy, 33 (5%) had received neoadjuvant/adjvant hormonal therapy and 11 (2%) had received other therapy for their cancer. The majority of patients (523, 86%) had been followed with watchful waiting.

#### *Laboratory hormone parameters*

For the ITT analysis set, the values for efficacy and pharmacodynamic parameters at baseline are shown in table 8 below.

Table 8: Laboratory hormone parameters – ITT analysis set

ITT analysis set	Degarelix		Leuprorelin 7.5 mg 201
	240@40/80@20	240/160@40	
	207	202	
<b>Testosterone (2.2, 10.3 ng/ml)</b>			
Mean (SD)	4.34 (1.77)	4.02 (1.70)	4.05 (1.65)
Median (range)	4.11 (0.73-10.6)	3.78 (0.07-10.6)	3.84 (0.37-12.5)
<b>LH (IU/L)</b>			
Mean (SD)	7.12 (4.51)	7.69 (7.53)	7.85 (5.95)
Median (range)	5.87 (1.24-28.0)	5.73 (0.66-61.0)	6.05 (1.25-37.0)
<b>FSH (1.4, 18.1 IU/L)</b>			
Mean (SD)	11.4 (11.1)	12.6 (13.3)	13.2 (13.4)
Median (range)	7.6 (0.7-73.6)	8.65 (0.8-112)	8.7 (1.4-92.2)
<b>PSA (ng/ml)</b>			
Mean (SD)	112 (375)	268 (1345)	218 (903)
Median (range)	19.8 (1.7-3187)	19.9 (1.5-7285)	17.4 (1.6-952)

*Ongoing concomitant medications*

The profile of concomitant medications was much as expected for this group of elderly patients with histological proven adenocarcinoma of the prostate. The concomitant medications used were also consistent with many of the patients having a medical history of cardiac disease or hypertension. Prohibited medications during the study were other hormone-manipulative drugs and medications which might prolong the QT interval and 5- $\alpha$ -reductase inhibitors. The pattern of use for ongoing concomitant medications was similar for the three treatment groups.

*Treatment-emergent concomitant medications*

Three hundred and fifty (57%) patients in the ITT analysis set received concomitant medications after starting treatment with IMP. The most frequently used treatment-emergent concomitant medications were antibacterials for systemic use, rennin-angiotensin system medications, anti-inflammatory products, antirheumatic products and analgesics: The results were presented in a table. All other classes of treatment emergent concomitant medications were used by <10% patients. With the exception of anti-androgens, the use of treatment emergent concomitant medications was similar for the three treatment groups.

*Anti-androgen therapy*

According to the applicant, a total of 27 (4%) of all patients received anti-androgens as endocrine therapy: 23 patients treated with leuprorelin and four patients treated with degarelix. Twenty (10%) patients in the leuprorelin and the four degarelix patients received anti-androgens as treatment-emergent concomitant medication. Among the patients treated with degarelix, three received anti-androgen (bicalutamide) to treat their prostate cancer and one received anti-androgen to treat his back pain.

## Numbers analysed

*Intention-to-Treat (ITT) analysis set*

The ITT analysis set comprised all patients who received at least one dose of degarelix/ leuprorelin. The primary efficacy endpoint and most of the secondary efficacy endpoints were analyzed for both the ITT and PP analysis sets. However, the ITT analysis set was considered primary.

*Per Protocol (PP) analysis set*

Of the ITT analysis set, 26 patients had at least one major protocol deviation and therefore the PP analysis set comprised 584 patients. A further 13 patients were partially excluded from the PP analysis due to major protocol violations which occurred at a post-dose visit: i.e. their data was used in the PP analysis up to the visit at which the protocol violation occurred.

Table 9: Size of ITT and PP data sets

	Degarelix			Total
	240@40/80@20	240/160@40	Leuprorelin 7.5 mg	
<b>Data set</b>				
<b>ITT</b>	<b>202</b>	<b>207</b>	<b>201</b>	<b>610</b>
<b>PP</b>	<b>189</b>	<b>200</b>	<b>195</b>	<b>584</b>

### Outcomes and estimation

#### Primary efficacy endpoint

The primary endpoint was the probability of testosterone levels  $\leq 0.5$  from Day 28 to Day 364, and the results for the ITT analysis set are shown in Table 10 and Figure 1. Results for the PP analysis set are shown in Table 11 below.

Table 10: Cumulative probability of one year testosterone suppression– ITT analysis set

	Degarelix 240@40/80@20			Degarelix 240/160@40			Leuprorelin 7.5 mg		
	T>0.5 ng/ml	Cens	(%)	T>0.5 ng/ml	Cens	(%)	T>0.5 ng/ml	Cens	(%)
ITT analysis set	207			202			201		
Day 28 -> 364	5	202	(97.2%)	3	199	(98.3%)	7	194	(96.4%)
95% CI			[93.5;98.8%]			[94.8;99.4%]			[92.5;98.2%]
Diff. to leuprorelin mg			0.875%			1.92%			
97.5% DI of diff. to leuprorelin 7.5 mg			[-3.21;4.96%]			[-1.82;5.67%]			

T > 0.5 ng/ml = Number of patients with testosterone > 0.5 ng/ml, Cens = Number of censored observations before (or at) Day 364  
(%) = Estimated probability of testosterone  $\leq 0.5$  ng/ml from Day 28 through Day 364

Within-treatment group 95% CI calculated by log-log transformation of survivor function; Between-treatment group 97.5% CI calculated by normal approximation using pooled standard error. Source: Module 2, Summary of clinical efficacy

Table 11: Cumulative probability of one year testosterone suppression – PP analysis set

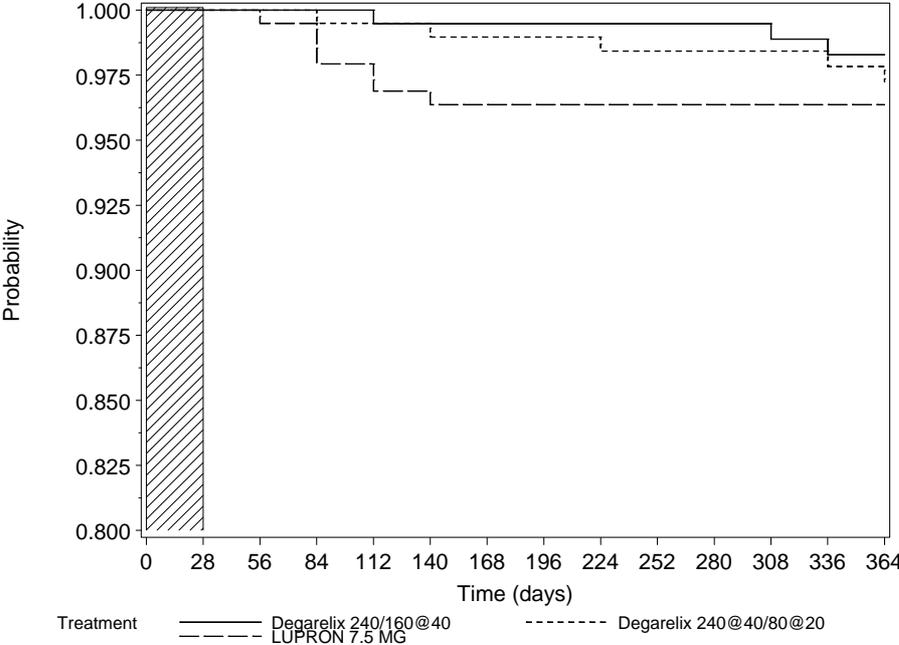
	Degarelix 240@40/80@20			Degarelix 240/160@40			Leuprorelin 7.5 mg		
	T>0.5 ng/ml	Cens	(%)	T>0.5 ng/ml	Cens	(%)	T>0.5 ng/ml	Cens	(%)
ITT analysis set	200			189			195		
Day 28 -> 364	5	195	(97.2%)	1	188	(99.4%)	7	188	(96.3%)
95% CI			[93.3;98.8%]			[95.6;99.9%]			[92.4;98.2%]
Diff. to leuprorelin mg			0.9%			3.1%			
97.5% DI of diff. to leuprorelin 7.5 mg			[-3.3;5.1%]			[-0.3;6.5%]			

T > 0.5 ng/ml = Number of patients with testosterone > 0.5 ng/ml, Cens = Number of censored observations before (or at) Day 364  
(%) = Estimated probability of testosterone  $\leq 0.5$  ng/ml from Day 28 through Day 364

Within-treatment group 95% CI calculated by log-log transformation of survivor function; Between-treatment group 97.5% CI calculated by normal approximation using pooled standard error. Source: Module 5, Clinical study report CS21

For patients withdrawn before Day 28, the time to testosterone >0.5 ng/ml was censored at the time from dosing for the last available testosterone measurement. Patients withdrawn between Day 28 and Day 364 (inclusive), with all testosterone measurements ≤0.5 ng/ml, were censored at the time from dosing for the last available testosterone measurement. After Day 28, if testosterone values were ≤0.5 ng/ml before and after a missing time point, then the missing value was set to ≤0.5 ng/ml. If one or both of the testosterone values surrounding a missing time point was >0.5 ng/ml, the patient was considered a failure at the first visit where testosterone was >0.5 ng/ml.

Figure 1: Kaplan-Meier plot of time to testosterone > 0.5 ng/ml (from Day 28 onwards) per treatment regimen -ITT analysis set



Source: Module 2, Summary of clinical efficacy

In the ITT analysis set, 15 patients had testosterone >0.5 ng/ml (escape) between Day 28 and Day 364 (see table 12 below). Of these, 7 were in the leuprorelin group: one patient escaped testosterone suppression on Day 56, three on Day 84, two on Day 112 and one on Day 140. In the degarelix 240/160 mg group, three patients escaped testosterone suppression on Days 112, 308 and 336, respectively. Five patients in the degarelix 240/80 mg group escaped testosterone suppression on Days 84, 140, 224, 336 and 364, respectively.

Table 12: Kaplan-Meier analysis from Day 28 to Day 364 for probability of testosterone  $\leq 0.5$  ng/ml from Day 28 to Day 364 – ITT analysis set

	Treatment Group											
	Degarelix 240/160 mg				Degarelix 240/80 mg				Leuprolide 7.5 mg			
	No. at risk	PSA fail	Cens (%)	(%)	No. at risk	PSA fail	Cens (%)	(%)	No. at risk	PSA fail	Cens (%)	(%)
ITT analysis set	202				207				201			
Day 0->28	193	1	8 (99.5%)		201	0	6 (100%)		194	1	5 (99.5%)	
-> Day 56	192	1	1 (99.5%)		197	0	4 (100%)		192	1	2 (99.5%)	
-> Day 84	190	1	2 (99.5%)		193	0	4 (100%)		190	1	2 (99.5%)	
-> Day 112	190	1	0 (99.5%)		189	1	3 (99.5%)		188	3	0 (98.4%)	
-> Day 140	187	2	2 (99.0%)		187	2	1 (99.0%)		182	7	2 (96.4%)	
-> Day 168	179	7	3 (96.3%)		185	4	0 (97.9%)		180	9	0 (95.3%)	
-> Day 196	173	11	2 (94.2%)		181	4	4 (97.9%)		175	11	3 (94.2%)	
-> Day 224	168	14	2 (92.5%)		175	7	3 (96.3%)		173	12	1 (93.7%)	
-> Day 252	165	16	1 (91.4%)		169	9	4 (95.2%)		168	14	3 (92.6%)	
-> Day 280	157	20	4 (89.2%)		165	11	2 (94.0%)		163	18	1 (90.4%)	
-> Day 308	153	23	1 (87.5%)		161	12	3 (93.5%)		156	21	4 (88.7%)	
-> Day 336	149	26	1 (85.8%)		156	15	2 (91.7%)		150	24	3 (87.0%)	
-> Day 364	0	26	149 (85.8%)		0	16	155 (91.1%)		0	26	148 (85.9%)	
95% CI			[79.8;90.1%]				[85.9;94.5%]				[79.9;90.2%]	

PSA failure = Two consecutive, at least two weeks apart, PSA increases from nadir of  $\geq 50\%$  and  $> 5$  ng/ml; No. at risk = Number of patients at risk. PSA fail = Number of patients with PSA failure; Cens = Number of censored observations; (%) = Estimated probability of no PSA failure. Within-treatment group 95% CI calculated by log-log transformation of survivor function. Source: Module 5, Study report CS21

## Secondary endpoints

### Proportion of patients with testosterone surge during the first two weeks of treatment

A patient was defined as having a testosterone surge if the testosterone level exceeded baseline by  $\geq 15\%$  on any two days during the first two weeks of treatment (i.e. two of Study Days 1, 3, 7 and 14).

In total, there was only one (0.2%) patient treated with degarelix, from the 240/160 mg group, who had a slight testosterone increase during the first two weeks of treatment compared with 161 (80.1%) patients in the leuprorelin group ( $p < 0.0001$ , Fisher's exact test) (see table 13 below). The testosterone surge experienced by the patient in the degarelix 240/160 mg group can be considered to be an artefact as this patient had a low baseline testosterone value of 0.065 ng/ml.

Table 13: Proportion of patients with testosterone surge during the first two weeks of treatment – ITT analysis set

	Treatment Group															
	Degarelix 240/160 mg				Degarelix 240/80 mg				Total				Leuprolide 7.5 mg			
	N	n	%		N	n	%		N	n	%		N	n	%	
ITT Analysis Set	202				207				409				201			
T surge	202	1 (0.5%)			207	0 (0.0%)			409	1 (0.2%)			201	161 (80.1%)		
95 % CI		[0.0;2.7%]				[0.0;1.8%]				[0.0;1.4%]				[73.9;85.4%]		
P-value from Fisher's exact test vs. leuprolide 7.5 mg			<.0001				<.0001								<.0001	

Testosterone surge: Percentage change from baseline  $\geq 15\%$  at any two of Day 1, 3, 7 and 14. N = Number of patients, n = Number of patients with testosterone surge, % =  $n/N \times 100$ ; Exact 95 % CI calculated by Clopper-Pearson method. Source: Module 5, Study report CS21

In the leuprorelin group, among the 22 patients who started anti-androgen therapy before or at Day 7, the proportion of patients who had a testosterone surge during the first two weeks of treatment was 72.7% compared with 80.9% among those patients who did not use anti-androgen therapy.

Proportion of patients with testosterone level  $\leq 0.5$  ng/ml at Day 3

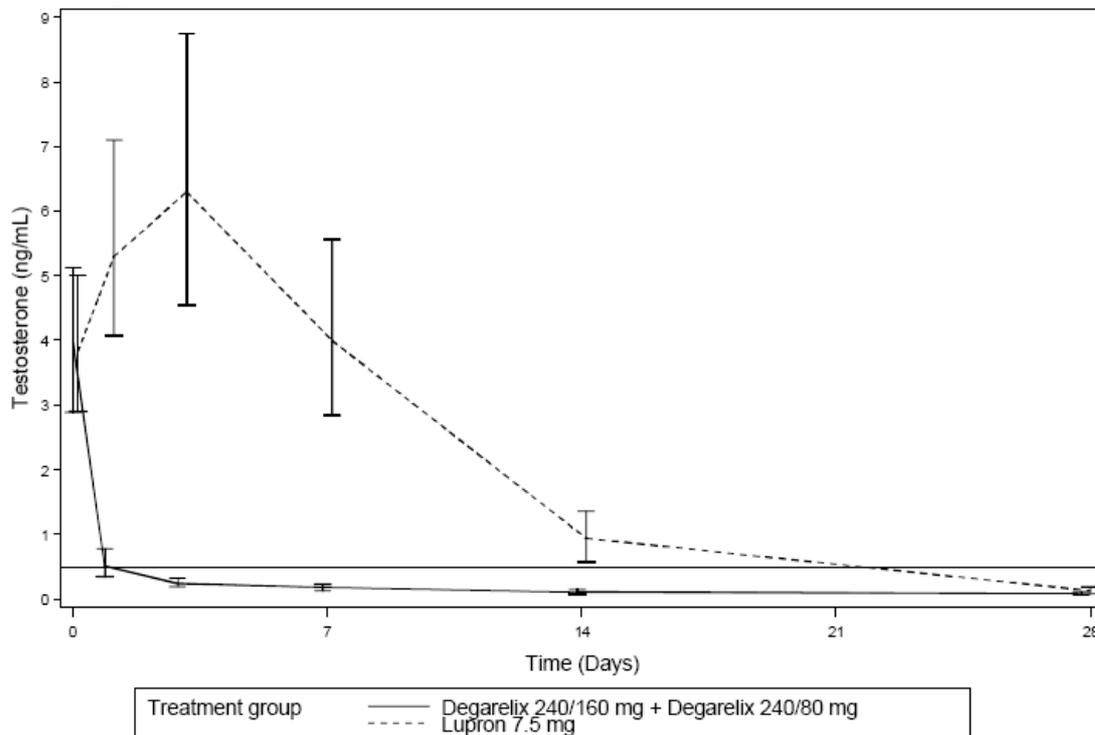
On Day 3, there were 392 (95.8%) patients in the pooled degarelix group with testosterone  $\leq 0.5$  ng/ml compared with no patients in the leuprolrelin group (see table 14 below). Rapid suppression of testosterone was observed for patients in the degarelix treatment groups with median testosterone levels reduced by  $>90\%$  from baseline by Day 3 (see figure 2 below). In contrast, patients in the leuprolrelin group had a 65% increase in testosterone by Day 3.

Table 14: Proportion of patients with testosterone  $\leq 0.5$  ng/ml at Day 3 – ITT analysis set

	Treatment Group							
	Degarelix						Leuprolide 7.5 mg	
	Degarelix 240/160 mg		Degarelix 240/80 mg		Total			
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
ITT analysis set	202		207		409		201	
T $\leq 0.5$ ng/mL	202	193 (95.5%)	207	199 (96.1%)	409	392 (95.8%)	201	0
95% CI		[91.7;97.9%]		[92.5;98.3%]		[93.4;97.6%]		[0.0;1.8%]
P-value from Fisher's exact test vs leuprolide 7.5 mg		<.0001		<.0001		<.0001		

N = Number of patients, n = Number of patients with testosterone  $\leq 0.5$  ng/ml, % =  $n/N \times 100$ ; Exact 95 % CI calculated by Clopper-Pearson method. Source: Module 5, Study report CS21

Figure 2: Change from baseline in median testosterone level ( $\pm$ IQR) from Day 0 to Day 28 – ITT analysis set



Source: Module 5, Study report CS21

Probability of sufficient testosterone response from Day 28 through Day 364

A patient was considered to have insufficient testosterone response if he had one testosterone value  $>1.0$  ng/ml or two consecutive testosterone values  $>0.5$  ng/ml, taken 28 days apart, from Day 28 to Day 364. This endpoint was designed to address the issue of patients having only one isolated testosterone value  $>0.5$  ng/ml.

Using this less strict definition of testosterone response, the probability of testosterone  $\leq 0.5$  ng/ml from Day 28 to Day 364 was 98.8%, 97.8% and 96.9% for the degarelix 240/160 mg, degarelix 240/80 mg and leuprorelin groups, respectively. The differences between the two degarelix treatment groups and the leuprorelin comparator group with respect to the probability of patients with testosterone  $\leq 0.5$  ng/ml from Day 28 to Day 364 were 2.0% (97.5% CI: -1.4 - 5.3) and 0.9% (97.5% CI: -2.8 - 4.7) for the degarelix 240/160 mg and degarelix 240/80 mg treatment groups, respectively. The 97.5% CI for the difference in probability compared with the leuprorelin group remained greater than the non-inferiority limit of -10 percentage points.

#### Cumulative probability of testosterone $\leq 0.5$ ng/ml from Day 56 through Day 364

The Kaplan-Meier estimates of the cumulative probability of testosterone  $\leq 0.5$  ng/ml from Day 56 to Day 364 were identical to those from Day 28 onwards because no patient had a testosterone value  $> 0.5$  ng/ml (escape) at Day 28.

#### Frequency and size of testosterone increases at Day 255 and/or Day 259 compared to the testosterone level at Day 252

Testosterone increases on Day 255 and/or on Day 259 compared with Day 252 were categorised as shifts of  $\leq -0.25$ ,  $> -0.25-0$ ,  $>0-0.25$ ,  $>0.25-0.5$  and  $>0.5$  ng/ml from mean testosterone levels on Day 252. Shifts in absolute testosterone castration status were categorised as  $\leq 0.5$  to  $\leq 0.5$  ng/ml (no change),  $\leq 0.5$  to  $>0.5$  ng/ml and  $>0.5$  to  $\leq 0.5$  ng/ml.

The majority of patients in each treatment group had changes in testosterone within  $\pm 0.25$  ng/ml on Day 255 and/or on Day 259 compared with testosterone levels on Day 252: 99.4%, 98.3% and 95.5% of patients in the degarelix 240/160 mg, degarelix 240/80 mg and leuprorelin groups, respectively. (see table 15 below). In the leuprorelin group, five patients had testosterone microsurgers of 0.25-0.5 ng/ml and three patients had microsurgers of  $>0.5$  ng/ml. Five of these patients had previously escaped testosterone suppression. No testosterone microsurgers were observed in patients treated with degarelix.

Analysis of shifts in absolute testosterone values from Day 252 to Day 255 and/or Day 259 showed that four patients in the leuprorelin group escaped testosterone suppression (shift from  $\leq 0.5$  to  $>0.5$  ng/ml). In addition, four patients treated with degarelix (one from the 240/160 mg group and three from the 240/80 mg group) who had escaped testosterone suppression on Day 252 were re-suppressed by Day 255/259.

Table 15: Frequency and size of testosterone increases at Day 255 and/or Day 259 compared to the testosterone level at Day 252

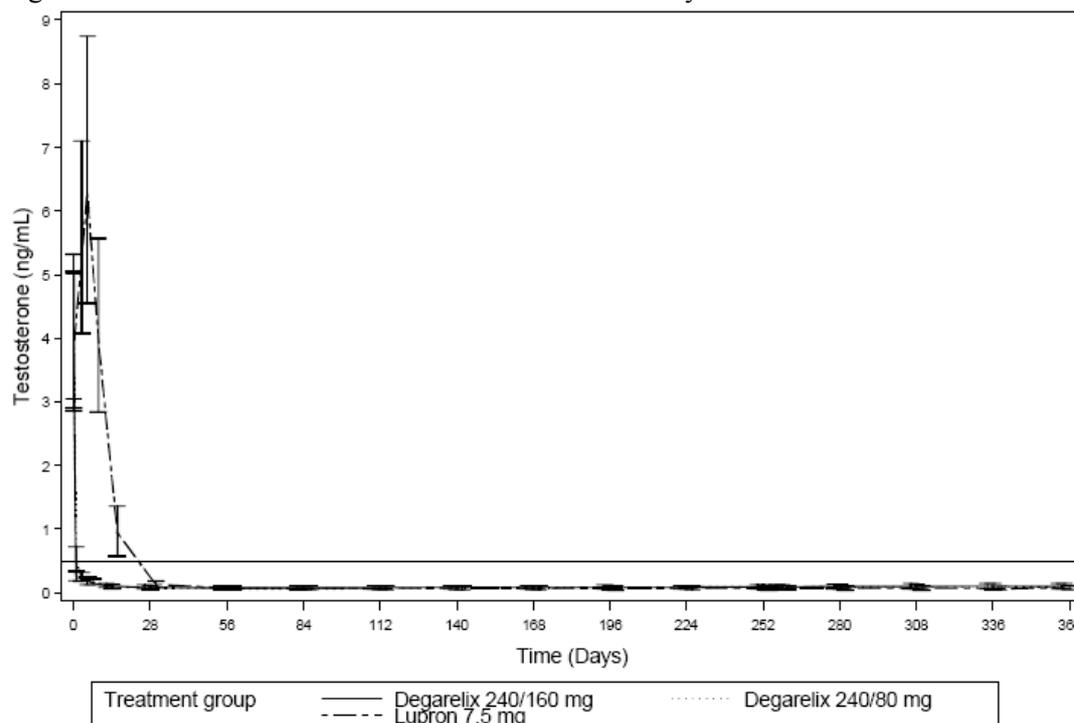
	Treatment Group		
	Degarelix 240/160 mg	Degarelix 240/80 mg	Leuprolide 7.5 mg
ITT analysis set	202	207	201
Testosterone level at Day 252 (ng/mL)			
N	179	180	183
Mean	0.107	0.120	0.089
SD	0.075	0.158	0.059
Median	0.093	0.089	0.077
Minimum	0.015	0.015	0.015
Maximum	0.520	1.53	0.450
Change[1] (ng/mL) from Day 252 to Day 255 and/or 259			
N	176	178	179
Mean	0.004	-0.015	0.045
SD	0.046	0.126	0.151
Median	0.003	0.001	0.017
Minimum	-0.270	-1.13	-0.080
Maximum	0.170	0.110	1.30
<= -0.25	1 ( 0.6%)	3 ( 1.7%)	
> -0.25 - 0	84 (47.7%)	85 (47.8%)	49 (27.4%)
> 0 - 0.25	91 (51.7%)	90 (50.6%)	122 (68.2%)
> 0.25 - 0.5			5 ( 2.8%)
> 0.5			3 ( 1.7%)
Total	176 (100%)	178 (100%)	179 (100%)
Shifts[1] in absolute values (ng/mL) from Day 252 to Day 255 and/or 259			
'<= 0.5' -> '<= 0.5'	175 (99.4%)	175 (98.3%)	175 (97.8%)
'<= 0.5' -> '> 0.5'			4 ( 2.2%)
'> 0.5' -> '<= 0.5'	1 ( 0.6%)	3 ( 1.7%)	
Total	176 (100%)	178 (100%)	179 (100%)

Largest value at Day 255 or Day 259 used  
Source: Module 5, Study report CS21

### Serum testosterone levels over time

Treatment with degarelix resulted in rapid suppression of testosterone levels to  $\leq 0.5$  ng/ml. By Day 3 median testosterone levels were 0.26 ng/ml and 0.24 ng/ml for the degarelix 240/160 mg and degarelix 240/80 mg treatment groups, respectively. Testosterone levels remained suppressed for both degarelix treatment groups until the end of the study on Day 364. In contrast, treatment with leuprorelin resulted in an initial surge in median testosterone levels which increased to 6.30 ng/ml on Day 3 before dropping to a suppressed level by Day 28, (see Figure 3 below)

Figure 3 : Median testosterone levels over time –ITT analysis set



Source: Module 5, Study report CS21

Percentage change in PSA from baseline to Day 14 and Day 28

The PSA levels decreased rapidly following degarelix administration, as shown in the tables 16 and 17 and figure 4 below. On Day 14 and 28 the median percentage change in PSA from baseline in the pooled degarelix groups was -64.3% and -83.6%, respectively. In contrast, in the leuprorelin group the median percentage change in PSA from baseline was -17.9% and -66.7% on Day 14 and Day 28, respectively.

Table 16: Percentage change in PSA from baseline to Day 14 – ITT analysis set

	Treatment Groups			Leuprolide 7.5 mg
	240/160 mg	Degarelix 240/80 mg	Total	
ITT analysis set	202	207	409	201
Median baseline	19.9	19.8	19.8	17.4
Median % change	-64.6%	-63.4%	-64.3%	-17.9%
Interquartile Range of % change	[-77.8;-40.8]	[-77.1;-48.4]	[-77.6;-45.2]	[-35.5;-5.2]
P-value from Wilcoxon test vs. leuprolide 7.5 mg[1]	<.0001	<.0001	<.0001	
Prob. (degarelix < leuprolide 7.5 mg) [2]	0.8090	0.8313	0.8203	

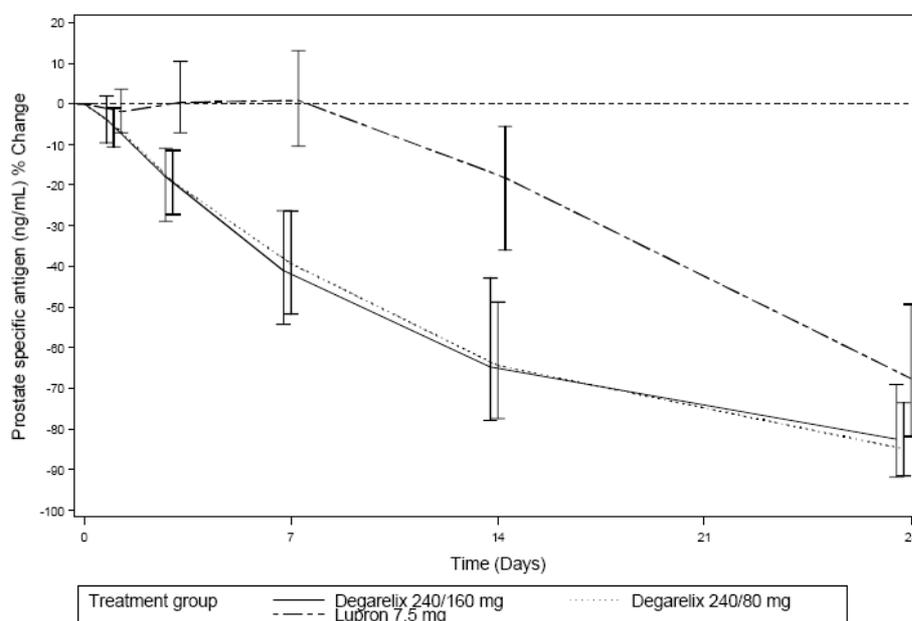
[1] P-value from Wilcoxon test based on normal approximations, [2] The estimated probability that an observation from the degarelix group will be less than a new observation from the leuprorelin group is calculated as:  $((\text{Sum of Squares})_{\text{lup}} - (1/2) * N_{\text{lup}} * (N_{\text{lup}} + 1)) / (N_{\text{dega}} * N_{\text{lup}})$ . Source: Module 5, Study report CS21

Table 17: Percentage change in PSA from baseline to Day 28 – ITT analysis set

	Treatment Groups			Leuprolide 7.5 mg
	240/160 mg	Degarelix 240/80 mg	Total	
ITT analysis set	202	207	409	201
Median baseline	19.9	19.8	19.8	17.4
Median % change	-82.3%	-84.9%	-83.6%	-66.7%
Interquartile Range of % change	[-91.4; -68.3]	[-91.6; -73.2]	[-91.4; -71.1]	[-81.3; -47.7]
P-value from Wilcoxon test vs. leuprolide 7.5 mg [1]	<.0001	<.0001	<.0001	
Prob. (degarelix < leuprolide 7.5 mg) [2]	0.6859	0.7197	0.7030	

[1] P-value from Wilcoxon test based on normal approximations, [2] The estimated probability that an observation from the degarelix group will be less than a new observation from the leuprorelin group is calculated as:  $((\text{Sum of Squares}_{\text{lup}} - (1/2) * N_{\text{lup}} * (N_{\text{lup}} + 1)) / (N_{\text{dega}} * N_{\text{lup}}))$ . Source: Module 5, Study report CS21

Figure 4: Percentage change (+/- Interquartile Range) from Day 0 to 28 – ITT analysis set



Source: Module 5, Study report CS21

In the leuprorelin group, a greater median percentage change in PSA levels from baseline was observed for patients who received anti-androgen therapy compared with those who did not. For patients who started anti-androgen therapy on or before Day 7, median PSA levels were reduced by 61.7% on Day 14 and 89.1% on Day 28. In contrast, median PSA levels were only reduced by 15.3% on Day 14 and 61.7% on Day 28 for patients not on anti-androgens.

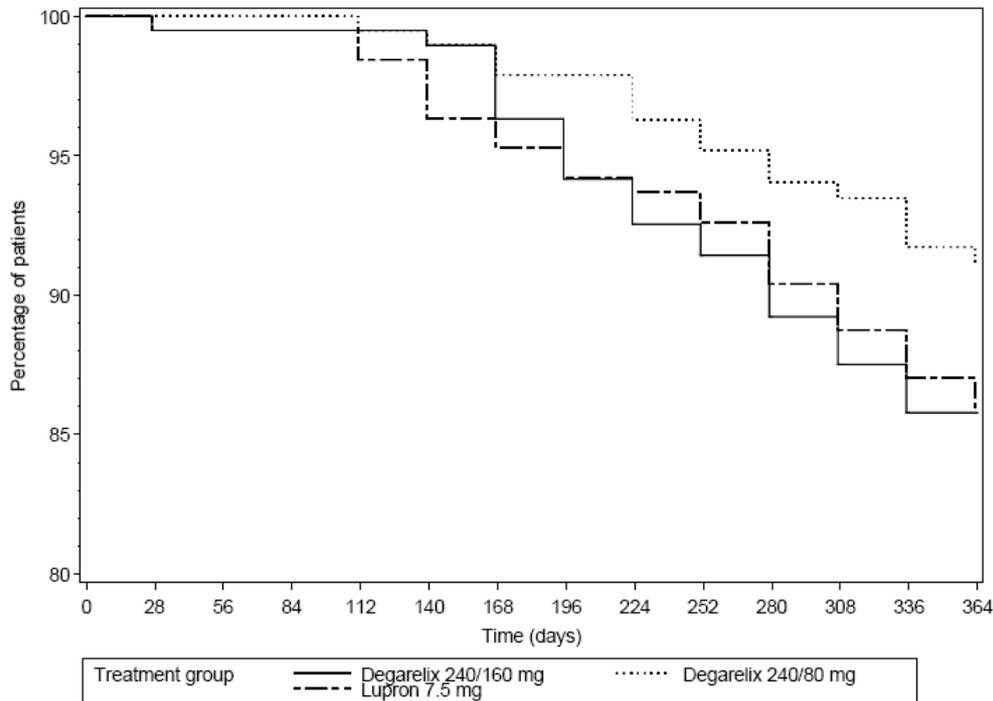
### Time to PSA failure

The time to PSA failure was defined as the number of days from first dosing (scheduled dosing days) where an increase in serum PSA of  $\geq 50\%$  from nadir and a least 5 ng/ml measured on two consecutive occasions at least two weeks apart was noted. The second occasion was the timepoint of meeting the criterion.

The proportion of patients observed to have PSA failure was: 26 (13%) patients in the degarelix 240/160 mg group, 16 (8%) patients in the degarelix 240/80 mg group, and 26 (13%) patients in the leuprorelin group. Approximately 50% of PSA failures for each treatment group were observed by Day 224 (see figure 5 below). The probability of completing the study without experiencing PSA failure on Day 364 was highest for the degarelix 240/80 mg group (91.1% [95% CI: 85.9-94.5%]). Almost identical Day 364 probabilities for completing the study without experiencing PSA failure

were observed for the degarelix 240/160 mg (85.8% [95% CI: 79.8-90.1%]) and leuprorelin (85.9% [95% CI: 79.9-90.2%]) groups.

Figure 5: Time to PSA failure – ITT analysis set

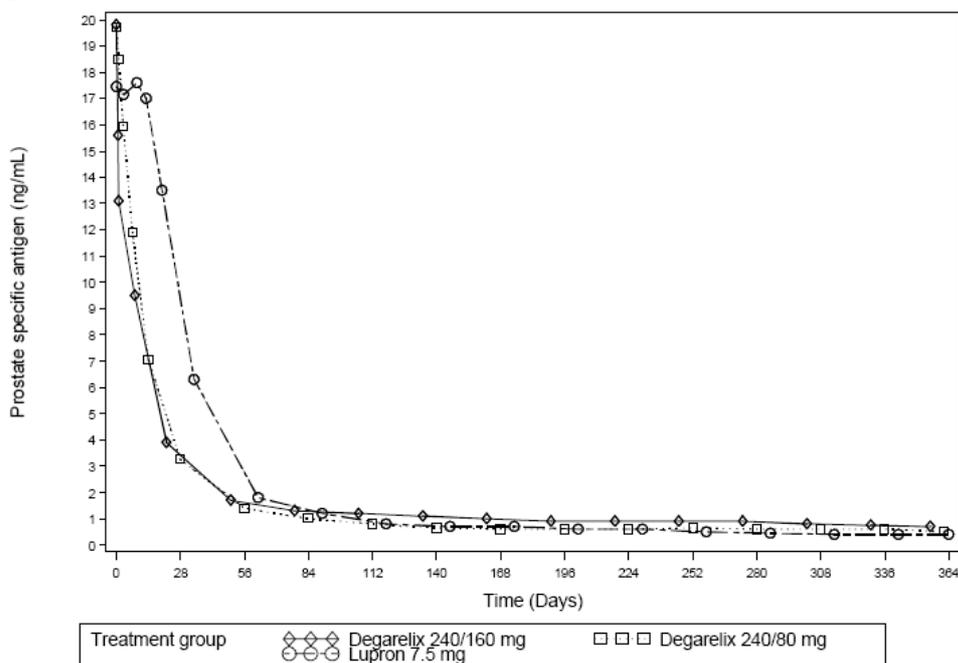


Source: Module 5, Study report CS21

*Serum PSA levels over time*

For patients who received degarelix treatment, PSA levels decreased in a nearly linear rate over time for the pooled degarelix arms, from a median baseline level of 19.9 ng/ml to 0.50-0.70 ng/ml at Day 364. In the leuprorelin group, median PSA levels stayed at a plateau of 17.0-17.6 ng/ml during the first 7 days of treatment, and then decreased in a nearly linear rate over time to a median value of 0.40 ng/ml on Day 364 (see figure 6 below).

Figure 6: Median PSA levels over time



Source: Module 5, Study report CS21

### Percentage change in PSA from baseline at Week 12 and at Year One

In addition to the predefined secondary end-points, an analysis of change in PSA from baseline at Week 12 and at Year One was performed and presented in the clinical summary.

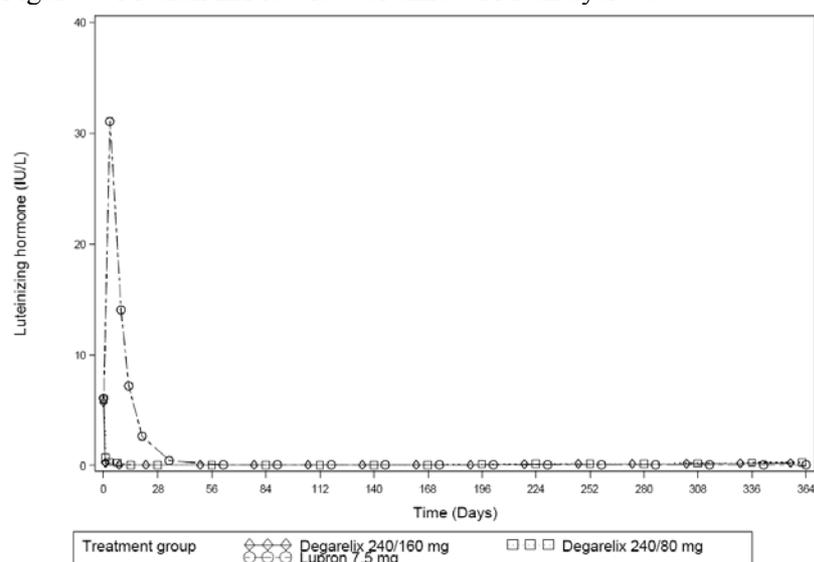
There were no statistically significant differences between the treatment groups in the median percentage decrease in PSA (observed cases) at week 12, which ranged from -94.1% to -95.2% across the groups. The median percentage decrease in PSA (observed cases) at one year was statistically significantly less ( $p=0.049$ ) in the 160 mg (40 mg/ml) group (-96.5% [IQR -98.9;-89.2%]) compared to the leuprorelin group (-97.7% [IQR -99.6;-92.2%]), but the difference between the treatments was small and not clinically relevant. There were no statistically significant differences after one year between the two degarelix groups ( $p=0.11$ ) or between the leuprorelin and the degarelix 80 mg (20 mg/ml) group ( $p=0.64$ ).

### Serum LH and FSH levels over time

The profiles for serum levels of LH over time were similar to those observed for testosterone (see figure 7 below). Following administration of degarelix, median LH levels decreased rapidly and were  $<0.7$  IU/L on Day 1, a decrease of approximately 88% from baseline. For both degarelix treatment groups median LH levels remained suppressed until the end of the study on Day 364. In contrast, a surge in median LH levels was observed for patients in the leuprorelin group, which peaked at 31.0 IU/L on Day 1 ( $>400\%$  increase from baseline) before decreasing exponentially to 0.035 IU/L by Day 56 and remaining at this level until Day 364.

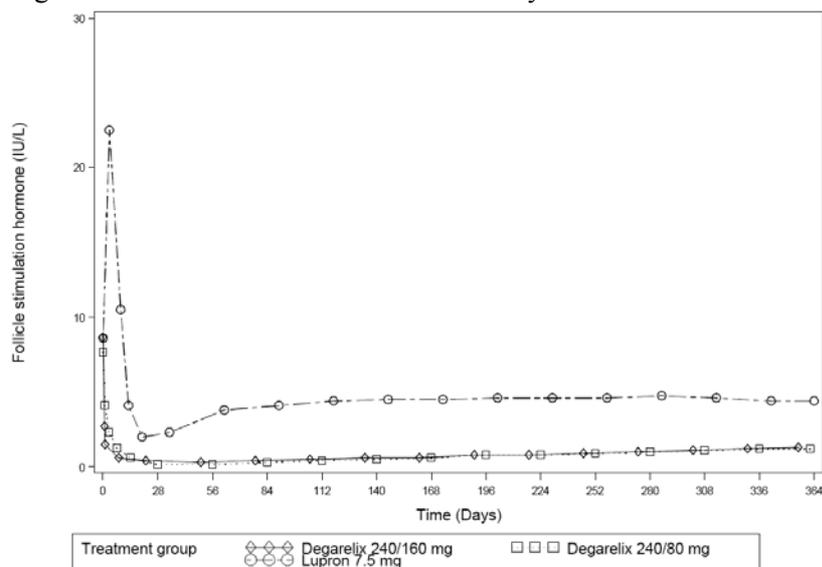
A rapid decrease in FSH levels was also observed in patients treated with degarelix (see figure 8 below). Administration of degarelix resulted in a reduction in median FSH levels to  $\leq 1.5$  IU/L by Day 7, a  $>80\%$  decrease from baseline. For both degarelix treatment groups median FSH levels remained suppressed until the end of the study on Day 364. For patients in the leuprorelin group there was an initial surge in FSH levels similar to that observed for LH levels which peaked at 22.5 IU/L on Day 1 (146% increase from baseline) before decreasing exponentially to 2.0 IU/L by Day 14. Median FSH subsequently increased around Day 56 to a plateau of approximately 4.40 IU/L and stayed there until Day 364.

Figure 7: Median LH levels over time – ITT analysis set



Source: Module 5, Study report CS21

Figure 8: Median FSH over time – ITT analysis set



Source: Module 5, Study report CS21

## Quality of Life

### Quality of Life on Days 0, 28, 84, 168 and End of Study

QoL for patients in this study was assessed on Days 0, 28, 84, 168 and at the End of Study Visit using the Short Form-12 v2 (SF-12-v2) and EORTC QLQ-C30 questionnaires to measure generic and cancer-specific QoL, respectively.

For the EORTC QLQ-C30 questionnaire, the scores for all three groups were stable. There were no changes from baseline in median scores for all subscales of the questionnaire at any timepoint in the study, except for early end of study. The removal of irregular data from the EORTC QLQ-C30 scores had no effect and all of the values for median changes from baseline remained the same. For the SF-12 v2 questionnaire, all scale scores were comparable across treatment groups and study days. Throughout the study there were no changes from baseline scores in any of the eight domains assessed.

### Hot Flush Frequency and Hot Flush Score

The frequency and severity of hot flushes reported by patients was measured using a hot flushes diary. This instrument measured a patient's daily assessment of hot flush frequency and severity (rated on a scale from 1='mild' to 4='very severe') enabling calculation of a hot flush score. Analysis of the overall number of hot flushes per day and hot flush score revealed no trend over time or across treatment groups (see table 18 below). During the course of the study (Days 1-364) the median number of hot flushes per day was very similar between the three treatment groups: 1.00, 1.07 and 1.06 for the degarelix 240/160 mg, degarelix 240/80 mg and leuprorelin groups, respectively. During the course of the study (Days 1-364), the median hot flush score per day was slightly higher for the leuprorelin group (1.59) compared with the degarelix 240/160 mg and 240/80 mg treatment groups (1.46 and 1.37, respectively). Similarly, analysis of the median number of mild and moderate hot flushes per day revealed no trend over time or across treatment groups, and very few patients experienced severe or very severe hot flushes.

Table 18: Summary of median daily number of hot flushes and median daily hot flush score - ITT analysis set

	Degarelix 240/160 mg				Degarelix 240/80 mg				Leuprorelin 7.5 mg			
	N	Recordings	Flush/day	Score/day	N	Recordings	Flush/day	Score/day	N	Recordings	Flush/day	Score/day
ITT analysis set	202				207				201			
Baseline	60	1.00	0.000	0.000	59	1.00	0.000	0.000	66	1.00	0.000	0.000

Days 1-28	67	20.0	0.481	0.500	70	19.9	0.367	0.394	81	23.0	0.069	0.069
Days 29-84	66	42.2	1.32	1.81	69	43.0	1.50	1.77	78	43.4	0.184	0.198
Days 85-168	60	67.8	1.55	2.04	65	69.6	1.07	1.43	75	66.2	0.871	1.21
Days 169-364	59	148	1.03	1.23	65	141	1.11	1.29	73	145	1.60	2.02
Days 1-364	75	226	1.00	1.46	81	223	1.07	1.37	88	236	1.06	1.59

#### *Degarelix concentration during the first month and trough levels at Days 308 and 336*

Plasma concentrations of degarelix increased rapidly following administration of the first dose on Day 0. For the pooled degarelix group, the mean maximum plasma concentration of degarelix ( $C_{max}$ ) was 61.2 ng/ml, which was observed on Day 1 (24 hours after administration) and the mean  $AUC_{0-28}$  was 635 .

The mean degarelix trough concentrations were at steady state after 11 and 12 doses of degarelix on Days 308 and 336, respectively. For the degarelix 240/160 mg group, the mean degarelix trough concentration was 22.1 ng/ml on Day 308 which increased slightly to a mean trough level of 22.7 ng/ml on Day 336. For the degarelix 240/80 mg, the mean degarelix trough concentration was 13.5 ng/ml on Day 308 and remained steady with a mean trough level of 13.6 ng/ml on Day 336.

#### *Ancillary analyses*

##### **Sensitivity analyses for the primary end-point**

Sensitivity analyses were performed to establish whether the conclusions drawn from the primary analysis of the primary end-point were robust. A Cox-proportional hazard analysis using testosterone monitoring frequency (number of missing testosterone values/ treatment months) as a covariate was added to the sensitivity analysis. The results showed that testosterone monitoring frequency did not have a significant additive effect in the model ( $p>0.05$ ), therefore its impact on the primary efficacy analysis was negligible.

In addition, the response rate to treatment (the proportion of patients with testosterone  $\leq 0.5$  ng/ml from Day 28 to Day 364) was analysed using the observed cases, which were defined as patients who either completed the study or had a testosterone measurement of  $>0.5$  ng/ml at Day 28 and onwards. This approach provides a conservative estimate of the response rate at Day 364 because patients with testosterone values  $\leq 0.5$  ng/ml who withdrew early are not carried forward, and hence the denominator is reduced. Using the observed cases approach, the overall proportion of patients in the ITT analysis set with testosterone  $\leq 0.5$  ng/ml from Day 28 to Day 364 was 98.2% (95% CI: 94.7-99.6%) for the degarelix 240/160 mg group and 97.0% (95% CI: 93.2-99.0%) for the degarelix 240/80 mg group, compared with 96.0% (95% CI: 91.8-98.4%) for leuprorelin group. The differences between the two degarelix treatment groups and the leuprorelin comparator group were 2.2% (97.5% CI: -1.4-5.8) and 1.1% (97.5% CI: -2.8-5.0) for the degarelix 240/160 mg and degarelix 240/80 mg treatment groups, respectively. These results are similar to those obtained for the primary analysis using the Kaplan-Meier method.

##### **Sensitivity analyses for the secondary end-points**

Sensitivity analyses were also performed for some of the secondary end-points.

#### *Proportion of patients with testosterone level $\leq 0.5$ ng/ml at Day 3*

When analysed by geographical region and weight, the proportion of patients with testosterone  $\leq 0.5$  ng/ml on Day 3 was similar for each stratum across the treatment groups and ranged from 93% to 100% in the degarelix groups. In the leuprorelin group there were no patients with testosterone  $\leq 0.5$  ng/ml on Day 3.

#### *Percentage change in PSA from baseline to Day 14 and Day 28*

The median percentage change in PSA from baseline was also analysed by geographical region and weight for each treatment group. For patients in the Americas, degarelix treatment reduced median PSA levels by approximately 60% on Day 14 and 80-84% on Day 28, while treatment with leuprorelin led to smaller reductions in PSA levels of approximately 14% on Day 14 and 56- 59% on Day 28. Similarly, for patients in Central and Eastern Europe, degarelix treatment reduced median PSA levels by 64-67% on Day 14 and 80-84% on Day 28, while treatment with leuprorelin led to smaller

reductions in PSA levels of 20-25% on Day 14 and 59-73% on Day 28. The number of patients recruited in Western Europe was too small to make legitimate comparisons with patients from the Americas and, Central and Eastern Europe.

The percentage change in PSA levels from baseline was not affected by the patient's weight.

### **Sub-group analysis**

Post-hoc sub-group analyses were presented in the summary of clinical efficacy. The efficacy endpoints were examined in greater detail for differences among the subgroups of the following subpopulations of patients:

- Age: < 65 years old, ≥ 65 to 75 years old, or ≥ 75 years old.
- Race: White, Black, or other races.
- Region: North America, Western Europe, or Central and Eastern Europe and other regions.
- Stage of prostate cancer: localized, locally advanced, metastatic, non-classifiable in patients with curative intent, non-classifiable in patients without curative intent.
- Weight: < 70 kg, ≥ 70 to < 90 kg, or ≥ 90 kg.

Overall, the results of the subgroup analyses for degarelix 240 mg (40 mg/ml)/80 mg (20 mg/ml), degarelix 240 mg (40 mg/ml)/ 160 mg (40 mg/ml), and leuprorelin were similar for the primary endpoint.

#### *Primary efficacy endpoint*

Cumulative probability of testosterone ≤0.5 ng/ml from Day 28 through Day 364, the results were as follows:

#### **Age:**

The probability ranged from 94.9% [95% CI 87.0;98.1%] to 100% in the degarelix subgroups and from 89.5% [95% CI 74.3;95.9%] to 98.5% [95% CI 89.9;99.8%] in the leuprorelin subgroups.

#### **Race:**

The probability ranged from 95.2% [95% CI 70.7;99.3%] to 100% in the degarelix subgroups and from 95.7% [95% CI 91.3;97.9%] to 100% in the leuprorelin subgroups.

#### **Region:**

The probability ranged from 96.3% [95% CI 90.5;98.6%] to 100% in the degarelix subgroups and from 96.2% [95% CI 90.2;98.6%] to 100% in the leuprorelin subgroups.

#### **Stage of prostate cancer:**

The probability ranged from 92.3% [95% CI 56.6;98.9%] to 100% in the degarelix subgroups and from 95.1% [95% CI 85.5;98.4%] to 100% in the leuprorelin subgroups.

#### **Weight:**

The probability ranged from 93.9% [95% CI 77.9;98.4%] to 100% in the degarelix subgroups and from 95.8% [95% CI 90.3;98.2%] to 97.3% [95% CI 82.3;99.6%] in the leuprorelin subgroups.

It should be noted that there were some discrepancies in the size of the subgroups.

#### *Secondary endpoints*

Sub-group analyses were also performed for some of the secondary endpoints and these analyses showed no discernable trends across the groups.

- Analysis performed across trials (pooled analyses and meta-analysis)

No analyses performed across trials were submitted.

- Clinical studies in special populations

#### *Hepatically impaired subjects*

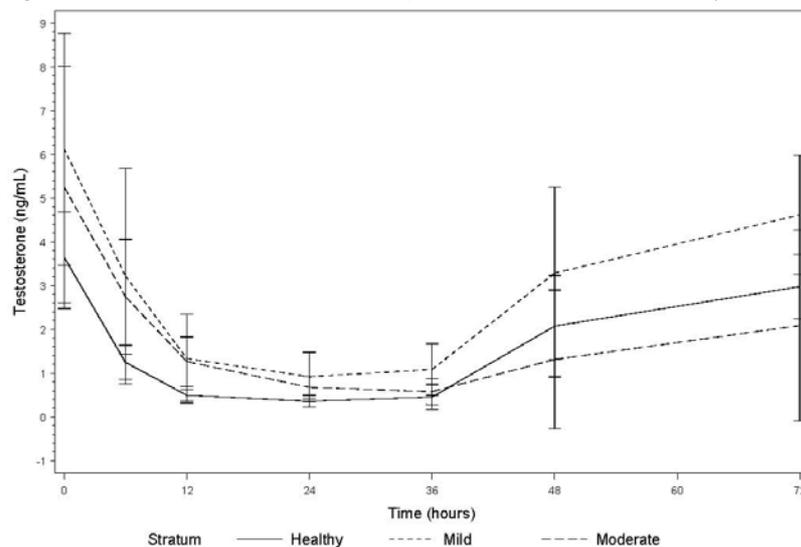
To investigate the effects of impaired hepatic function on the pharmacokinetics of degarelix, one study has been carried out. Study CS23 was an open-label, single center, single-dose, controlled study conducted in three parallel groups of eight subjects each, two test groups of subjects with hepatic

diseases (mild or moderate hepatic impairment) and a control group of healthy subjects,. Subjects with a Child-Pugh score  $\leq 6$ , Grade A were in the mild hepatic impairment group and subjects with a Child-Pugh score 7-9, Grade B were in the moderate hepatic impairment group. The subjects were administered one single dose of degarelix (1 mg) as a 1-hour continuous i.v. infusion. Pharmacokinetics for degarelix, pharmacodynamic parameters of testosterone and LH, metabolites of degarelix, and safety parameters were monitored up to 72 hrs post-dose and at the follow-up visit performed on Day 7.

Both the mild and moderate hepatic impairment groups displayed lower AUC, AUC<sub>t</sub>, and C<sub>max</sub> mean values compared to the healthy group of subjects. None of the 90% confidence intervals fell completely within the 80-125% boundaries, and C<sub>max</sub> for both the mildly and the moderately impaired, and AUC and AUC<sub>t</sub> for the moderately impaired, were significantly lower compared to the healthy subjects. In addition, V<sub>z</sub> for both the mildly and the moderately impaired and CL for the moderately impaired were significantly higher compared to the healthy subjects. There was no relationship between hepatic function and pharmacokinetic parameters. Only minor differences in excreted metabolites were observed arguing against any major effect of hepatic impairment on degarelix metabolism. Protein binding was approximately 90% in all three groups. No signs of a prolonged half-life of degarelix that could result in accumulation were observed in subjects with mild or moderate hepatic impairment.

Testosterone concentrations decreased subsequent to degarelix administration with the lowest individual levels recorded 24-36 hrs post dosing in the healthy subjects and in the mild impairment group, and 24-72 hrs post dosing in the moderate impairment group. The lowest mean levels occurred at 24 hours post dosing in the healthy and mild impairment groups and at 36 hours in the moderately impaired group (see figure 9 below).The lowest mean concentrations of testosterone compared to baseline were similar in the three groups, being 15%, 11%, and 9% of the baseline level in the mild and moderately impaired patients, and in the healthy subjects, respectively. As for testosterone, the LH concentration decreased subsequent to the degarelix administration, the minimum mean values recorded at 12 hrs post dosing in the healthy subjects and in the mild impairment group, and 36 hrs post dosing in the moderate impairment group.

Figure 9: Testosterone mean concentration vs time – PP analysis set



Source: Study report CS23

- Supportive study(ies)

No supportive studies were provided.

- **Discussion on clinical efficacy**

The CHMP raised a major objection with regards to the initially proposed indication for degarelix, which was subsequently restricted to “treatment of patients with advanced hormone-dependent prostate cancer”, taking into account that non-inferiority had been investigated using biological criteria and not clinical endpoints indicative of a direct benefit. The studies submitted had not documented tumour reduction or improved overall survival for patients with localized prostate cancer and therefore the initial indication for degarelix (treatment of patients with prostate cancer in whom androgen deprivation is warranted, including patients with rising PSA after having undergone prostatectomy or radiotherapy) was not considered acceptable. Additionally, the comparator in the non-inferiority pivotal study (i.e., leuprorelin) had been granted a more restricted indication as compared to inclusion criteria and to the initial claimed indication for FIRMAGON.

The starting dose of degarelix treatment is 240mg administered as two subcutaneous injections of 120mg each. The maintenance dose (as monthly administrations) is of 80mg, administered as one subcutaneous injection. The first maintenance dose should be given one month after the starting dose.

The therapeutic effect of degarelix should be monitored by clinical parameters and prostate specific antigen (PSA) serum levels. Clinical studies showed that testosterone (T) suppression occurs immediately after administration of the starting dose with 96% of the patients having plasma testosterone levels corresponding to medical castration ( $T \leq 0.5$  ng/ml) after three days and 100% after one month. Long term treatment with the maintenance dose up to 1 year shows that 97% of the patients have sustained suppressed testosterone levels ( $T \leq 0.5$  ng/ml). In case the patient's clinical response appears to be sub-optimal, it should be confirmed that serum testosterone levels are remaining sufficiently suppressed. Since degarelix does not induce a testosterone surge it is not necessary to add an anti-androgen as surge protection at initiation of therapy.

Degarelix should be reconstituted prior to administration, and only administered subcutaneously, in the abdominal region. Degarelix should not to be administered intravenously. Intramuscular administration is not recommended either, as it has not been studied. As with other drugs administered by subcutaneous injection, the injection site should vary periodically. Injections should be given in areas where the patient will not be exposed to pressure e.g. not close to waistband or belt and not close to the ribs.

There was no need to adjust the dose for the elderly or in patients with mild or moderate liver or kidney function impairment. A reference to this effect was made in section 5.2 of the SPC. Patients with severe liver or kidney impairment were not studied and caution was therefore warranted. A reference to this effect was made in section 4.4 of the SPC. There was no relevant indication for use of degarelix in women, children and adolescents

### **Clinical safety**

- Patient exposure

A total of 1836 prostate cancer patients and 138 healthy subjects were treated with degarelix. Of these, 1148 patients have received degarelix for more than one year, including 171 on the dosing regimen of 240 mg/80 mg.

As of September 28, 2007, 132 patients received degarelix for the first time in the extension study CS21A after receiving leuprorelin 7.5 mg.

Overall, at enrolment, the demographic and baseline disease characteristics of the pivotal study population were very similar to that of the total degarelix population, and within CS21 the treatment groups were well balanced:

- mean age was 72 years, 82% were  $\geq 65$  years and 42% were  $\geq 75$  years.
- 87% were Caucasian patients
- 42% from Central and Eastern Europe/Other, 34% from North America, and 24% from Western Europe.

- 61% localized or locally advanced prostate cancer, 22% metastatic prostate cancer,
- Approximately 14% had treatment of a curative intent.
- 55% patients had a Gleason score of 7-10
- 80% patients were fully active as rated on the ECOG performance scale.
- The mean duration of prostate cancer from diagnosis was 1.3 years (range: 0.014 to 18.3 years).

Many patients had concurrent medical conditions and were receiving concomitant medications. In all studies patients receiving other concurrent drugs with anti-androgenic or estrogenic activity for the management of their prostate cancer were excluded. In the pivotal study, medications which might prolong the QT/QTcF interval were prohibited.

Of the 178 patients in the leuprorelin group, only 22 patients were given anti-androgens within 7 days of the first dosing. The majority of these patients (19/22) received anti-androgens for  $\leq 28$  days suggesting that anti-androgen therapy was administered as flare protection, although prophylaxis of flare was only recorded in the eCRF/data listings for four of these patients. A similar number of patients in the Americas and Central and Eastern Europe received anti-androgens.

- Adverse events

The incidence of adverse events occurring at  $> 1\%$  by System Organ Class and Preferred Term for either degarelix or leuprorelin in the Phase 3 active control study or for total degarelix is summarized in table 19 below:

Table 19: Common Adverse Events ( $> 1\%$ ) by System Organ Class and Preferred Term in Phase 2/3 Studies for One-Month Dosing Regimen

	Phase 3 Controlled		Phase 2/3 Uncontrolled	Total
	Degarelix n (%)	Leuprorelin 7.5 mg n (%)	Degarelix n (%)	Degarelix n (%)
Exposed Patients	409	201	1090	1256
<b>Any adverse event</b>	<b>330 (81%)</b>	<b>156 (78%)</b>	<b>681 (62%)</b>	<b>972 (77%)</b>
<b>BLOOD AND LYMPHATIC SYSTEM DISORDERS</b>	16 (4%)	12 (6%)	44 (4%)	60 (5%)
<b>CARDIAC DISORDERS</b>	36 (9%)	27 (13%)	120 (11%)	155 (12%)
Myocardial ischaemia	2 ( $<1\%$ )*	5 (2%)*	9 ( $<1\%$ )	11 ( $<1\%$ )
<b>EAR AND LABYRINTH DISORDERS</b>	9 (2%)	3 (1%)	22 (2%)	31 (2%)
<b>EYE DISORDERS</b>	10 (2%)	5 (2%)	58 (5%)	68 (5%)
<b>GASTROINTESTINAL DISORDERS</b>	71 (17%)	39 (19%)	213 (20%)	284 (23%)
<b>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</b>	194 (47%) ***	36 (18%) ***	313 (29%)	501 (40%)
Injection site pain	119 (29%) ***	1 ( $<1\%$ ) ***	105 (10%)	221 (18%)
Injection site erythema	84 (21%) ***	0	55 (5%)	138 (11%)
Fatigue	20 (5%)	13 (6%)	69 (6%)	89 (7%)
Pyrexia	20 (5%)	4 (2%)	39 (4%)	59 (5%)
Injection site nodule	19 (5%) ***	0	27 (2%)	46 (4%)
Injection site swelling	27 (7%) ***	0	18 (2%)	44 (4%)
Oedema peripheral	8 (2%)*	10 (5%)*	32 (3%)	40 (3%)
Injection site induration	19 (5%) ***	0	17 (2%)	36 (3%)
Asthenia	16 (4%)	5 (2%)	24 (2%)	40 (3%)
Injection site pruritus	12 (3%)*	0	21 (2%)	33 (3%)
Chills	18 (4%) **	0	13 (1%)	31 (2%)
Injection site inflammation	11 (3%)*	0	11 (1%)	22 (2%)
Influenza like illness	9 (2%)*	0	10 ( $<1\%$ )	19 (2%)
Chest pain	2 ( $<1\%$ )*	6 (3%)*	17 (2%)	19 (2%)
Pain	6 (1%)	1 ( $<1\%$ )	8 ( $<1\%$ )	14 (1%)
Injection site reaction	7 (2%)	0	11 (1%)	18 (1%)
Malaise	1 ( $<1\%$ )	1 ( $<1\%$ )	12 (1%)	13 (1%)

	Phase 3 Controlled		Phase 2/3	Total
	Degarelix	Leuprorelin 7.5 mg	Uncontrolled	Degarelix
			Degarelix	
	n (%)	n (%)	n (%)	n (%)
Injection site irritation	11 (3%)*	0	3 (<1%)	14 (1%)
<b>HEPATOBIILIARY DISORDERS</b>	4 (<1%)	3 (1%)	14 (1%)	18 (1%)
<b>INFECTIONS AND INFESTATIONS</b>	83 (20%)	49 (24%)	250 (23%)	331 (26%)
<b>INJURY, POISONING AND PROCDURAL COMPLICATIONS</b>	21 (5%)	17 (8%)	97 (9%)	118 (9%)
<b>INVESTIGATIONS</b>	113 (28%)	62 (31%)	216 (20%)	326 (26%)
<b>METABOLISM AND NUTRITION DISORDERS</b>	40 (10%)	15 (7%)	87 (8%)	124 (10%)
<b>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</b>	68 (17%) **	53 (26%) **	214 (20%)	282 (22%)
Arthralgia	17 (4%)*	18 (9%)*	57 (5%)	74 (6%)
Musculoskeletal stiffness	0	3 (1%)*	4 (<1%)	4 (<1%)
<b>NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED</b>	22 (5%)	15 (7%)	79 (7%)	100 (8%)
<b>NERVOUS SYSTEM DISORDERS</b>	51 (12%)	23 (11%)	174 (16%)	224 (18%)
<b>PSYCHIATRIC DISORDERS</b>	32 (8%)	21 (10%)	92 (8%)	123 (10%)
<b>RENAL AND URINARY DISORDERS</b>	54 (13%)	39 (19%)	153 (14%)	204 (16%)
Urinary retention	5 (1%)*	9 (4%)*	28 (3%)	33 (3%)
Cystitis noninfective	0	4 (2%)*	2 (<1%)	2 (<1%)
<b>REPROCTIVE SYSTEM AND BREAST DISORDERS</b>	22 (5%)*	21 (10%)*	97 (9%)	118 (9%)
Erectile dysfunction	6 (1%)*	9 (4%)*	22 (2%)	28 (2%)
<b>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</b>	42 (10%)	18 (9%)	127 (12%)	169 (13%)
<b>SKIN AND SUBCUTANEOUS TISSUE DISORDERS</b>	39 (10%)	10 (5%)	135 (12%)	174 (14%)
<b>SURGICAL AND MEDICAL PROCEDURES</b>	2 (<1%)	0	13 (1%)	15 (1%)
<b>VASCULAR DISORDERS</b>	137 (33%)	60 (30%)	343 (31%)	479 (38%)
Hot flush	106 (26%)	43 (21%)	288 (26%)	394 (31%)
Deep vein thrombosis	0	3 (1%)*	3 (<1%)	3 (<1%)

P values for comparison of degarelix versus leuprorelin 7.5 mg in the Phase 3 controlled study, \* = 0.01 < P ≤ 0.05, \*\* 0.001 < P ≤ 0.01, \*\*\* P ≤ 0.001 (Fisher exact, two-sided)

### Treatment Emergent Adverse Events

In the Phase 3 control study CS21, comparable proportions of patients in each of the treatment groups reported TEAEs: 81% degarelix and 78% leuprorelin.

Globally, the most common TEAEs observed with degarelix were: hot flush (26%), injection site pain (29%), injection site erythema (21%), back pain (7%), fatigue (5%), nasopharyngitis (7%), weight increased (7%), urinary tract infection (6%), arthralgia (6%), ALT increased (6%), dizziness (6%), constipation (5.5%), hypertension (5.3%), and diarrhoea (5.3%).

There was a statistically significant difference in favour of degarelix for the incidence of: musculoskeletal and connective tissue disorders, Reproductive system and breast disorders, urinary tract infection, arthralgia, oedema peripheral, erectile dysfunction, chest pain, Cystitis non infective, cardiac murmur, musculoskeletal stiffness, libido decreased, deep vein thrombosis, myocardial ischaemia. In contrast, there was a highly statistically significant difference in favour of leuprorelin for the incidence of Injection site reactions, Influenza like illness, chills.

### Adverse Drug Reactions

There were 57% of degarelix patients with drug-related adverse events (adverse drug reactions). This was comparable to the percentage seen in the Phase 3 active control study for degarelix (58%) and more than that seen for leuprorelin (42%). The overall lower incidence of ADRs for leuprorelin compared to degarelix is due to the higher incidence of injection site reactions reported for degarelix.

In CS21 study, a greater proportion of patients in the degarelix dose groups had injection site reactions considered by the investigator to be related to the study drug compared to the leuprorelin group.

A greater proportion of patients treated with leuprorelin had musculoskeletal and connective tissue disorders and reproductive system and breast disorders such as erectile dysfunction considered related to treatment compared to degarelix treated patients in the CS21 study.

Of the 14 common AEs in degarelix patients, six of the AEs were also judged as related to degarelix by the investigator: hot flush (31%), injection site pain (17%), injection site erythema (11%), fatigue (5%), weight increased (4%), and ALT increased (4%).

Excluding injection-site ADRs, the incidences of the remaining ADRs were similar in the three treatment groups:

- 44% patients reported 194 ADRs, in the degarelix 240/160 mg group
- 43% patients reported 216 ADRs in the degarelix 240/80 mg group
- 42% patients reported 142 ADRs in the leuprorelin 7.5 mg group.

These limited results suggest that both the degarelix maintenance doses (80@20 mg/mL or 160@40 mg/ml) resulted in a similar incidence of ADRs.

#### *Reactions due to androgen deprivation*

Expected reactions occurring from androgen deprivation include hot flushes, weight increase, fatigue and adverse events relating to the reproductive system such as erectile dysfunction, testicular atrophy, and gynecomastia.

Adverse events relating to the reproductive system were reported at a low incidence in both treatment groups (<4%) in the Phase 3 active control study and <2% for total degarelix in the Phase 2/3 one-month dosing regimen studies.

The incidence of hot flush and weight increase were comparable between degarelix and leuprorelin groups:

- The incidence of hot flush with degarelix decreased after Month 1 (Month 1:15%, Month 2-4: 8%, Month 5-7: 3%, Month 8-10: 3%, Month 11-13: 1%) and after Month 2-4 with leuprorelin (8%, 12%, 1%, 2%, 2%, respectively). The increase of the hot flush incidence after Month 1 for leuprorelin is most likely related to the delay in testosterone suppression.
- The consistency over time in the hot flush prevalence suggests that the duration of the event was long for most patients who experienced this event.
- Incidence of weight increase was greatest at the end for both degarelix and leuprorelin.
- 

#### *Local Tolerability: Injection site reactions*

In the Phase 3 active control study, 40% of all degarelix patients (N=194) reported an injection site reaction, while only one leuprorelin patient reported an injection site reaction. There were a numerically greater percentage of patients reporting injection site erythema and injection site nodule in the 240 mg/160 mg group compared to the 240 mg/80 mg group, suggesting that the maintenance dose of 80mg may result in fewer injections site reactions.

The most frequently reported TEAEs in the degarelix 240mg/80mg group were injection site reactions, including pain (28%), erythema (17%), swelling (6%), induration (4%), and nodule (3%). These adverse events were mostly transient of mild to moderate intensity. The events occurred primarily with the starting dose (32% of patients), whereas few injection site reactions (3% of patients) were reported

with administration of each maintenance dose. Very few injection site reactions (<1%) led to discontinuation. The incidence rates of these events per 100 injections were: injection site pain 2.8, injection site erythema 1.6, injection site swelling 0.5, injection site induration 0.3, and injection site nodule 0.2.

In many cases, two or more injection site reactions occurred simultaneously after dosing. The incidence of injection site pain and injection site erythema decreased after Month 1 for degarelix. None of the injection site reactions were considered to be SAEs, and no immediate onset hypersensitivity reactions occurred after dosing.

Injection site reactions were rarely observed with leuprorelin in the pivotal study. Since a high rate of injection site reactions are associated with leuprorelin administered S.C., the applicant suggested that the difference in the route of administration would be the primary reason for the difference in local tolerability of leuprorelin versus S.C. degarelix.

#### *Immunological events*

No cases of clinically significant hypersensitivity reactions related to degarelix were identified using MedDRA SMQs for “anaphylaxis”, “angioedema”, or “severe cutaneous skin reactions”. In the CS21 study, there was a low incidence of other adverse events associated with hypersensitivity reactions for degarelix 20mg/ 80 mg, such as rash (<1%) and pruritus (<1%), and no clinically relevant differences observed when compared to leuprorelin.

- Serious adverse event/deaths/other significant events

There were 18% of patients treated with degarelix who had serious adverse events and 5% of the patients died; this was comparable to what was seen for leuprorelin in the Phase 3 active control study.

In the Phase 3 active control study, the incidence of SAEs was comparable between treatment groups: 11% degarelix and 14% leuprorelin. Death during treatment and within 30 days after the last dose occurred in 2.4% of the degarelix patients (10 deaths) compared to 4.5% of the leuprorelin group (9 deaths).

The most common SAEs were cardiac disorders (2% degarelix and 5% leuprorelin) and renal and urinary disorders (2% degarelix and 3% leuprorelin). None of the SAEs were considered related to study drug except for abnormal prostate examination experienced by one patient in the leuprorelin group.

The causes of death were similar among the treatment groups (cardiac disorders, malignancies), and none was considered related to treatment.

The incidence of discontinuation for each treatment group in the Phase 3 active control study was stable over time (9% first six months vs. 11% last six month of the study) for any reason.

#### *Cardiovascular events*

Androgen deprivation therapy has been associated with an increased risk of cardiovascular disease in older men. Given the prevalence of cardiovascular disorders in the population of elderly men, an analysis of the effect of exposure to degarelix on the incidence of cardiovascular events was undertaken.

In the Phase 3 active control study, the proportion of patients with markedly abnormal changes in ECG variables was comparable between degarelix and leuprorelin. There were no dose related changes noted. Approximately 20% of patients had markedly abnormal increases in QTc Fridericia of > 450 msec with 3% having increases > 480 msec. Seven patients, 3 in the pooled degarelix group and 4 in the leuprorelin group, had a markedly abnormal QTcF  $\geq$  500 msec. None of the degarelix patients with QTcF  $\geq$  500 msec had outcomes of syncope, Torsade de pointes, ventricular fibrillation, or

sudden death. There was one leuprorelin patient with a cardiovascular history, who reported syncope and cardiac arrhythmia 20 days after a QTc measurement of 503 msec. This patient also had a prior episode of syncope 4 months earlier. All three events were rated as Grade 2 (moderate) and considered related to study drug leuprorelin. The patient continued in the study.

- Laboratory findings

In the Phase 3 study, a decrease in haemoglobin was observed in 40% patients in the degarelix 240 mg/ 80 mg and in 36% patients in the leuprorelin group. Two patients in the degarelix group and three in the leuprorelin group had anaemia that was considered serious. Overall, 8 degarelix patients in the one-month dosing regimen studies had anaemia reported as a serious adverse event.

No patients were discontinued due to a clinically significant haematology abnormality, except one degarelix patient, who developed neutropenic sepsis (SAE) in study CS07A, 6 weeks after his second dose, which led to discontinuation; otherwise, no adverse trends in decreased neutrophil counts were identified in patients exposed to degarelix.

In the pivotal study, there were no unexpected observable trends across the treatment groups in clinical chemistry parameters. The abnormal values for urea nitrogen, potassium, and serum creatinine were mainly in patients with pre-existing renal abnormalities, but were not clinically significant and were reported for both degarelix and leuprorelin.

Regarding liver toxicity, more patients in the degarelix 240 mg/ 80 mg group had increased ALT compared with the leuprorelin group in the pivotal study (10% and 5%, respectively). Increased AST and hypercholesterolemia occurred in 5% and 3% of degarelix 240 mg/ 80 mg patients (3% and 2%, respectively leuprorelin), and gamma-GT in 2% of degarelix 240 mg/ 80 mg patients (1% leuprorelin) were also reported. One patient in the degarelix 240/80 mg group, with elevated gamma-GT at baseline, was discontinued due to the AE of hepatic enzyme increase.

Overall in the phase 2/3 one-month dosing regimen studies, fewer than 1% of patients had laboratory value abnormalities reported as SAEs: haematuria (n = 7, <1%) was the most commonly reported serious adverse event. There were very few (<1%) patients withdrawn from treatment due to laboratory abnormalities: 4 patients discontinued due to increased ALT, 3 patients due to increased gamma-GT, and 2 patients due to increased alkaline phosphatase.

- Safety in special populations

Degarelix was studied in a pharmacokinetic study CS23 in patients with mild to moderate hepatic impairment. No signs of increased exposure in the hepatically impaired patients were observed compared to healthy subjects. No shifts in liver function tests were observed 24 hours post-dose compared to baseline in patients with hepatic impairment. Dose adjustment is not necessary in patients with mild or moderate hepatic impairment. Patients with severe hepatic dysfunction have not been studied and caution is therefore warranted in this group

Because only a relatively small amount of degarelix is excreted unchanged via the kidneys, dose adjustment is not necessary in patients with mild or moderate renal impairment, but degarelix should be used with caution in patients with severe renal impairment due to lack of data to support its use.

- Safety related to drug-drug interactions and other interactions

The only prohibited medications during these studies were other hormone-manipulative drugs, and, in CS21, those which might prolong the QT interval and 5- $\alpha$ -reductase inhibitors. Therefore, during the clinical study program, the use of concomitant medication in the study populations has been extensive, without evidence of any impact on the therapeutic effect or safety of either degarelix or the concomitant treatment.

Although anti-arrhythmic drugs are not contra-indicated, physicians should consider whether the benefit of androgen deprivation treatment outweighs the potential risk to patients who are taking these medications.

Since androgen deprivation treatment may prolong QTc interval, careful consideration should be given to patients receiving Class IA (e.g. quinidine, procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic medications.

No studies on the effects of degarelix on the ability to drive and operate machinery have been performed, but it is not associated with drowsiness and should not affect a patient's ability in this respect.

- Discontinuation due to adverse events

For the Phase 3 active control study, the percentage of patients completing the study was comparable between the degarelix groups (81%) and the leuprorelin group (86%). The incidence of non-fatal adverse events leading to discontinuation for the degarelix groups was 5.8% for degarelix compared to 1.5% in the leuprorelin group.

In the total degarelix treatment group, of the 34 AEs that led to withdrawal, 11 of these were ADRs. In comparison, all AEs leading to withdrawal in the leuprorelin group were considered unrelated to the IMP. The table below summarizes the disposition of patients in phase 2/3 studies for degarelix one – month dosing regimen.

Table 20: Disposition of Patients in Phase 2/3 Studies (Main and Extension) for Degarelix One-Month Dosing Regimen

	Phase 3 Controlled		Phase 2/3 Uncontrolled	Total
	Degarelix	Leuprorelin 7.5 mg	Degarelix	Degarelix
<b>Exposed Patients</b>	409	201	1090	1256 <sup>1</sup>
<b>Completed</b>	332 (81%)	172 (86%)	168 (15%)	257 (20%)
<b>Ongoing</b>	0	0	459 (42%)	459 (37%)
<b>Discontinued</b>	77 (19%)	29 (14%)	463 (42%)	540 (43%)
<b>Reason for discontinuation</b>				
Adverse Event	34 (8%)	12 (6%)	111 (10%)	145 (12%)
Non fatal event	24 (6%)	3 (1%)	63 (6%)	87 (7%)
Fatal during treatment	9 (2%)	9 (4%)	36 (3%)	45 (4%)
Fatal post treatment	1 (<1%)	0	12 (1%)	13 (1%)
Lack of PSA suppression <sup>2</sup>	2 (<1%)	0	84 (8%)	86 (7%)
Lack of testosterone suppression <sup>2</sup>	0	0	148 (14%)	148 (12%)
Lost to follow-up	5 (1%)	1 (<1%)	6 (<1%)	11 (<1%)
Other	36 (9%)	16 (8%)	114 (10%)	150 (12%)

<sup>1</sup> Includes 1124 from the main studies and 132 patients who received degarelix in CS21A after receiving leuprorelin in CS21.

<sup>2</sup> Forced withdrawal as per protocol in studies CS02/A, CS06/A, CS07/A, CS12/A, CS14/A

- Post marketing experience

There is no post-marketing experience with degarelix as this product has not been previously authorised.

- Discussion on clinical safety

Since no post-marketing studies were proposed by the applicant, considering the very limited safety data base for degarelix, the applicant was asked to commit to continue the ongoing long term extension studies for the one month depot (CS12A, CS14A and CS21A) independently of MA approval. The applicant agreed to commit to continue these studies until all patients in the given study had received treatment with degarelix for a period of 5 years.

The CHMP raised concerns over the long term efficacy and safety for patients developing antibodies against degarelix, as this matter had not been fully investigated. Therefore, the CHMP asked the applicant to explore the long term consequences of developing anti-degarelix antibodies, providing literature concerning antibody formation after GnRH agonist treatment. In addition, the information on section 5.1 of the SPC on antibody formation was updated to reflect that long term efficacy and safety data in relation to antibody development was not available: “Anti-degarelix antibody development has been observed in 10% of patients after treatment with FIRMAGON for one year. There is no indication that the efficacy or safety of FIRMAGON treatment is affected by antibody formation after one year of treatment. Efficacy and safety data in relation to antibody development beyond one year is not available.”

The CHMP considered that section 4.4 of the SPC should include a warning with regards to the lack of new data (efficacy and safety) beyond one year from Study CS21 (“the data available on clinical and safety experience with degarelix is limited to one year treatment.”) In addition, warnings were included on the effect of degarelix on QT/QTc interval, patients with known or suspect hepatic disorders, patients with severe renal impairment, severe untreated asthma, anaphylactic reactions, severe urticaria, angioedema, or patients with orchietomy or who have been treated with a GnRH agonist.

#### Effect on QT/QTc interval

During the evaluation, the CHMP considered that the original warning submitted by the applicant was insufficient as clinical and pre-clinical data should be mentioned in the SPC. The applicant argued that the use of androgen deprivation therapy was not considered an absolute contraindication (hence no mention of it in section 4.3) in the patient population excluded from the pivotal study CS21 based on risk factors related to the QT interval. However, the applicant and the CHMP agreed to update section 4.4 with information on the clinical data as follows:

Long-term androgen deprivation therapy may prolong the QT interval. In the confirmatory study comparing degarelix to leuprorelin periodic, both therapies showed QT/QTc intervals exceeding 450 msec in approximately 20% of the patients, and 500 msec in 1-2% of the patients. A reference to this effect was also made in section 5.1.

Degarelix has not been studied in patients with a history of a corrected QT interval over 450 ms, history of or risk factors for torsades de pointes; concomitant medications that might prolong the QT interval. Therefore the CHMP considered that, in such patients, the benefit/risk ratio of degarelix should be thoroughly appraised. References to this effect were also made in sections 4.5 and 4.8 of the SPC.

In addition to this, the Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs” ICH guideline (CHMP/ICH/2/04) recommends that all new compounds with systemic bioavailability undergo a “thorough QT/QTc” study to determine if the compound (or its metabolites) causes prolongation of the QT interval. These recommendations are primarily concerned with the development of New Chemical Entities; however, the CHMP considered that it may be applicable to approved drugs when a new dose or route of administration is being developed. Following this recommendation, the applicant committed to perform a QT/QC study and update the risk management plan accordingly.

#### Hepatic impairment

Patients with known or suspected hepatic disorder have not been included in long-term clinical trials with degarelix. Mild, transient increases in ALT and AST has been seen, these were not accompanied by a rise in bilirubin or clinical symptoms. Monitoring of liver function in patients with known or suspected hepatic disorder is advised during treatment. The pharmacokinetics of degarelix has been investigated after single intravenous administration in subjects with mild to moderate hepatic impairment. A reference to this effect was also made in section 5.2 of the SPC.

#### Renal impairment

Degarelix has not been studied in patients with severe renal impairment and caution is therefore warranted.

#### Hypersensitivity

Degarelix has not been studied in patients with a history of severe untreated asthma, anaphylactic reactions or severe urticaria or angioedema.

#### Changes in bone density

The CHMP considered that the applicant had not adequately justified why a similar long term effect on decreased bone density between degarelix and other androgen deprivation therapies may be expected. The applicant provided references to this respect, suggesting that bone mass density continues to decrease during long-term treatment with GnRH agonists and the development of osteoporosis appears to increase steadily with duration of therapy. Therefore the SPC was amended as follows: Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with a GnRH agonist. It can be anticipated that long periods of testosterone suppression in men will have effects on bone density. Bone density has not been measured during treatment with degarelix.

#### Glucose tolerance

The CHMP noted the need to include a warning regarding reduced glucose tolerance related to androgen deprivation. This warning was further updated to include information that the influence of degarelix on insulin and glucose levels has not been studied: A reduction in glucose tolerance has been observed in men who have had orchiectomy or who have been treated with a GnRH agonist. Development or aggravation of diabetes may occur; therefore diabetic patients may require more frequent monitoring of blood glucose when receiving androgen deprivation therapy. The effect of degarelix on insulin and glucose levels has not been studied.

In section 4.7, the absence of studies on the effects of degarelix on the ability to drive and use machines was stated. However, the CHMP considered that fatigue and dizziness are common adverse reactions that might influence the patient's ability to drive and use machines.

Section 4.8 was amended to include the most commonly observed adverse reactions during degarelix therapy in the confirmatory phase III study, which were due to the expected physiological effects of testosterone suppression, including hot flushes and weight increase (reported in 25% and 7%, respectively, of patients receiving treatment for one year), or injection site adverse events. Transient chills, fever or influenza like illness were reported to occur hours after dosing (in 3%, 2% and 1% of patients, respectively).

The injection site adverse events reported were mainly pain and erythema, reported in 28% and 17% of patients, respectively, less frequently reported were swelling (6%), induration (4%) and nodule (3%). These events occurred primarily with the starting dose whereas during maintenance therapy the incidence of these events pr 100 injections was: 3 for pain and <1 for erythema, swelling, nodule and induration. The reported events were mostly transient, of mild to moderate intensity and led to very few discontinuations (<1%).

The frequency of undesirable effects reported in the confirmatory phase II study was provided in a tabular format in the SPC.

#### *Changes in laboratory parameters:*

Changes in laboratory values seen during one year of treatment were in the same range for degarelix and the GnRH-agonist (leuprorelin) used as comparator. Markedly abnormal ( $>3*ULN$ ) liver transaminase values (ALT, AST and GGT) were seen in 2-6% of patients with normal values prior to treatment, following treatment with both drugs. Marked decrease in haematological values, hematocrit ( $\leq 0.37$ ) and hemoglobin ( $\leq 115g/l$ ) were seen in 40% and 13-15%, respectively, of patients with normal values prior to treatment, following treatment with both drugs. It is unknown to what extent this decrease in haematological values was caused by the underlying prostate cancer and to what extent it was a consequence of androgen deprivation therapy.

In addition, the CHMP requested that the proportion of patients with abnormal values for urea nitrogen, potassium, and creatinine be included in this section: Markedly abnormal values of potassium ( $\geq 5.8mmol/L$ ), creatinine ( $\geq 177\mu mol/L$ ) and BUN ( $\geq 10.7mmol/L$ ) in patients with normal values prior to treatment, were seen in 6%, 2% and 15% of degarelix treated patients and 3%, 2% and 14% of leuprorelin treated patients, respectively.

#### *Changes in ECG measurements:*

Changes in ECG measurements seen during one year of treatment were in the same range for degarelix and the GnRH-agonist (leuprorelin) used as comparator. Three ( $<1\%$ ) out of 409 patients in the degarelix group and four (2%) out of 207 patients in the leuprorelin 7.5 mg group, had a QTcF  $\geq 500$  msec. From baseline to end of study the median change in QTcF for degarelix was 12.3 msec and for leuprorelin was 16.7 msec.

Section 4.9 was updated to reflect that there is no clinical experience with the effects of an acute overdose with degarelix. In the event of an overdose, the CHMP recommended that the patient should be monitored and appropriate supportive treatment should be given, if considered necessary.

## **2.5 Pharmacovigilance**

### **Detailed description of the Pharmacovigilance system**

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

### **Risk Management Plan**

The MAA submitted a risk management plan, which included a risk minimisation plan.

**Table 21 Summary of the risk management plan**

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Injection site reactions	Enhanced pharmacovigilance with monitoring of injection site reactions reported in PSURs.	Injection site reactions are included in section 4.8 of the SPC. An information package consisting of the SPC, Package Leaflet and Labelling and educational materials are to be provided to the health care professional as agreed with the National Competent Authorities. The educational material will include information on posology, instructions for administration, information on gel depot formation and possible injection site reactions.

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Anti-degarelix antibodies	Reporting in PSUR of results from analysis of blood samples for anti-degarelix antibodies	None
T-prolongation	Enhanced pharmacovigilance with evaluation of adverse events potentially associated with QT prolongation included in PSURs.	SPC sections 4.4, 4.5, 4.8 and 5.1. An information package consisting of the SPC, Package Leaflet and Labelling and educational materials are to be provided to the health care professional as agreed with the National Competent Authorities. The educational material to be provided to all physicians will contain information on class effects, including QT-prolongation and the need for thorough appraisal of the benefit/risk ratio of androgen deprivation therapy in patients with risk factors for QT-prolongation, in accordance with the SPC
Elevated hepatic enzymes	Enhanced pharmacovigilance with evaluation of patients with markedly elevated hepatic enzymes included in PSURs.	None
Hypersensitivity	Enhanced pharmacovigilance with monitoring of potential hypersensitivity reactions reported in PSURs.	None
Decreased bone density	Enhanced pharmacovigilance with evaluation of adverse events potentially associated with decreased bone density included in PSURs.	SPC section 4.4. An information package consisting of the SPC, Package Leaflet and Labelling and educational materials are to be provided to the health care professional as agreed with the National Competent Authorities. The educational material will include information on class effects, including decreased bone density as well as standard medical advice for maintenance of bone health and prevention of osteoporosis.
Cardiovascular disease	Enhanced pharmacovigilance with evaluation of cardiovascular adverse events included in PSURs.	An information package consisting of the SPC, Package Leaflet and Labelling and educational materials are to be provided to the health care professional as agreed with the National Competent Authorities. The educational material will contain information on class effects, including metabolic changes and weight increase associated with androgen deprivation therapy and information on standard medical advice for prevention of cardiovascular disease.

The CHMP, having considered the data submitted in the MA application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product: see as detailed in section 2.3 of this CHMP Assessment Report.

## 2.6 Overall conclusions, risk/benefit assessment and recommendation

### Quality

The drug substance and the drug product have been appropriately characterised and generally satisfactory documentation has been provided. The excipients used in the preparation of the drug product and manufacturing process selected are typical for injectable preparations. The results indicate that the drug substance and the drug product can be reproducibly manufactured.

At the time of the CHMP opinion, there were minor unresolved quality issues which have no impact on the Benefit/Risk ratio of the product. The applicant gave a Letter of Undertaking and committed to resolve it as a Follow-up Measures after the opinion, within an agreed time-frame.

### Non-clinical pharmacology and toxicology

Animal reproduction studies showed that degarelix caused infertility in male animals. This is due to the pharmacological effect; and the effect was reversible.

In female reproduction toxicity studies degarelix revealed findings expected from the pharmacological properties. It caused a dosage dependent prolongation of the time to mating and to pregnancy, a reduced number of *corpora lutea*, and an increase in the number of pre- and post-implantation losses, abortions, early embryo/foetal deaths, premature deliveries and in the duration of parturition.

Preclinical studies on safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential revealed no special hazard for humans. Especially, both *in vitro* and *in vivo* studies showed no signs of QT prolongation.

No target organ toxicity was observed from acute, subacute and chronic toxicity studies in rats and monkeys following subcutaneous administration of degarelix. Drug-related local irritation was noted in animals when degarelix was administered subcutaneously in high doses.

### Efficacy

The data submitted suggest that a single dose of 240 mg degarelix, followed by a monthly maintenance dose of 80 mg, rapidly causes a decrease in the concentrations of LH, FSH and subsequently testosterone. The plasma concentration of dihydrotestosterone (DHT) decreases in a similar manner to testosterone.

The efficacy and safety of degarelix were evaluated in an open-label, multi-centre, randomised, active comparator controlled, parallel-group phase III study. The study investigated the efficacy and safety of two different degarelix monthly dosing regimens with a starting dose of 240 mg (40 mg/ml) followed by monthly doses subcutaneous (s.c.) administration of 160 mg (40 mg/ml) or 80 mg (20 mg/ml), in comparison to monthly intramuscular (i.m) administration of 7.5 mg leuprorelin in patients with prostate cancer requiring androgen deprivation therapy. In total 620 patients were randomised to one of the three treatment groups, of which 504 (81%) patients completed the study. In the degarelix 240/80 mg treatment group 41 (20%) patients discontinued the study, as compared to 32 (16%) patients in the leuprorelin group.

Of the 610 patients treated

- 31% had localised prostate cancer
- 29% had locally advanced prostate cancer
- 20 % had metastatic prostate cancer
- 7% had an unknown metastatic status
- 13% had previous curative intent surgery or radiation and a rising PSA

Baseline demographics were similar between the arms. The median age was 74 years (range 47 to 98 years). The primary objective was to demonstrate that degarelix is effective with respect to achieving

and maintaining testosterone suppression to below 0.5 ng/ml, during 12 months of treatment. The lowest effective maintenance dose of 80 mg degarelix was chosen.

*Attainment of serum Testosterone (T)  $\leq$ 0.5 ng/ml:*

A table showing the percentage of patients attaining testosterone levels of  $\leq$ 0.5 ng/ml after start of treatment with degarelix and leuprorelin was included in the SPC. Degarelix was effective in achieving testosterone suppression well below the medical castration level of 0.5 ng/ml.

*Avoidance of testosterone surge:*

Surge was defined as testosterone exceeding baseline by  $\geq$ 15% within the first 2 weeks.

None of the degarelix-treated patients experienced a testosterone surge; there was an average decrease of 94% in testosterone at day 3. Most of the leuprorelin-treated patients experienced testosterone surge; there was an average increase of 65% in testosterone at day 3. This difference was statistically significant ( $p < 0.001$ ).

A graph depicting the percentage change in testosterone from baseline by treatment group until day 28 (median with interquartile ranges) was included in the SPC. The primary end-point in the study was testosterone suppression rates after one year of treatment with degarelix or leuprorelin. The clinical benefit for degarelix compared to leuprorelin plus anti-androgen in the initial phase of treatment was not demonstrated.

*Long-term effect:*

Successful response in the study was defined as attainment of medical castration at day 28 and maintenance through day 364 where no single testosterone concentration was greater than 0.5 ng/ml.

A table showing the cumulative probability of attaining medical castration from Day 28 to Day 364 was included in the SPC. Degarelix showed a response rate of 97.2% (CI: 93.5; 98.8%) and leuprorelin showed a response rate of 96.4% (CI: 92.5; 98.2%)

*Attainment of prostate specific antigen (PSA) reduction:*

Tumour size was not measured directly during the clinical trial programme, but there was an indirect beneficial tumour response as shown by a 95% reduction after 12 months in median PSA for degarelix.

The median PSA in the study at baseline was:

- for the degarelix 240/80 mg treatment group 19.8 ng/ml (interquartile range: P25 9.4 ng/mL, P75 46.4 ng/ml)
- for the leuprorelin 7.5 mg treatment group 17.4 ng/ml (interquartile range: P25 8.4 ng/mL, P75 56.5 ng/ml)

A graph depicting the percentage change in PSA from baseline by treatment group until day 56 (median with interquartile ranges) was included in the SPC showing a statistically significant difference ( $p < 0.001$ ) at the pre-specified analysis at day 14 and day 28.

Prostate specific antigen (PSA) levels are lowered by 64% two weeks after administration of degarelix, 85% after one month, 95% after three months, and remained suppressed (approximately 97%) throughout the one year of treatment.

From day 56 to day 364 there were no significant differences between degarelix and the comparator in the percentage change from baseline.

In the confirmatory study comparing FIRMAGON to leuprorelin periodic electrocardiograms were performed. Both therapies showed QT/QTc intervals exceeding 450 msec in approximately 20% of the patients. From baseline to end of study the median change for FIRMAGON was 12.3 msec (3.2%) and for leuprorelin was 16.7 msec (3.5%).

Anti-degarelix antibody development was observed in 10% of patients after treatment with degarelix for one year. There was no indication that the efficacy or safety of degarelix treatment is affected by

antibody formation after one year of treatment. However, efficacy and safety data in relation to antibody development beyond one year is not available.

## **Safety**

The most commonly observed adverse reactions during degarelix therapy in the confirmatory phase III study (N=409) were due to the expected physiological effects of testosterone suppression, including hot flushes and weight increase (reported in 25% and 7%, respectively, of patients receiving treatment for one year), or injection site adverse events. Transient chills, fever or influenza like illness were reported to occur hours after dosing (in 3%, 2% and 1% of patients, respectively).

The injection site adverse events reported were mainly pain and erythema, reported in 28% and 17% of patients, respectively, less frequently reported were swelling (6%), induration (4%) and nodule (3%). These events occurred primarily with the starting dose whereas during maintenance therapy the incidence of these events pr 100 injections was: 3 for pain and <1 for erythema, swelling, nodule and induration. The reported events were mostly transient, of mild to moderate intensity and led to very few discontinuations (<1%). The frequency of adverse drug reactions reported in confirmatory phase III study was included in the SmPC.

Changes in laboratory values seen during one year of treatment were in the same range for degarelix and the GnRH-agonist (leuprorelin) used as comparator. Markedly abnormal (>3\*ULN) liver transaminase values (ALT, AST and GGT) were seen in 2-6% of patients with normal values prior to treatment, following treatment with both drugs. Marked decrease in haematological values, hematocrit ( $\leq 0.37$ ) and hemoglobin ( $\leq 115\text{g/l}$ ) were seen in 40% and 13-15%, respectively, of patients with normal values prior to treatment, following treatment with both drugs. It is unknown to what extent this decrease in haematological values was caused by the underlying prostate cancer and to what extent it was a consequence of androgen deprivation therapy. Markedly abnormal values of potassium ( $\geq 5.8\text{mmol/L}$ ), creatinine ( $\geq 177\mu\text{mol/L}$ ) and BUN ( $\geq 10.7\text{mmol/L}$ ) in patients with normal values prior to treatment, were seen in 6%, 2% and 15% of degarelix treated patients and 3%, 2% and 14% of leuprorelin treated patients, respectively.

Changes in ECG measurements seen during one year of treatment were in the same range for degarelix and the GnRH-agonist (leuprorelin) used as comparator. Three (<1%) out of 409 patients in the degarelix group and four (2%) out of 207 patients in the leuprorelin 7.5 mg group, had a QTcF  $\geq 500$  msec. From baseline to end of study the median change in QTcF for degarelix was 12.3 msec and for leuprorelin was 16.7 msec.

From the safety database all the adverse reactions reported in clinical trials <and post-marketing> have been included in the Summary of Product Characteristics

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

## **Risk-benefit assessment**

### Advanced Hormone-Dependent Prostate Cancer

Degarelix is a GnRH receptor blocker, intended initially for the treatment of patients with prostate cancer in whom androgen deprivation is warranted which includes patients with rising PSA after having undergone prostatectomy or radiotherapy.

Degarelix was shown to achieve and maintain a castrate level of testosterone  $\leq 0.5$  ng/ml throughout the 12-month treatment period without an initial surge in testosterone. Degarelix also demonstrated to be non-inferior to the active comparator, leuprorelin. Therefore, degarelix was considered to be an effective treatment, and could be approved for patients with advanced prostate cancer. The major clinical added value of this medicinal product was the avoidance of the testosterone flare seen with

GnRH agonists (in other words, no need for concomitant anti-androgen therapy), and degarelix is thus especially useful when a rapid reduction in the testosterone levels is of critical importance.

The product is now intended for treatment of patients with advanced hormone-dependent prostate cancer. This indication was restricted following the major objection raised by the CHMP. The first claimed indication for degarelix was not acceptable since the applicant did not document tumour reduction or improved overall survival for patients with localized prostate cancer. In addition, no new data beyond one year from the pivotal phase III study, CS21A, were provided by the applicant. Therefore the SPC was updated to clearly mention that clinical experience is limited to one year.

- User consultation

The Package Leaflet (PIL) for FIRMAGON has been tested in English in accordance with Articles 59(3) and 61(1) of Directive 2001/83/EC, as amended by Directive 2004/27/EC. The Patient Information Leaflet for FIRMAGON was found to contain all the necessary information in a way that is accessible and understandable to those who participated in this test.

It is considered that the tested PIL meets the requirements set for User Testing.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns and the following additional risk minimisation activities were required: see as detailed in section 2.5.

## **Recommendation**

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of FIRMAGON in the treatment of “FIRMAGON is a gonadotrophin releasing hormone (GnRH) antagonist indicated for treatment of adult male patients with advanced hormone-dependent prostate cancer” was favourable and therefore recommended the granting of the marketing authorisation.