

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

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22-201

MEDICAL REVIEW(S)

Clinical and Statistical Reviews

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Established Name	Degarelix
Proposed Trade Name	TRADENAME®
Therapeutic Class	Gonadotropin releasing hormone receptor inhibitors
Applicant	Ferring Pharmaceuticals

Priority Designation	Standard Review
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Formulation:	Powder _____ for injection
Dosing Regimen:	The depot _____ of degarelix is recommended to be administered subcutaneously with a starting dose of 240 mg, followed by a monthly maintenance dose of 80 mg.
Proposed Indication:	For treatment of patients with prostate cancer _____
Intended Population:	Adult patients with prostate cancer requiring androgen deprivation therapy

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Commonly Used Abbreviations in the Review

Abbreviation	Full Term
ADT	Androgen Deprivation Therapy
AR	Adverse Reaction
CRF	Case Report Form
DRAR	Drug-Related Adverse Reaction
EKG	Electrocardiogram
FSH	Follicle-Stimulating Hormone
GGT	Gamma-Glutamyltransferase
GnRH	Gonadotropin Releasing Hormone
LH	Luteinizing Hormone
PSA	Prostate Specific Antigen
PK	Pharmacokinetics
TEAE	Treatment-Emergent Adverse Events

1. Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

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This degarelix NDA 22-201, submitted by Ferring Pharmaceuticals, Inc. on February 29th, 2008, requested marketing approval of degarelix, a new gonadotropin releasing hormone (GnRH) receptor inhibitor, for the treatment of patients with prostate cancer

The application provided adequate evidence demonstrating that degarelix, administered at the dosing schedule proposed for marketing, is effective in attaining and maintaining biochemical castration levels of testosterone (≤ 0.5 ng/mL) in the studied patient population and has an acceptable safety profile. The reviewers concur with the submitted data and the sponsor's analyses of the data in support of the NDA.

Based on the key findings as discussed below and with the fact that efficacious biochemical castration suppression of testosterone has been recognized and accepted as an established surrogate endpoint for evaluating agents intended to treat prostate cancer through suppressing testosterone, the reviewers recommend regular approval of degarelix at the proposed dosing schedule for the treatment of patients with advance prostate cancer. This also includes patients with advanced symptomatic disease that may be exacerbated by a testosterone surge induced by a GnRH receptor agonist.

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1.2 Risk Benefit Analysis

The safety and efficacy of degarelix were assessed in an open-label, randomized, multi-center, parallel-group study in patients with prostate cancer. A total of 620 patients were randomized to receive one of the following three treatment regimens for 12 months.

- a) Degarelix 240/160 mg: administered subcutaneously at a starting dose of 240 mg, followed by monthly doses of 160 mg initiated after the first month;
- b) Degarelix 240/80 mg: administered subcutaneously at a starting dose of 240 mg, followed by monthly doses of 80 mg initiated after the first month;
- c) Leuprolide 7.5 mg: administered intramuscularly at a does of 7.5 mg monthly initiated at the first day.

Of the patients randomized, 20% had metastatic disease and 80% had non-metastatic disease, including locally advanced disease, localized disease, and PSA relapse only disease after primary definitive therapy. Approximately 81% of patients completed the 12-month treatments.

The primary endpoint was to evaluate the probability of testosterone ≤ 0.5 ng/mL from Day 28 to Day 364 in each of the three arms. The results demonstrated that the probabilities of medical castration were 98.3% (95% CI: 94.8% - 99.4%), 97.2% (93.5% - 98.8%) and 96.4% (92.5% - 98.2%) for the degarelix 240/160 mg, degarelix 240/80 mg and leuprolide 7.5 mg arms, respectively, indicating that degarelix is effective in achieving and maintaining efficacious biochemical castration during 12 months treatment.

The secondary endpoints included comparing changes in serum testosterone within the first month and evaluating proportions of patients achieving medical castration during the period, and assessing changes in other biomarkers including serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), and prostate specific antigen (PSA) during the 12 months. The results showed that no testosterone surges were observed in the degarelix arms and that approximately 96% of patients in the degarelix arms attained medical castration when monitored at 3 days after dosing, compared to none in the leuprolide arm. Nevertheless, almost all the patients in the three arms achieved medical castration by the end of the first month. The changes in LH and FSH were consistent with the mechanism of the study agents and the changes in PSA consistent with the hormone responsiveness of the diseases in the studied patients.

The safety analyses of the study showed that adverse reactions, regardless of causality, were generally comparable between the degarelix arms and leuprolide arm except for injection site reactions and hepatic laboratory abnormalities. The most commonly observed adverse reactions with a frequency of $\geq 10\%$ on any either degarelix arm were injection site reactions (e.g. pain, erythema, swelling or induration), hot flushes, weight increases, and increases in transaminases and gamma-glutamyltransferase (GGT).

Injection sites reactions occurred in approximately 40% of patients receiving degarelix compared to less than 1% of patients receiving leuprolide. Between the two degarelix arms, the 240/80 mg arm had 7% less occurrences of the reactions. Hepatic laboratory abnormalities occurred in 10% of patients in the degarelix arms compared to 5% in the leuprolide arm, but with no difference between the two degarelix arms. The abnormalities were generally reversible with the majority as Grade 1/2. Grade 3 hepatic laboratory abnormalities occurred in less than 1% of patients.

Overall, the safety profile appears well acceptable based on the current data. The high incidences of degarelix injection site reactions would not constitute a safety concern.

Relative to the leuprolide, degarelix was associated with 5% greater occurrences of the hepatic laboratory abnormalities. This may be related to degarelix metabolism. Given the majorities of the detected abnormalities were reversible and with the consideration of the known degarelix's pharmacokinetics in patients with hepatic impairment, the differences revealed in this study do not suggest the need of regular monitoring of hepatic function at the proposed degarelix dosing schedule or of a dose modification in patients with hepatic impairment. Other adverse reactions were basically related to the medical castration. Due to the short term of the study by design, the adverse reactions do not reflect long-term safety of medical castration or androgen deprivation.

The current safety and efficacy results are adequate to support regular clinical use of degarelix as an androgen deprivation approach for palliative treatment of advanced prostate cancer.

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One important feature revealed in the study along with other studies in the NDA is that, unlike a GnRH receptor agonist or activator, degarelix rapidly reduced serum testosterone to the castration levels in approximately 96% patients within a week and with no surges observed, representing an advantage of using a GnRH receptor inhibitor in achieving medical castration. This may be very important in treatment of symptomatic advanced diseases that require an effective urgent medical castration (e.g. newly diagnosed metastasis disease with neurological compromise or with urinary obstructions) in patients who refuse orchiectomy. Currently, there is not a GnRH receptor inhibitor in the market of the States. Clearly, there is a need for this small group of patients.

1.3 Recommendations for Risk Evaluation and Mitigation Strategies

Not indicated with the current analysis results based on the submitted data.

1.4 Recommendations on Post Marketing Requirements/Phase 4 Commitments

Complete and submit the final study report and datasets for the ongoing extension trial CS21A. The specified dates for the requirement are as follows.

Protocol Submission: 01/2007

Study Start Date: 03/2007

Final Report Submission: — /2012

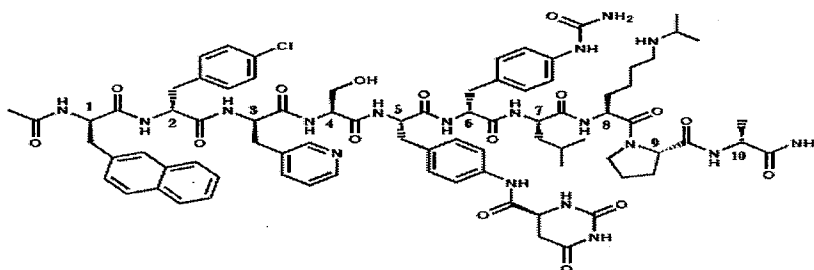
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This requirement is necessary since long-term safety of degarelix administered in the monthly dosing schedules has not been established. The applicant is currently conducting an extension trial of the key study (CS21) that supports this NDA, Study CS21A. Patients who completed the one-year study of CS21 were eligible to enroll into CS21A. Patients receiving degarelix in CS21 continued monthly maintenance degarelix at the doses (160 mg or 80 mg) as assigned at randomization, and patients from the leuprolide arm were randomized upon completion of the one-year CS21 study to receive degarelix at either 160 mg or 80 mg monthly. A total of 375 patients were enrolled, with approximately 180 patients in each of the degarelix doses. Of the 375 patients, approximately 65% were from the previous degarelix arms. The study was planned to continue until patient withdrawal, sponsor discontinuation of the development, or the time degarelix becomes commercially available. With the timelines reported about Study CS21, estimated times of exposure to monthly degarelix treatment for the patients who continued degarelix from CS21 to CS21A would be about 2-3 years. Therefore, the safety information from CS21A is important to help understand long-term safety profile of degarelix.

2 Introduction and Regulatory Background

2.1 Product Information

Degarelix is a synthetic linear decapeptide GnRH receptor inhibitor. It has seven unnatural amino acids, of which five are D-amino acids. The chemical name of degarelix is D-Alaninamide, N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-4-[[[(4S)-hexahydro-2, 6-dioxo-4-pyrimidinyl] carbonyl] amino]-L phenylalanyl-4-[(aminocarbonyl) amino]-D-phenylalanyl-L leucyl-N6-(1-methylethyl)-L-lysyl-L-prolyl. It has an empirical formula of C₈₂H₁₀₃N₁₈O₁₆Cl and a molecular weight of 1632.3 daltons (free base), with a structural formula as below:



For this NDA, degarelix will be administered subcutaneously. After administration, a local depot will be formed, from which degarelix will be released gradually into blood over a period of time. The proposed dose schedule in this application is degarelix of 240 mg administered as two subcutaneous injections of 120 mg (at the concentration of 40 mg/mL), followed by degarelix of 80 mg given one month after the initial dose and then monthly as one subcutaneous injection (at the concentration of 20 mg/mL).

2.2 Tables of Currently Available Treatments for Proposed Indications

Androgen deprivation or castration, either surgically or medically, has been used for palliative treatment of advanced prostate cancer since the 1940s. One effective, well accepted noninvasive approach toward achieving the deprivation is to use drugs manipulating GnRH receptor activity. The drugs approved for this purpose are summarized in Table 1. Although both a GnRH agonist and a GnRH antagonist can lead to medical castration, their mechanisms differ as implicated by their classification. In general, a GnRH agonist induces an initial surge in serum testosterone before attaining suppression; whereas a GnRH antagonist produces testosterone suppression without causing an early testosterone flare. It is necessary to point out here that clinical benefit associated with the lack of testosterone surge has not been demonstrated in the general population of patients with metastatic prostate cancer.

Table 1: FDA-Approved GnRH Based Androgen Deprivation Agents

Class	Product Name	Year of Initial Approval
GnRH Agonist*	Leuprolide**	1985
	Goserelin	1987
	Triptorelin	2001
	Histrelin	2004
GnRH Antagonist	Abarelix	2003
* Products may have different formulations or delivery system for longer drug action (up to 12 month with one administration) after their initial approval.		
** Other leuprolide products approved after Lupron include Viadur and Eligard.		

2.3 Availability of Proposed Active Ingredient in the United States

None

2.4 Important Safety Issues With Consideration to Related Drugs

GnRH-based androgen deprivation agents have been known for their adverse reactions secondary to their perturbing physiologic function of androgens' actions. Besides the commonly known reactions such as hot flushes, reductions in muscular mass but increases in weight, androgen deprivation can cause profound metabolic changes that may aggravate the pathological processes of other diseases frequently seen in patients with prostate cancer at their advanced age. Increased risks of the development of osteoporosis and related fragility fractures have become known for years.^[4] Recently, several retrospective studies, based on the patient populations in the US, suggest that continuous androgen deprivation therapy may also be associated with an increased risk of diabetes and cardiovascular diseases such as myocardial infarction.^[5-7] Most recently, another similar study using a linked administrative database, collected in Canada, found that androgen deprivation use for at 6 months is associated with an increased risk of diabetes and fragility fractures, but not acute myocardial infarction or hypercholesterolemia.^[8] Despite the differences, these studies underscore the importance of appropriate use of androgen deprivation therapy. Inappropriate use in early disease settings of prostate cancer, e.g. use as primary therapy for patients with localized prostate cancer with favorable prognostic factors or for patients with PSA only relapse disease (without evidence of metastasis) after initial definitive primary therapy, may not benefit patients, but conversely may increase risks of developing serious adverse reactions with long-term deprivation of androgens, since the natural history of prostate cancer progression takes many years to distant metastasis and death due to prostate cancer.^[9]

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The pre-submission regulatory activities with the FDA are summarized in Table 2.

Table 2: Regulatory Activities in Degarelix's Clinical Development

Milestone	Date	Comments related to clinical perspectives
Pre-IND meeting	03/12/2001	Sufficient nonclinical toxicology data were found to support a single dose from 40 mg to 240 mg in patients with prostate cancer and surrogate endpoints (testosterone, FSH, LH and PSA) were appropriate. Also, the sponsor was advised to observe patients at least one hour post-dosing for monitoring any hypersensitivity reaction.
Initial IND 51,222 Submission	07/09/2001	Recommended to restrict enrollment to men with Stage D ₀ or more severe prostate cancer disease.

End-of Phase 2 Meetings	03/14/2005	Recommended that the primary efficacy endpoint for all Phase 3 trials should be the proportion of patients with serum testosterone concentrations ≤ 0.5 ng/mL from Day28 until the end-of-treatment and that the proportion of patients attaining castration by Day 3 and the proportion who demonstrate a testosterone surge _____	b(4)
	09/30/2005	The proposed phase 3 study for the one-month dosing regimen (CS21) was evaluated. Use of leuprolide as a comparator was accepted for reference only, _____ The sponsor was reminded that the approved GnRH agonists are for palliative treatment of advanced prostate cancer.	b(4)
Special Protocol Assessment	01/19/2006	An agreement reached for the Phase 3 study (CS21) that, to establish efficacy, the lower bound of the 95% CI of degarelix's castration rate (Days 28-364) should be at least 90% or more.	
Pre-NDA Meeting	10/17/2007	Advice and agreements reached on the submission of the NDA supporting a one-month dosing regimen.	
NDA-submission	2/29/2008	Regular review designation	

2.6 Other Relevant Background Information

The first GnRH agonist leuprolide was approved in 1985.^[1] The approval was based on improvements in patient symptoms (e.g. pain) and tumor response as well as on biochemical evidence of leuprolide-induced medical castration in patients with symptomatic advanced prostate cancer. Since the improvements in symptoms and tumor responses were related to the achievement of biochemical castration, it was agreed and accepted later that effective demonstration of achieving and maintaining medical castration can serve as the primary endpoint for similar studies in the same patient population. Since then, other formulations of leuprolide and other GnRH agonists have been approved on the basis of efficacious testosterone suppression. For majority of these products, the rates of achieving and maintaining medical castration in their approvals were more than 90% in the patients studied. For the first GnRH antagonist, abarelix, it was noted the rates of maintaining medical castration declined with time. Nevertheless, effective sustained suppression of testosterone to well-defined medical castration levels has been recognized as an established surrogate for the evaluation of agents intended to treat prostate cancer through castration. This surrogate was agreed to

as the primary efficacy endpoint in the development of degarelix and will be evaluated for efficacy in the NDA review.

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3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The quality and integrity of the submitted data are found sufficient and acceptable. Although some problems were noticed, e.g, incomplete documentation of laboratory abnormalities in the adverse event dataset or a few discrepancies in tabulating the reasons for withdrawal, these problems would be unlikely to affect the overall analysis of the results of the application.

3.2 Compliance with Good Clinical Practices

Three study sites were selected for inspection by the Division of Scientific Investigation (DSI). One domestic site _____ had relatively high patient numbers and was considered essential for the approval of the application. Two foreign sites _____, both in Romania, had high numbers of patients enrolled _____ of patients receiving degarelix) and also were considered essential for the approval of the application. Importantly, the ratios of patients with documented medical castration (Day 28 – Day 364) to patients enrolled per center appear to be generally higher in Romania as compared in USA. This may be ascribed to socioeconomic differences; _____

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For the domestic site, the DSI audited the clinical records of 50% of the randomized patients for inclusion/exclusion criteria, adverse events, consistency between source data and case report forms, primary endpoint verification, informed consent, and drug accountability. The DSI verified that all protocol deviations were reported and concluded that the inspectional findings indicate adequate adherence to good clinical

practice regulations and the study protocol and that the data integrity from the site is acceptable.

For the two centers in Romania, the current inspection reports are based on communication with the field inspector. The preliminary review shows adequate adherence to good clinical practice and acceptable data integrity from the centers. Further review and evaluation of the findings will be made and an inspection summary addendum will be generated after the whole process of inspection is completed.

No FDA form 483 was issued to any of the three centers.

In addition, an inspection of the applicant was also conducted. The inspection was conducted as part of the routine pre-NDA clinical investigation data validation in support of this NDA. The inspectional findings indicate adequate adherence to good clinical practice regulations and the study protocol. There was no evidence of late reporting of adverse events. Although the overall drug accountability was found to be problematic, with lack of adequate records covering disposition of an investigational drug (Form FDA-483), this issue does not compromise data integrity or affect study conclusions based on the data.

3.3 Financial Disclosures

Disclosure of financial interests of the investigators who conducted the clinical studies supporting this NDA was submitted in the FDA form 3455. The disclosure was certified by Ronald T. Hargreaves, Ph.D, Vice President of Regulatory Affairs for the applicant. All of the investigators disclosed no financial conflict of interest, either a proprietary interest or a significant equity in the applicant.

The key study that supports the efficacy and safety labeling claims involved 80 study centers in 11 countries, with centralized laboratory analyses of serum testosterone and other surrogate markers important for understanding how degarelix works. This study design and conduct would minimize the effect of financial conflicts, if any, on the outcome of the study.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The CMC reviewers had the following concerns conveyed to the applicant to address.

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- Define the amount of overfill for each strength of the drug product. Include complete scientific justification for the proposed overfill and the differences in dilution and extraction volumes (amount withdrawn to provide desired dose) (4.2 mL and 4 mL, and 3 mL and 3 mL for the 80 mg and 120 mg, respectively) described in the directions for use. Based on the directions for use, it appears that the 80 mg vial containing _____ of degarelix is diluted to a concentration of _____ mg/mL not the 20 mg/mL as claimed in the labeling. Also it appears that the 120 mg vial containing _____ of degarelix is diluted to a concentration of _____ mg/mL not the 40 mg/mL as claimed in the labeling. The target reconstituted concentration for each strength must be the exact concentration as stated in the labeling (20 mg/mL and 40 mg/mL for the 80 mg and 120 mg vials, respectively)
 - Describe the quality control (QC) testing performed at Kiel Germany, providing method numbers and other details as pertinent.
 - _____ Provide a single acceptance criterion for degarelix content in the drug products that will be used for both release and stability testing.
 - Update your drug substance and drug product specifications to appropriately reflect the acceptance criteria as outlined in ICH Q3. Use following format when reporting values less than one: 0.5 should be 0.50.

The applicant provided detailed explanations to each of them and the CMC reviewers found those responses were adequate and acceptable for addressing the concerns on quality and production of degarelix. For details, please see the chemistry review.

In addition, with the CMC recommendations, the applicant also revised artwork for the cartons of degarelix, vial labels and "Instructions for Proper Use" and had submitted these changes as a formal amendment to the NDA.

4.2 Product Quality Microbiology

The microbiology reviewer requested the applicant to provide information about sterilization validation of the product. The specific questions conveyed are listed below:

- The test method used for demonstration of container closure integrity for the sterile powder.
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4.3 Preclinical Pharmacology/Toxicology

The toxicology reviewer was concerned about immediate increases in blood pressure and heart rate after dosing, since these changes were observed in a dog in the applicant's preclinical studies. The dog had a spike in blood pressure and a heart rate of 170 at 30 minutes post an intravenous dose of degarelix at 60 mg/m², followed by severe hypotension (~40/20) that slowly recovered back to mild hypertension. In addition, mild fluctuations in blood pressure were observed in dogs and monkeys with low subcutaneous doses of degarelix and a pattern of development of hypertension was suggested. Moreover, the reviewer noticed mild increases in creatinine, cholesterol, and glucose with long term dosing of degarelix. With these concerns, relevant safety parameters are examined in the safety section of the review.

4.4 Clinical Pharmacology

The clinical pharmacology reviewers considered the NDA submission acceptable from a clinical pharmacology perspective. However, the reviewers were concerned about clinical implications of the results of a small study (CS23, see Section 5.1), which was conducted in patients with mild and moderate hepatic impairment intended for evaluation of the effects of hepatic impairment on degarelix's pharmacokinetics. Although the results indicated that patients with hepatic impairment had exposures 16-30% lower than that seen in patients with normal hepatic function, the exposure difference was considered not significant enough to warrant a contraindication or dose modification. On the other hand, because of the lower exposure in patients with hepatic impairment, the reviewers recommended that testosterone should be monitored in these patients until medical castration is achieved. Moreover, the reviewers specified that patients with severe hepatic dysfunction have not been studied and caution is therefore warranted in this group. Furthermore, the pharmacometric review suggests no impact of age, body weight, race, or renal function on degarelix trough levels or testosterone concentrations.

The important clinical pharmacology information is summarized as follows.

4.4.1 Mechanism of Action

Degarelix is a competitive inhibitor of the GnRH receptor. It binds reversibly to the pituitary GnRH receptors, thereby reducing the release of gonadotrophins (LH and FSH), and consequently leading to testosterone suppression mainly through the lowered levels of LH.

4.4.2 Pharmacodynamics

A single subcutaneous dose of degarelix 240 mg causes a decrease in the plasma concentrations of LH and FSH, and subsequently testosterone. Clinical evidence indicates that degarelix is effective in achieving and maintaining testosterone suppression below the castration level of 0.5 ng/mL.

4.4.3 Pharmacokinetics

Absorption: Degarelix forms a depot upon subcutaneous administration, from which degarelix is released to the circulation. Following administration of degarelix 240 mg at a product concentration of 40 mg/mL, the mean C_{max} was 26.2 ng/mL (coefficient of variation, CV 83%) and the mean AUC was 1054 ng·day/mL (CV 35%). Typically C_{max} occurred within 2 days after subcutaneous administration. In patients with prostate cancer, the pharmacokinetics of degarelix were linear over a dose range of 120 to 240 mg at a product concentration of 40 mg/mL. The pharmacokinetic behavior of degarelix is strongly influenced by its concentration in the injection suspension.

Distribution

The distribution volume of degarelix after intravenous (> 1 L/kg) or subcutaneous administration (> 1000L) shows that degarelix is distributed throughout total body water. *In vitro* plasma protein binding of degarelix is estimated to be approximately 90%.

Metabolism

Degarelix is subject to peptidic degradation during the passage of the hepato-biliary system and is mainly excreted as peptide fragments in the feces. No quantitatively significant metabolites were detected in plasma samples after subcutaneous administration. *In vitro* studies have shown that degarelix is not a substrate, inducer or inhibitor of the CYP450 or p-glycoprotein transporter systems.

Excretion

Following subcutaneous administration of 240 mg degarelix at a concentration of 40 mg/mL to patients with prostate cancer, degarelix is eliminated in a biphasic fashion, with a median terminal half-life of approximately 53 days. The long half-life after subcutaneous administration is a consequence of a very slow release of degarelix from the degarelix depot formed at the injection site(s). Approximately 20-30% of a given dose of degarelix was excreted through the kidneys, suggesting that approximately 70-

80% is excreted via the hepato-biliary system in humans. Following subcutaneous administration of degarelix to patients with prostate cancer the clearance is approximately 9 L/hr.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

Table 3: Clinical Studies in Support of the Degarelix Application

Phase	Study ID (time)	Study Population	Key Objectives	Key Design Elements	Major Findings
Phase 1	CS01 (02/00-06/01)	Healthy male (N=80)	Dose finding; Safety and tolerability; PK/PD analyses.	Placebo-controlled, double blind; single sq dosing; dose-escalation in 10 cohorts (0.5-40 mg)	Tolerated and safe; dosing at 40 mg sq effective for achieving 1-2 month castration
	CS05 (12/01-03/02)	Healthy male (N=36)	Safety and tolerability; PK/PD	Comparison among three dosing routes: intravenous, intramuscular, or subcutaneous single dosing	Tolerated at the doses tested; a very long terminal half-life (3-4 weeks) associated with sq or im dosing.
	CS08 (10/02-03/03)	Healthy elderly male (N=48)	Relationship between drug plasma concentration and response in suppression of testosterone	Randomized, placebo-controlled, open-labeled; 48 hour-constant iv infusion as a single dose	A rapid and pronounced fall in testosterone in all subjects treated, and a clear concentration-response relationship was observed.
	CS11 (10/04-06/06)	Patients with prostate cancer (N=18)	Safety and tolerability; PK/PD	Open-labeled; Single sq dosing; dose-escalation of three doses (160, 200, and 240 mg)	Tolerated; Doses at 200 mg and 240 mg led to castration within 7 days and at Day 28; candidate doses for initial dosing
	CS23 (11/06-05/07)	Healthy male and patients with mild or moderate hepatic impairment (N=18)	Differences in PK among the three groups; Safety and tolerability	Open-label, parallel group; single iv dosing	Hepatic impairment had no major effects on degarelix metabolism
Phase 2	CS02 (03/01-05/02)	Patients with prostate cancer (N=129)	Selection of dosing regimens based on	Randomized (1:1:1), open-label; Three dosing	The 80/80/40 regimen was the most effective;

			suppression of testosterone	regimens: 80 (day 0)/80 (day 3)/40 (monthly for 6 months); 40/40/40; and 80/-/40.	however, the monthly maintenance dose of 40 mg was not sufficient. None of the three was regarded as a optimal regimen
	CS06 (05/02-01/04)	Patients with prostate cancer (N=82)	Suppression of testosterone of escalating single doses	Open-label, single sq dosing at four dose levels (40, 80, 120, and 160 mg). continued follow-up till recovery of testosterone	None of the tested doses considered as an efficacious induction dose. Well-tolerated.
	CS07 (11/02-10/04)	Patients with prostate cancer (N=172)	Pharmacological effects of ascending single doses	Open-label, single sq dosing at 8 dose/concentration levels. Three concentrations used: 20, 40, and 60 mg/mL; and 5 doses tested: 120, 160, 200, 240, and 320 mg.	The dose/concentration levels 200 mg (40 mg/mL) and 240 mg (40 mg/mL) reached 95% of patients castrated on day 28.
	CS12 (02/04-06/05)	Patients with prostate cancer (N=187)	Dosing finding through comparing differences in the efficacy with different one-month dosing combinations during a period of 196 days	Randomized, Open-label, parallel comparison; loading dose 200 or 240 mg (40 mg/mL) sq; followed by a monthly maintenance dose 80, 120, or 160 mg (40 mg/mL).	240 mg (40 mg/mL) resulted in a castration rate of 95%, suitable as an initial dose; the loading dose of 200 mg related to a rate of 88%. The monthly maintenance doses resulted in a castration rate of 96% 100%, and 100% to day 196 in the 80, 120, and 160 mg dosing, respectively.
	CS14 (02/04-08/05)	Patients with prostate cancer (N=127)	Differences in the efficacy of two dosing regimens during a period of one-year	Randomized, Open-label, parallel comparison; loading dose 200 mg (40 mg/mL) sq; followed by a monthly maintenance dose either 60 or 80 mg (20 mg/mL).	The loading dose 200 mg did not meet the goal for being used as an efficient initial dose for Phase 3 trials, but the efficacy of the monthly maintenance doses appeared acceptable for long-term testosterone suppressions.
Phase 3	CS21 (02/06-10/07)	Patients with prostate cancer	Probability of patients with	Randomized (1:1:1), open-label,	The probabilities of testosterone ≤ 0.5

		(N=610)	castration levels of testosterone suppression (Day 28-364); Evaluation of responses in PSA, LH, FSH; Safety profile.	parallel control; Three dosing arms: degarelix 240/loading/160 mg (monthly) or 240/80; leuprolide 7.5 mg (loading and monthly)	ng/mL during Day 28-364 were 98.3%, 97.2%, and 96.4% for the degarelix 240/160 mg, degarelix 240/80 mg, and leuprolide 7.5 mg arms, respectively. The lower bounds of 95% CI were >90% for all the arms.
Phase 2/3	CS15* (01/05-11/06)	Patients with prostate cancer (N=447)	Proportion of patients with castration levels at least 80% during a 12- or 13 month period.	Randomized (1:1:1), open-label; dose finding for three-month dosing regimens: loading 240 mg (40 mg/mL) followed by maintenance 240 mg (40 mg/mL) or 240 mg (60 mg/mL) at 1 month, and after 3, 6, and 9 months or after 4, 7, and 10 months.	

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5.2 Review Strategy

The reviewers examined the data across different relevant datasets, investigated information listed in datasets against information contained in case report forms, conducted independent analyses on efficacy and safety, and compared the results to the applicant's analyses in the study report, with special attention paid to differences in certain safety parameters relevant to its pharmacokinetics (PK) and pharmacodynamics, particularly to the important known adverse reactions secondary to androgen deprivation. The reviewers also evaluated consistency in the main findings and conclusions of the clinical studies.

5.3 Discussion of Individual Studies

All the studies submitted to the application and their key features and findings are evaluated and summarized in Section 5.1. Among them, the key study that supports the efficacy and safety claims of degarelix is Study CS21, which is reviewed and discussed in details in Sections 6 and 7.

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The 5 Phase 1 studies, CS01, CS05, CS08, CS11 and CS23, provided the general tolerability, pharmacokinetic and pharmacodynamic information of degarelix at the early stage of the development, and helped establish the initiation doses for achieving effective medical castration in patients with prostate cancer. All the study subjects in Studies CS01, CS05 and CS08 were healthy male volunteers and they received one time dosing of degarelix administered through different routes, intravenously, intramuscularly, or subcutaneously. The results showed that degarelix was tolerated with a few acceptable adverse reactions and that degarelix induced a rapid decline in serum testosterone levels, consistent with its mechanism of action. Study CS11 extended the observations to patients with prostate cancer and found that degarelix administered at doses 200 mg or 240 mg subcutaneously led to castrations within 7 days, which was sustained to Day 28. These two doses were considered for initial effective dosing. Study CS23 was designed and conducted for assessing effects of hepatic impairment on the pharmacokinetics and safety of degarelix. There were no major differences detected between the healthy men and the men with mild-moderate hepatic impairment. However, the conclusions on PK and tolerability for men with hepatic impairment may not be generalized in that the study had only 16 individuals with hepatic impairment. Caution should be exercised in monitoring on both safety and efficacy for patients with hepatic impairment.

The 4 Phase 2 studies, CS02, CS06, CS07 and CS 14, were intended to explore the efficacy of degarelix administered subcutaneously at different doses and concentrations for initiation and monthly maintenance treatment in patients with prostate cancer. The first two studies CS02 and CS06 revealed that an initiation dose up to 160 mg and a monthly maintenance dose at 40 mg were not sufficient for achieving efficacious suppressions of testosterone. Study CS07 investigated the effectiveness of higher doses with the three different concentrations of preparation of degarelix and found that the dosing at 200 mg or 240 mg with the 40 mg/mL preparation induced a medical castration in >95% of patients studied. These doses were considered candidates for initial castration induction to provide one month testosterone suppression in that the percentages of patients who remained castrated at 3 months after the dosing decreased to approximately 80%. The results of CS07 also demonstrated a clear dose and concentration effect such that higher doses of degarelix provided a longer duration of testosterone suppression whereas higher degarelix concentrations in the injection suspension tended to provide a shorter duration of testosterone suppression. The candidacy of the initial doses at 240 mg or 200 mg were further examined in Studies CS12 and CS14 along with testing different monthly maintenance doses at 60 mg, 80 mg, 120 mg, or 160 mg for 6 months in CS12 or 12 months in CS14. The results showed that the initial dose of 240 mg was suitable as a loading dose, but not the loading dose of 200 mg as the 200 mg dose did not induce a sufficiently high castration rate (<90%) at the end of one month in both studies. Therefore, the 240 mg dose was recommended for effective initiation of testosterone suppression in phase 3 studies. On the other hand, all the three maintenance doses of 80, 120, or 160 mg in CS12 and the two maintenance doses 60 mg or 80 mg in CS14 yielded adequate 6 month or 12-month testosterone suppression in > 93% of patients at the end

of the studies. As such, the Phase 3 study CS21 used an initial dose of 240 mg (at the concentration of 40 mg/mL) with two different monthly maintenance doses 80 mg (at 20 mg/mL) or 160 mg (at 40 mg/mL).

The early phase studies also suggested that degarelix was generally well tolerated. A pooled safety analysis is presented in Section 7 for exploring the general tolerability and safety profile of degarelix.

6 Review of Efficacy

6.1 Indication

Based on the product label in the NDA submission, the proposed indication for degarelix is for treatment of patients with prostate cancer _____

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6.1.1 Methods

Since the clinical efficacy and safety claims of degarelix basically rely on Study CS21, a randomized, active-controlled, Phase 3 trial, the reviewers evaluated its original protocol and follow-up amendments in relation to the FDA recommendations associated with the study. With the study design, efficacy endpoints were evaluated through analyzing laboratory values. Factors that may affect the laboratory values and/or efficacy analyses were assessed based on the protocol and amendments. Analysis results were verified and compared to the applicant's analyses. Sensitivity analyses were conducted when indicated for assessing reliability of the results and conclusions. Importance and implications of the results are also addressed accordingly.

Protocol Review for Study CS21

Study Design

Study CS21 was an open-label, randomized, active-controlled, three-arm, international, phase 3 trial of monthly degarelix vs leuprolide (Lupron Depot) in patients with prostate cancer in whom androgen deprivation therapy was warranted. Eligible patients were randomized 1:1:1 to one of the following three treatment arms as shown in Table 4. Patients assigned to the two degarelix arms received the same starting dose 240 mg at a concentration of 40 mg/ml subcutaneously, followed by monthly maintenance doses of either 160 mg at a concentration of 40 mg/ml or 80 mg at a concentration of 20 mg/ml starting 28 days after the initiation dosing. Patients assigned to the leuprolide arm received the same doses of 7.5 mg intramuscularly for both treatment initiation and monthly maintenance. Treatment for the three arms continued for a total of 12 months. Patients were monitored monthly with clinical visits up to a year. Efficacy of

degarelix was evaluated as the proportion of patients with testosterone suppression ≤ 0.5 ng/mL during 12 months treatment.

Table 4: Three Treatment Arms in Study CS21

Treatment Group	Starting Dose	Maintenance Doses
Degarelix 240/160 mg	240@40 (as 2 doses on Day 0)	160@40 (as 12 single doses, one every 28 days)
Degarelix 240/80 mg	240@40 (as 2 doses on Day 0)	80@20 (as 12 single doses, one every 28 days)
Leuprolide 7.5 mg	7.5 mg administered at Day 0 and every 28 days via single intramuscular injection. Bicalutamide was given at the Investigator's discretion.	

Protocol Amendments

The original protocol was developed in December, 2005. Since then, there were a total of 5 protocol amendments. Major modifications and other significant protocol events are summarized in Table 5. Among these amendments, the modification of primary endpoint analysis plans, from proportion of patients with testosterone levels ≤ 0.5 ng/mL Day 28 through 364 to probability of testosterone ≤ 0.5 ng/mL Day 28 through Day 364, should be noted.

Table 5: Protocol Milestones of Study CS21

Milestone	Date	Comments or Major Changes
Original Protocol	12/01/2005	
Initiation of Protocol	2/7/2006	First patient, First visit.
Amendment 1	2/14/2006	<ul style="list-style-type: none"> Modifications of the primary endpoint analysis plans based on the FDA and EMEA recommendations, with the introduction of separated analyses of castration efficacy of dagarelix vs leuprolide, which increased the number of randomized patients required for completion from 540 to 600. Use of NCI CTCAE guidelines to grade adverse reactions
Amendment 2	2/14/2006	<ul style="list-style-type: none"> A subgroup of patients selected for performing MRI studies of tumor lesions in order to assess tumor response to the treatment. This was planned to be conducted in approximately 45 patients from 7 study sites.
Amendment 3	4/10/2006	<ul style="list-style-type: none"> An update on the product half-life from

		18 to 24 months when stored below 25°C
Amendment 4	09/25/2006	<ul style="list-style-type: none"> An update of the list of drugs suspected for QT prolongation, which were prohibited in the study.
Completion of Study	10/08/2007	<ul style="list-style-type: none"> Last patient, last visit.
Database Lock	10/18/2007	<ul style="list-style-type: none"> Adjusted on 10/26/07 for a patient who was assigned to the leuprolide arm, but was treated with dagarelix during the study.
Statistical Method Amendment	10/2007	<ul style="list-style-type: none"> Proposed to change the statistical analysis method for the primary endpoint from life-table estimation to Kaplan-Meier estimation of cumulative probability of castration levels of testosterone suppression.
NDA-submission	2/29/2008	<ul style="list-style-type: none"> Regular Review

Objectives

Primary:

- To determine the probability of testosterone ≤ 0.5 ng/mL from Day 28 through Day 364.

Secondary:

- To compare serum levels of testosterone and PSA using a degarelix dosing regimen versus monthly Lupron depot at 7.5 mg during the first 28 days of treatment
- To compare the safety and tolerability using a degarelix dosing regimen versus monthly Lupron depot at 7.5 mg
- To compare testosterone, LH, FSH, and PSA response using a degarelix dosing regimen versus monthly Lupron depot at 7.5 mg during the entire treatment period

-
- To evaluate the pharmacokinetics using a degarelix dosing regimen

Inclusion criteria

- Patients with a histologically confirmed adenocarcinoma of the prostate (any stage), in whom androgen ablation treatment, except for neoadjuvant hormonal

therapy, was warranted. Patients with rising PSA after having undergone prostatectomy or radiotherapy with curative intention were also included per the protocol

- Serum testosterone at screening > 1.5 ng/mL
- Serum PSA value at screening ≥ 2 ng/mL
- Performance score of ≤ 2 , assessed by the Eastern Cooperative Oncology Group (ECOG) criteria
- Age 18 years or older, with a life expectancy of at least 12 months
- Had offered written informed consent prior to receiving treatment

Exclusion criteria

- Had had previous or were receiving hormonal management of prostate cancer, including surgical castration or other hormonal manipulation with GnRH agonists or antagonists, anti-androgens, or estrogens. Patients who had received neoadjuvant or adjuvant hormonal therapy for a maximum duration of 6 months were allowed for screening only if the hormonal treatment was terminated at least 6 months prior to the screening visit.
- Considered to be candidate for curative therapy, either radical prostatectomy or radiotherapy
- Receiving any 5- α -reductase inhibitors
- Had a baseline prolongation of QT/QTc interval (e.g., repeated demonstration of a QTc interval >450 ms) or took medications that prolong the QT/QTc interval
- A history of severe untreated asthma, anaphylactic reactions or severe urticaria and/or angioedema
- A history of cancer within the last five years except prostate cancer and surgically removed basal or squamous cell carcinoma of the skin
- Known hypersensitivity to any component of the investigational products
- Previous participation in any study of degarelix
- Received an investigational drug within the last 28 days preceding a screening visit or longer if considered to possibly influence the outcome of the current study
- With elevated serum ALT level more than the upper limit of normal or serum total bilirubin level above the upper level of normal range as measured by the laboratory at a screening visit and confirmed with a second measurement within 21 days.
- Had a clinically significant disorder (other than prostate cancer) or any other condition including clinically significant laboratory abnormalities which in the judgment of the investigator would interfere with the patient's participation in this study or evaluation of study results

***Reviewer's Comments:** The eligibility criteria appear acceptable in general. However, the intention to recruit patients with rising PSA after having undergone primary therapy (either prostatectomy or radiotherapy) and patients with localized disease not considered for either of the primary therapies may not be appropriate. This was most likely related to the lack of standards for management of these disease settings. So far, ADT has not been shown to have clinical benefit in these settings; in contrast, it may increase risks of metabolic dysfunction and cardiac morbidity and mortality.*

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Study Center and Conduct

Approximately 140 centers from Europe and the Americas were planned to be invited to participate in the study.

Eligible patients were randomized 1:1:1 by the sponsor through a centralized computer system into the three treatment arms. The stratification information included geographic region and weight. Randomization had to be performed before or on Day 0. However, the treatment arm information was designed to be blinded to the laboratory personnel for performing laboratory analyses.

Treatment Plan

Randomized patients received one of the three following treatments depending on their assignment arm.

Patients assigned to the 240/160 degarelix arm received a starting dose 240 mg of degarelix at a concentration of 40 mg/ml subcutaneously on day 0 as two 120 mg subcutaneous injections, followed by a maintenance dose of 160 mg every 28 days as a single subcutaneous injection.

Patients assigned to the 240/80 degarelix arm received the same starting dose 240 mg of degarelix at a concentration of 40 mg/ml subcutaneously on day 0 as two 120 mg subcutaneous injections; however, they received a maintenance dose of 80 mg of degarelix at a concentration of 20 mg/mL every 28 days as a single subcutaneous injection.

Patients assigned to the leuprolide arm received 7.5 mg of the agent as an intramuscular injection on day 0 and then once every 28 days for a total of 13 injections. The leuprolide used in the study was manufactured by the TAP Pharmaceutical Inc. and was obtained commercially. To prevent clinical flare associated with the GnRH agonist, bicalutamide was allowed at the discretion of the investigator.

Concomitant Therapy: Other hormonal and disease managements including surgical castration, treatment with GnRH receptor agonists or antagonists, or prostatectomy were not allowed during the study. However, additional therapy could be added to treat the prostate cancer if a patient developed signs of disease progression (e.g. increased clinical signs and symptoms, or rising PSA).

Investigational drugs besides the study agent were not allowed.

Reviewer's Comments: The specified non-permitted hormonal therapy may affect assessments of the primary endpoint. Protocol violations involving use of non-

permitted therapies were examined and analyzed in the review of efficacy. Additional therapies were not specified in the protocol. Since additional non-hormonal therapy can mainly affect PSA, efficacy claims by PSA, if any, will also be examined against protocol violations.

Efficacy Assessments

Primary Endpoint

The primary objective of this study was to demonstrate the effectiveness of degarelix in achieving and maintaining testosterone suppression to castrate levels, evaluated as the probability of testosterone ≤ 0.5 ng/mL from Day 28 through Day 364.

Blood samples for testosterone were collected at all visits, basically at screening, on days 0, 1, 3, 7, 14, and 28 in the first month, and then monthly until the end of the study. Collection was recommended to be within the same time period of the day at each visit to mitigate the diurnal variation in testosterone. Blood concentration of testosterone was assayed in triplicates using a Liquid Chromatography-Mass Spectrometry/Mass Spectrometry (LC-MS/MS) method in a central laboratory certified according to College of American Pathologists. The median value of the triplicates was reported to the sponsor.

Secondary Endpoints

Key secondary efficacy endpoints included assessing testosterone surge during the first 2 weeks, changes in PSA, LH and FSH during the study, and differences in

Blood samples for PSA, LH and FSH were collected along with collections for testosterone at all visits. Measurement of PSA, LH and FSH were undertaken in a central laboratory by using appropriate validated methods.

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Statistical Methods

The primary efficacy endpoint was planned to be analyzed using the Kaplan-Meier method. For each of the three treatment arms, the probabilities of testosterone ≤ 0.5 ng/mL from Day 28 through Day 364 with 95% confidence interval (CI) were calculated by log-log transformation of survivor function. Differences between the degarelix treatment arms and the leuprolide 7.5 mg arm were assessed using a 97.5% CI calculated by normal approximation using pooled standard error.

Analyses of the primary endpoint were intended in both the Intention-to-Treat (ITT) and the Per Protocol (PP) analysis sets, with the ITT analysis set considered primary. The ITT population consisted of randomized patients who received at least one dose of study agent. The PP analysis set consisted of all ITT patients who had not had any major protocol deviations.

For the secondary endpoints, actual values of serum levels of testosterone, PSA, LH, and FSH over time and their percentage changes from baseline were to be summarized and tabulated by treatment regimen. Proportions of patients with testosterone level ≤ 0.5 ng/mL at different time points within the first 28 days were also planned to be analyzed by treatment arm.

Statistical Reviewer's comments:

1. In October 2007, the sponsor submitted a statistical analysis amendment to change the statistical analysis method for the primary endpoint. The original method was life-table estimation. The proposed method is Kaplan-Meier method. The Agency accepted the change.
2. There were two different criteria to assess the efficacy of degarelix. The FDA criterion was to determine whether the lower bound of the 95% confidence interval (CI) for the cumulative probability of testosterone ≤ 0.5 ng/mL from Day 28 to Day 364 was no lower than 90%. The EMEA criterion was to determine whether degarelix was non-inferior to leuprolide 7.5 mg with respect to the cumulative probability of testosterone ≤ 0.5 ng/mL from Day 28 to Day 364. The noninferiority limit for the difference between treatments (degarelix versus leuprolide 7.5 mg) was - 10 percentage points. In October 2007, the following comments were sent to the sponsor:

Please note the non-inferiority analyses will be considered as exploratory. The study has to demonstrate a response rate with the lower bound of the 95% CI no lower than 90% in the degarelix arm.

3. Statistical analysis plan stated the following:

No formal adjustment for multiplicity will be performed where a formal statistical analysis is used. Results of the secondary analyses, both where a test is applied and where results 'only' are displayed descriptively, should be interpreted cautiously and the robustness of the results will be discussed.

Therefore, without any type I error adjustments for the multiple comparisons, the p-values from secondary analyses are not interpretable.

6.1.2 Demographics

A total of 620 patients were randomized to the three treatment arms in Study CS21. They were distributed in 80 study centers from 11 countries, as shown in Table 6.

Table 6: Geographic Distribution of the Patients in Study CS21

Region	Country	Number of Centers	Number of Patients per Country	Total Patient Number per Region
North Americas	USA	20	133	265
	Canada	13	75	
	Mexico	10	57	
Western Europe	Netherlands	3	5	14
	United Kingdoms	2	5	
	Germany	2	4	
Eastern and Central Europe	Romania	7	128	341
	Russia	6	103	
	Czech Republic	6	43	
	Ukraine	4	36	
	Hungary	7	31	

The distribution of patients assigned to each of the three arms is summarized in Table 7. A few patients did not receive study treatment after randomization for different reasons. Therefore, these patients are not included in the ITT populations for planned efficacy analyses. One patient (ID 40085494) who was randomized to the leuprolide arm but received treatment with degarelix 240/160 in Romania is counted in the ITT population of the degarelix 240/160 treatment arm instead of in the leuprolide arm.

Table 7: Assignment of Patients to the three Treatment Arms in CS21

	Degarelix (240/160 mg)	Degarelix (240/80 mg)	Leuprolide (7.5 mg)	Total (%)
Randomized	206	210	204	620 (100%)
Not Treated	4	3	3	10 (1.6%)
ITT Set	202	207	201	610 (98.4%)

Demographic and baseline disease characteristics of the ITT population are examined and the results are shown by treatment arm in Tables 8 and 9.

Table 8: Basic Demographics of the Patients in CS21

	Degarelix (240/160 mg) N=202	Degarelix (240/80 mg) N=207	Leuprolide (7.5 mg) N=201	Total N=610
Age				
Median (Range)	72 (50-88)	72 (51-89)	74 (52-98)	73 (50-98)
Race (%)				
White	168 (84%)	171 (83%)	172 (86%)	511 (84%)
Black	11 (5%)	17 (8%)	10 (5%)	38 (6%)
Others*	23 (11%)	19 (9%)	19 (9%)	51 (8%)
BMI (kg/m²) (Range)	26.4 (16.1-38.9)	25.8 (17.3-42.2)	26.4 (19.3-43.7)	26.3 (16.1-43.7)
* including American Indians and Asian				

Table 9: Disease Characteristics of the Patients in CS21

	Degarelix (240/160 mg) N=202	Degarelix (240/80 mg) N=207	Leuprolide (7.5 mg) N=201	Total N=610
Disease Stage (%)				
Metastatic	41 (20%)	37 (18%)	47 (23%)	125 (20%)
Locally advanced ^a	62 (31%)	64 (31%)	52 (26%)	178 (29%)
Localized ^b	59 (29%)	69 (33%)	63 (31%)	191 (31%)
Others ^c	40 (20%)	37 (18%)	39 (19%)	116 (19%)
Gleason Score (%)				
≤ 6	87 (43%)	88 (43%)	87 (43%)	262 (43%)
≥ 7	112 (56%)	119 (57%)	113 (56%)	344 (56%)
Unclassified	2 (1%)	0	1 (1%)	3 (1%)
Prior Treatment (%)*				
Watchful waiting	175 (87%)	177 (86%)	171 (85%)	523 (86%)
Prostatectomy	10 (5%)	15 (7%)	12 (6%)	37 (6%)
Radiotherapy	19 (9%)	22 (11%)	17 (8%)	58 (10%)
Neoadjuvant/Adjuvant	12 (6%)	12 (6%)	9 (4%)	33 (5%)
Others**	3 (2%)	2 (1%)	6 (3%)	11 (2%)
PSA (ng/mL)				
Median	19.9	19.8	17.4	19.0

Testosterone (ng/mL)	3.78	4.11	3.84	3.93
Median (Range)	(0.065-10.6)	(0.73-10.6)	(0.37-12.5)	(0.065-12.5)
TNM stages at enrollment a: T3/T4 Nx M0 or N1 M0 b: T1 or T2 N0 M0 c: not classifiable, including patients whose disease metastatic status could not be determined definitively, e.g. patients with PSA relapse only disease after primary curative therapy. * Patients could have more than one prior treatment(s). ** including brachytherapy, cryosurgery, cryotherapy, or non-hormonal study agents.				

Reviewer Comments:

All the listed characteristics appear balanced among the three treatment arms. Since the key purpose of the study was to examine and compare the effectiveness of the study agents on suppressing testosterone in male patients, the disease characteristics, except testosterone levels, have less significant effects on laboratory based measurement of testosterone. The baseline levels of testosterone were generally balanced. Few patients were enrolled with ineligible levels of testosterone. They will be excluded in a sensitivity analysis to assess the reliability of the study results. It is necessary to point out that many patients enrolled in the study might not need ADT, e.g, patients with localized disease or PSA relapse only disease.

6.1.3 Patient Disposition

Overall patient disposition in the ITT population is examined and summarized in Table 10.

Table 10: Patients Disposition in CS21

	Degarelix (240/160 mg) N=202	Degarelix (240/80 mg) N=207	Leuprolide (7.5 mg) N=201	Total N=610
Completed (%)	163 (79%)	169 (80%)	172 (84%)	504 (81%)
Withdrawn (%)				
AR/AE*	15 (7%)	10 (5%)	3 (2%)	28 (4%)
Voluntary**	11 (5%)	11 (5%)	10 (5%)	32 (5%)
Others***	9 (4%)	12 (6%)	7 (4%)	28 (5%)
Death (%)	5 (2%)	5 (2%)	9 (5%)	19 (3%)
Disease	1	0	1	
Others	4	5	8	
*adverse reaction or event ** including withdrawal of consent and lost to follow-up *** including disease progression, other therapies for prostate cancer, relocation, etc.				

Major protocol violations and/or deviations that may have an important impact on the assessment of the primary endpoint are scrutinized and summarized in Table 11. Unlike

the sponsor's inclusions of major violations for defining the per protocol set, patients with the violations that would not affect primary endpoint assessment are not listed in the table, which include patients with ineligible levels of baseline PSA, patients who missed a visit after the first month, and patients who violated an exclusion requirement of hormonal therapy but had normal baseline testosterone.

Table 11: Major Protocol Violations/Deviations that Most Likely Impact on Assessment of the Primary Endpoint

	Degarelix (240/160 mg) N=202	Degarelix (240/80 mg) N=207	Leuprolide (7.5 mg) N=201
Testosterone \leq 1.5 ng/mL at Enrollment (%)	10 (5%)	4 (2%)	4 (2%)
Lost to Follow-up within 28 days after the First Dose (%)	5 (3%)	1 (<1%)	3 (2%)
Use of Prohibited Hormonal Therapy* (%)	0	1 (1%)	0
Dosing Error (%)	1 (<1%)	2 (1%)	1 (<1%)
Total** (%)	13 (6%)	8 (4%)	7 (3%)
<p>* Two patients (ID 01271044, 01282014) in the degarelix 240/80 mg arm did not meet exclusion criteria 1, but with baseline testosterone >1.5 ng/mL.</p> <p>** The sum may not be equal to the number shown as few patients had more than one violation(s)/deviation(s).</p>			

6.1.4 Analysis of Primary Endpoint(s)

Analysis of Primary Endpoints

The primary endpoint was the probability of testosterone levels \leq 0.5 from Day 28 to Day 364. For each treatment arm, the cumulative probability of testosterone \leq 0.5 ng/mL was estimated by the Kaplan-Meier method.

In the ITT population, Kaplan-Meier estimates of the cumulative probabilities of testosterone \leq 0.5 ng/mL from Day 28 to Day 364 were 98.3% (95% CI: 94.8% -

99.4%), 97.2% (93.5% - 98.8%) and 96.4% (92.5% - 98.2%) for the degarelix 240/160 mg, degarelix 240/80 mg and leuprolide 7.5 mg groups, respectively (Table 12).

In the PP population that excludes all sponsor's identified protocol violations, Kaplan-Meier estimates of the cumulative probabilities of testosterone ≤ 0.5 ng/mL from Day 28 to Day 364 were 99.4% (95% CI: 95.6% - 99.9%), 97.2% (95% CI: 93.3% - 98.8%) and 96.3% (92.4% - 98.2%) for the degarelix 240/160 mg, degarelix 240/80 mg and leuprolide 7.5 mg groups, respectively (Table 13).

In the ITT population, the differences between the two degarelix treatment arms and the leuprolide 7.5 mg comparator arm with respect to the cumulative probability of testosterone ≤ 0.5 ng/mL from Day 28 to Day 364 were 1.9% (97.5% CI: -1.8; 5.7) and 0.9% (97.5% CI: -3.2; 5.0) for the degarelix 240/160 mg and degarelix 240/80 mg treatment groups, respectively (Table 14). These comparisons between the degarelix treatment arms and the leuprolide arm are considered as exploratory.

Table 12: Cumulative Probability of Testosterone ≤ 0.5 ng/mL from Day 28 to Day 364 –Kaplan-Meier Estimates of Individual Response Rates – ITT Analysis set

	Degarelix 240/160 mg			Treatment Group Degarelix 240/80 mg			Leuprolide 7.5 mg		
	T>0.5 ng/mL	Cens	(%)	T>0.5 ng/mL	Cens	(%)	T>0.5 ng/mL	Cens	(%)
ITT analysis set	202			207			201		
Day 28 -> 364	3	199	(98.3%)	5	202	(97.2%)	7	194	(96.4%)
95% CI			[94.6;99.4%]			[93.5;98.8%]			[92.5;98.2%]
T>0.5 ng/mL = Cumulative number of patients with testosterone > 0.5 ng/mL									
Cens = Number of censored observations before or at Day 364									
(*) = Estimated probability of all testosterone values ≤ 0.5 ng/mL									
Within-treatment group 95% CI calculated by log-log transformation of survivor function									
Data source: FE200486/PROSTATE/CS21/06DEC2007 /EFF_LI_ITT.SAS (Table 30)									

Source: Table 9-1 in the sponsor's report

Table 13: Cumulative Probability of Testosterone ≤ 0.5 ng/mL from Day 28 to Day 364: Kaplan-Meier Estimates of Individual Response Rates – PP Analysis set

	Degarelix 240/160 mg			Treatment Group Degarelix 240/80 mg			Leuprolide 7.5 mg		
	T>0.5 ng/mL	Cens	(%)	T>0.5 ng/mL	Cens	(%)	T>0.5 ng/mL	Cens	(%)
PP analysis set	189			200			195		
Day 28 -> 364	1	188	(99.4%)	5	195	(97.2%)	7	188	(96.3%)
95% CI			[95.6;99.9%]			[93.3;98.8%]			[92.4;98.2%]
T>0.5 ng/mL = Cumulative number of patients with testosterone > 0.5 ng/mL									
Cens = Number of censored observations before or at Day 364									
(*) = Estimated probability of all testosterone values ≤ 0.5 ng/mL									
Within-treatment group 95% CI calculated by log-log transformation of survivor function									
Data source: FE200486/PROSTATE/CS21/06DEC2007 /EFF_LI_PP.SAS (Table 31)									

Table 14: Kaplan-Meier Analysis from Day 28 to Day 364 for Probability of Testosterone ≤0.5 ng/mL from Day 28 to Day 364 – ITT Analysis set

	Degarelix 240/160 mg				Treatment Group Degarelix 240/80 mg				Leuprolide 7.5 mg			
	No. at risk	T> 0.5 ng/ mL	Cens	(%)	No. at risk	T> 0.5 ng/ mL	Cens	(%)	No. at risk	T> 0.5 ng/ mL	Cens	(%)
ITT analysis set	202				207				201			
Day 28	194	0	8	(100%)	201	0	6	(100%)	195	0	5	(100%)
-> Day 56	193	0	1	(100%)	197	0	4	(100%)	192	1	2	(99.5%)
-> Day 84	191	0	2	(100%)	192	1	4	(99.5%)	187	4	2	(97.9%)
-> Day 112	190	1	0	(99.5%)	189	1	3	(99.5%)	185	6	0	(96.9%)
-> Day 140	188	1	2	(99.5%)	187	2	1	(99.0%)	181	7	3	(96.4%)
-> Day 168	183	1	5	(99.5%)	187	2	0	(99.0%)	181	7	0	(96.4%)
-> Day 196	180	1	3	(99.5%)	181	2	6	(99.0%)	178	7	3	(96.4%)
-> Day 224	178	1	2	(99.5%)	177	3	3	(98.4%)	176	7	2	(96.4%)
-> Day 252	173	1	5	(99.5%)	172	3	5	(98.4%)	173	7	3	(96.4%)
-> Day 280	168	1	5	(99.5%)	170	3	2	(98.4%)	173	7	0	(96.4%)
-> Day 308	165	2	2	(98.9%)	167	3	3	(98.4%)	168	7	5	(96.4%)
-> Day 336	160	3	4	(98.3%)	165	4	1	(97.8%)	166	7	2	(96.4%)
-> Day 364	0	3	160	(98.3%)	0	5	164	(97.2%)	0	7	166	(96.4%)
95% CI				[94.8;99.4%]				[93.5;98.8%]				[92.5;98.2%]
Diff to leuprolide 7.5 mg				(1.9%)				(0.9%)				
97.5% CI of diff. to leuprolide 7.5 mg				[-1.8;5.7%]				[-3.2;5.0%]				

No. at risk = Number of patients at risk

T>0.5 ng/mL = Cumulative number of patients with testosterone > 0.5 ng/mL

Cens = Number of censored observations

(*) = Estimated probability of all testosterone values ≤ 0.5 ng/mL

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

The non-inferiority margin for the difference to leuprolide 7.5 mg is -10 percentage points.

Data source: FE200486/PROSTATE/CS21/06DEC2007 — EFF_FLT_ITT.SAS (Table 36)

Source: Table 9-3 in the sponsor's report

To further validate the analysis results of the primary endpoint, we conducted a sensitivity analysis excluding only the patients whose protocol violations were most likely affect the assessment of the primary endpoint. As shown in Table 15, the lower bounds of 95% CI of the estimated response rates in both degarelix arms are basically unchanged as compared to the results based on the ITT sets. Similar observations are also seen for the leuprolide arm.

Table 15: A Sensitivity Analysis of Cumulative Probability of Testosterone ≤ 0.5 ng/mL from Day 28 to Day 364 –Kaplan-Meier Estimates of Individual Response Rates

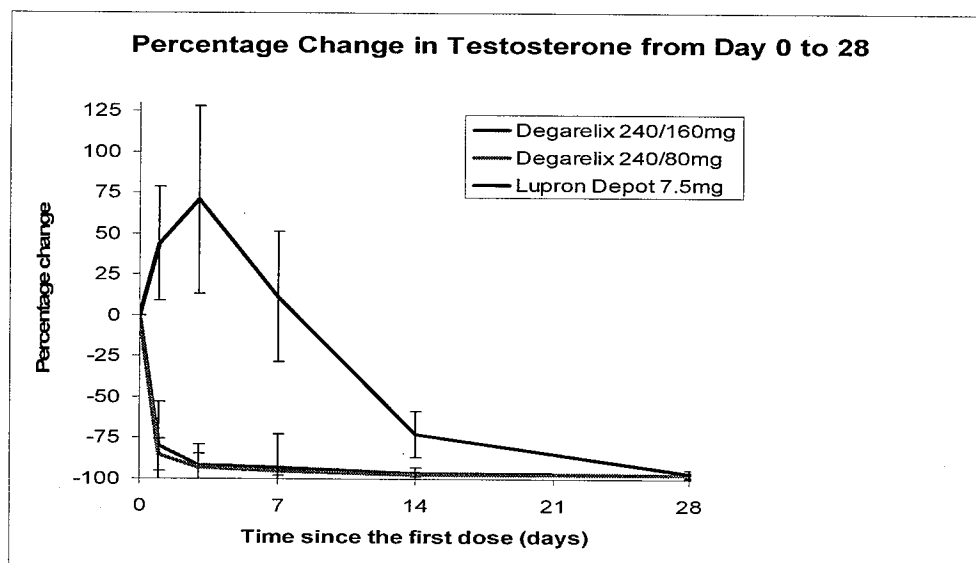
	Degarelix (240/160 mg) N=202	Degarelix (240/80 mg) N=207	Leuprolide (7.5 mg) N=201
The Sensitivity Set*	189	199	194
Response Rate (95% CI)	99.4% (95.7%; 99.9%)	97.2% (93.3%; 98.8%)	96.3% (92.4%, 98.2)
* Sub-ITT populations that exclude patients with ineligible levels of testosterone at enrollment, patients withdrawn during the first 28 days, and patients who used prohibited hormone agents or had major dosing errors. See Table 11 for details.			

Reviewer's Comments

The primary endpoint analysis results show that degarelix administered at either of the two dose schedules is effective in attaining and maintaining medical castration, with the lower 95% CI bounds greater than 90%, satisfying the pre-specified requirement for demonstrating the efficacy of degarelix. Also, the efficacy demonstrated appears to be comparable to that observed with leuprolide, an approved GnRH agonist used for palliative treatment of advanced prostate cancer.

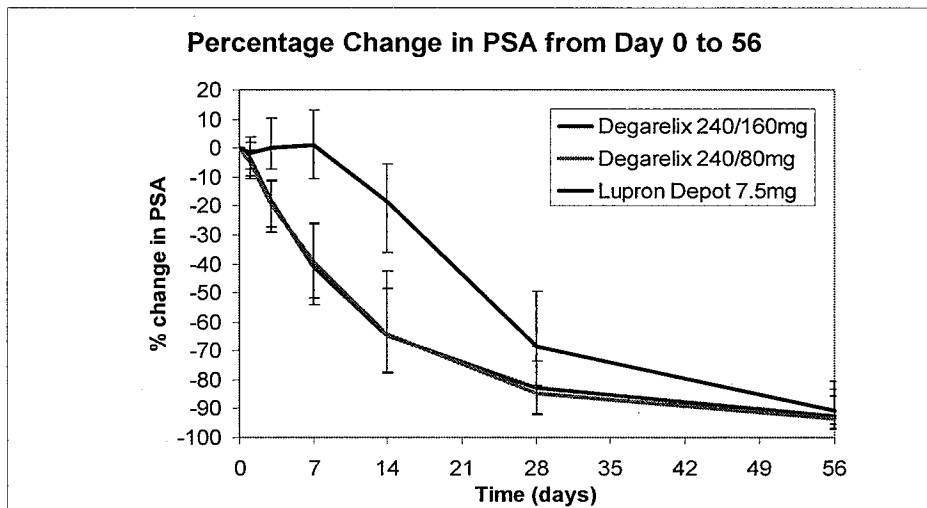
6.1.5 Analysis of Secondary Endpoints(s)

The key secondary endpoint of the study was to compare serum levels of testosterone and PSA using a degarelix dosing regimen versus monthly Lupron depot at 7.5 mg during the first 28 days of treatment. To reveal any differences in serum testosterone in the three arms, percent changes from baseline in median testosterone are calculated at the pre-specified time points of sampling after the loading dose. As shown in Figure 1, testosterone declined rapidly and approached 100% suppression 3 days after the degarelix dosing; whereas in the leuprolide arm, testosterone surged first within a week, followed by suppression that reached 100% around day 28. Similarly, the differences can also be reflected by estimating percentages of patients who had achieved castration at these time points. As shown in Table 16, almost all the patients in the degarelix arms reached the castration criteria 3 days after the loading dose of degarelix; whereas only 18% of patients in the leuprolide arm met the castration criteria 14 days after the initial dose of leuprolide. Nevertheless, the difference vanished when testosterone levels were measured on day 28. These results show clearly that the main important difference between the two agents is in the velocity of induction of medical castration. The observed differences are consistent with the known mechanisms of the two agents.

Figure 1: Changes in Testosterone within the First 28 Days after the Initial Dosing**Table 16: Percentage of Patients Achieving Testosterone < 0.5 ng/mL within the First 28 Days**

	Degarelix (240/160 mg) N=202	Degarelix (240/80 mg) N=207	Leuprolide (7.5 mg) N=201
Day 1	44%	52%	0%
Day 3	96%	96%	0%
Day 7	99%	99%	1%
Day 14	99%	99%	18%
Day 28	99%	100%	100%

Percent changes in median PSA within the first 28 days are also analyzed and the results are shown in Figure 2. The velocities of declines in PSA appear parallel to those revealed in the changes of testosterone, consistent with the hormone responsive nature of the disease in the population studied. As shown in Figure 4, the differences also disappeared with time, similar to the results seen in the analyses for testosterone.

Figure 2: Changes in PSA within the first 2 Months after the Initiation of the Study

The other important secondary endpoint was to compare serum testosterone, PSA response, LH, and FSH using a degarelix dosing regimen versus monthly leuprolide depot at 7.5 mg during the entire treatment period. The changes in median levels of these parameters during the entire study course are verified and summarized in Figures 3, 4, 5, 6, respectively. The changes in testosterone are consistent with the results shown in Figure 1 and its levels basically remained suppressed in all the three arms throughout the study after the first 28 days. Similarly, median PSA values declined to plateaus of <1.0 ng/mL in the three arms over time. Although the velocity of PSA declines within the first 2 months in the leuprolide arm is slower compared to that in the degarelix arms, the difference generally does not associate with any clinical significance for majority of patients simply due to its biochemical surrogacy for suppression of testosterone. As the pituitary hormones corresponding to GnRH receptor's activity, both the LH and FSH levels decreased rapidly and remained suppressed in the degarelix arms due to the degarelix inhibition of the receptor; in contrast, both the levels of LH and FSH increased first in the leuprolide arm, followed by suppression after 28 days. Between the degarelix arms and leuprolide arm, the extent of suppression of LH, the key stimulator for androgen synthesis from the testes, was basically same after day 28, thereby providing a basis for the similar efficacy results on testosterone suppression as shown in Table 12 or Figure 3.

Figure 3: Changes in Testosterone during the 12 Months Study

(Adopted from the sponsor after verification)

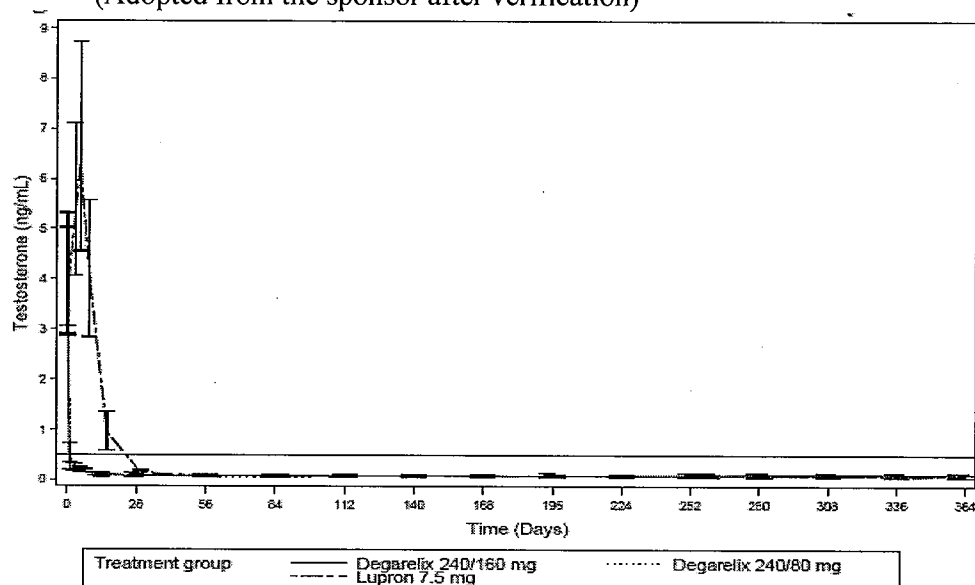


Figure 4: Changes in PSA during the 12 Months Study

(Adopted from the sponsor after verification)

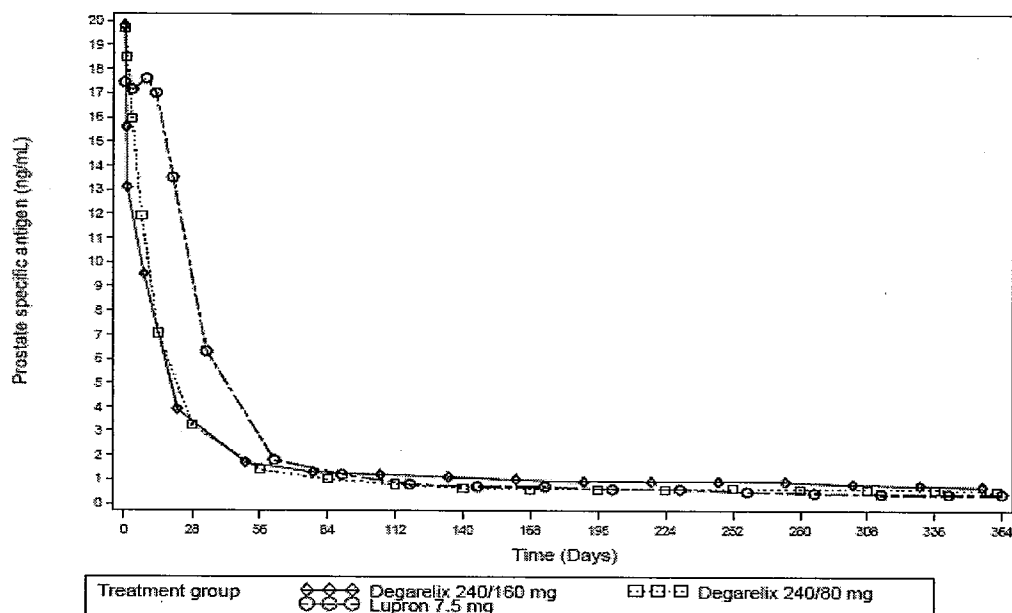


Figure 5: Changes in LH during the 12 Months Study

(Adopted from the sponsor after verification)

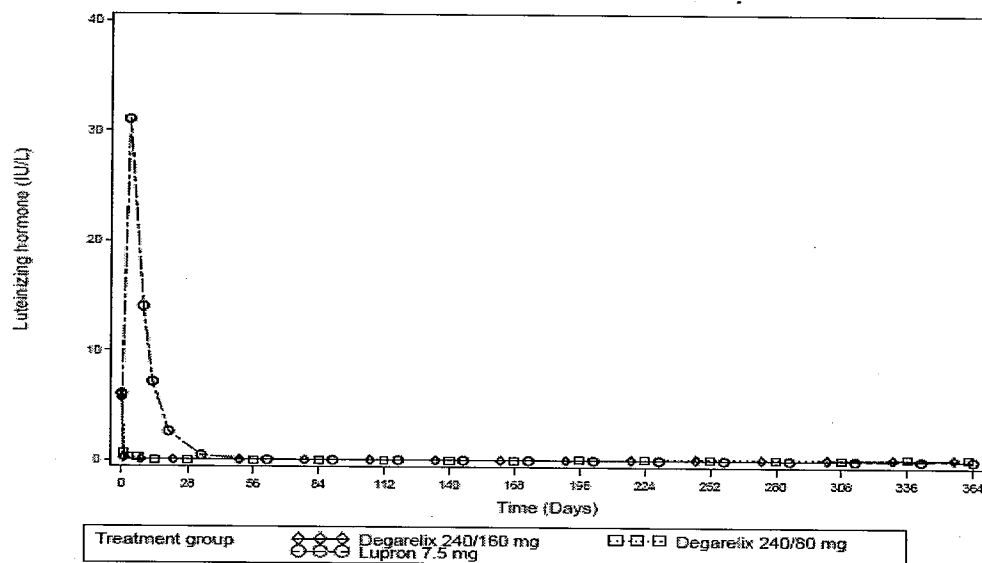
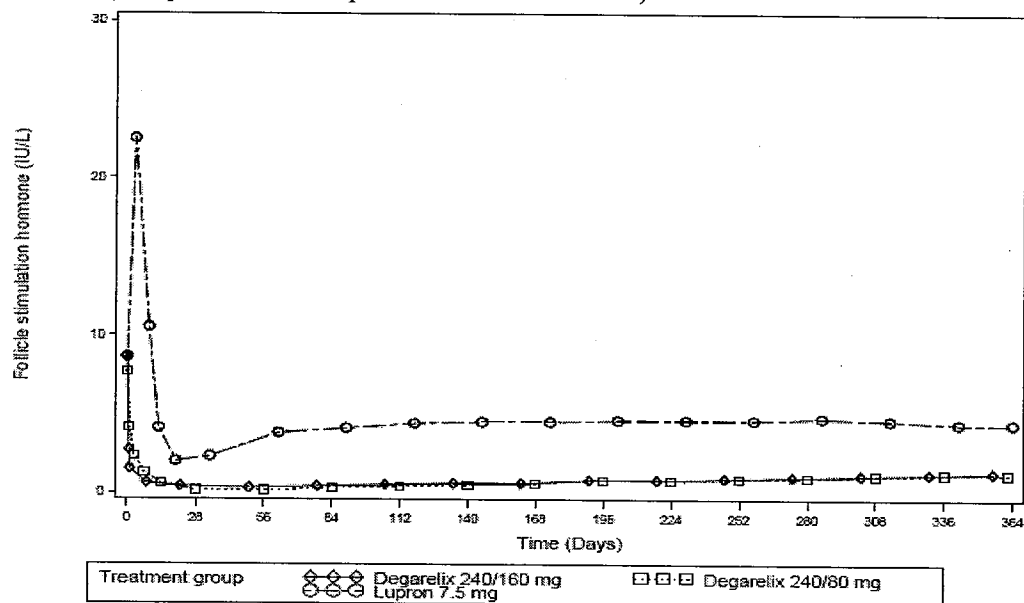


Figure 6: Changes in FSH during the 12 Months Study

(Adopted from the sponsor after verification)



b(4)

Reviewer's Comments

Overall, the secondary endpoint analysis results do not only support the reliability of the primary endpoint analysis results, but also provide clinical information on the mechanisms underlying the action of degarelix. Apparently, degarelix differs from leuprolide in its ability to quickly achieve biochemical castration within the first month after initial dosing without a surge in testosterone. Although no clinical evidence has demonstrated that such rapidity is clinically beneficial, this difference may be theoretically important for treatment of patients with prostate cancer under certain clinical conditions (e.g., metastatic disease causing neurological compromise or ureteral or bladder obstruction) in whom biochemical castration is needed urgently with an assurance of no surges in testosterone.

6.1.6 Subpopulations

None planned or none indicated for subgroup analysis explorations for this study.

6.1.7 Analysis of Clinical Information Relevant to Dosing Recommendations

As discussed previously, the two degarelix arms in Study CS21 differ in their monthly maintenance doses, 160 mg vs 80 mg, despite the same starting dose of 240 mg. However, the efficacy results as demonstrated above suggest that the two dosing schedules produce comparably adequate medical castration rates in the population of patients with prostate cancer. When the two arms are compared in safety profile, as discussed in the following section Review of Safety, there were fewer adverse reactions in the 240/80 mg arm than in the 240/160 mg arm, e.g. fewer injection site reactions, fewer withdrawals due to adverse events, and the absence of Grade 3 or 4 hepatic laboratory abnormalities. Therefore, the 240/80 mg dosing schedule appears to be associated with a relatively better safety profile, representing a good risk-benefit dosing regimen. As such, the 240/80 mg dosing regimen is recommended for use if the agent is approved for marketing. This recommendation is also consistent with the common sense that the lower exposure is preferred with same efficacy.

6.1.8 Discussion of Persistence of Efficacy and/or Tolerance Effects

The current efficacy data, as shown above, have not provided adequate evidence on whether the monthly dosing regimens would result in the same efficacy after 12 months of treatment. This limitation is simply due to the design of study CS21. Currently, this study has been conducted in an extension phase to evaluate long-term efficacy and safety of degarelix. Despite the approximately 40% reduction in patient numbers in the extension phase, its results may help understand how persistent the efficacy and/or tolerance of long-term use of degarelix will be. With the large molecular size (1632 Daltons) of degarelix, one important concern is whether degarelix antibodies are generated during treatment and whether its efficacy may be compromised by the antibodies. The results of the immunogenicity studies in CS21, as discussed in Section 7.4.6, provided preliminary evidence suggesting that the appearance of antibodies against degarelix does not have an effect on sustainability of the efficacy during the 12 month treatment period.

6.1.9 Additional Efficacy Issues/Analyses

None suggested with the submitted data and intended efficacy claim.

7 Review of Safety

7.1 Methods

To review the safety and tolerability of degarelix in patients with prostate cancer, both submitted datasets and case report forms (CRFs) were examined. Internal consistency between the datasets and CRFs was checked and compared in selected patients who had important adverse reactions or events. Special attention was paid to the adverse reactions known for other approved GnRH receptor agonists and antagonist and the long-term adverse reactions related to androgen deprivation therapy. Patients who died during the study were checked in CRFs and narratives of deaths for causality and its relationship to degarelix. Important laboratory or physical abnormalities reported in the adverse event dataset are checked against the values in laboratory tests or physical examinations. The 120-day safety update report based on the few currently ongoing studies is reviewed for any new safety signals in comparison with the findings based on the initial submitted data and report.

Adverse events or reactions recorded in Medical Dictionary for Regulatory Activities (MedDRA)-preferred terms were analyzed based on the submitted datasets. A treatment-emergent adverse events (TEAE) was defined as any new adverse events during study (after the first dose of degarelix until 30 days after the last dose); whereas a drug-related adverse reaction (DRAR) was defined as any AR with causal relationship to the drug, classified by investigators as “certain”, “probable”, and “possible” in the datasets. Adverse events designated as “not likely” or “not related” in causality were not considered to be drug-related.

7.1.1 Clinical Studies Used to Evaluate Safety

The evaluations of safety and tolerability were mainly based on the active-controlled Phase 3 study CS21. Patients who received at least one dose of treatment with degarelix from various studies are included for a pooled analysis of the safety. These studies are listed in Table 17. The detailed dosing information can be found in Table 3.

Table 17: Clinical Studies Used for Safety Analyses of Degarelix

Phase	Study ID	Number of patients	Dosing Schedule
Phase 3	CS21	610	Monthly for 12 months at doses: 240* /160 mg or 80 mg
Phase 2	CS02	129	Monthly for 6 months with lower doses: 80* /40 or 20 mg, or 40* /40 mg
	CS06	82	Single dosing at doses: 40, 80, 120, or 160 mg
	CS07	172	Single dosing at doses: 120, 160, 200, 240, or 320 mg
	CS12	187	Monthly for 6 months at doses 200* or 240* /80, 120, or 160 mg
	CS14	127	Monthly for 12 months at doses: 200* /60 or 80 mg
Phase 1	CS11	18	Single dosing at doses 160, 200, or 240 mg

7.1.2 Adequacy of Data

The submitted datasets were examined for their integrity, content and types. Physical, laboratory, and EKG examination information was included in the submission. The submitted CRFs are in agreement with the requirements as specified in the pre-NDA meeting and provide adequate information about the safety and tolerability of degarelix.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

A pooled analysis of the degarelix safety profile was conducted in the population of 1325 patients from all the studies listed in Table 18. These patients had similar treatments, monthly or one single dosing. Some of the patients continued their treatment in an extension phase after completion of the trial and their safety information is also included in this analysis. In contrast, patients who received high doses of degarelix in the current ongoing trials _____ are not included in the analysis as the safety profile of high doses may differ from that of doses administered monthly or one time and thus is less compatible for the purpose of this analysis.

b(4)

TEAEs and DRARs with an incidence frequency of $\geq 5\%$ are tabulated as shown in Table 18. The frequently observed TEAEs are similar to the observed DRARs, including hot flush, injection site reactions, increases in weight or hepatic transaminases and gamma-glutamyltransferase. This information would serve as a general control in estimating the adequacy of the safety profile of the key study CS21, which is summarized in Table 24. There appear to be no important differences between the pooled and CS21 analyses in the toxicities, suggesting that the safety analysis results based on Study CS21 are reliable.

Table 18: Adverse Events or Reactions Reported in $\geq 5\%$ of Patients who Received Degarelix Monthly or Single Dose Only (A Pooled Exploratory Analysis)

Adverse Event or Reaction (%)	TEAE N=1325		DRAR N=1325	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Hot Flush	419 (32%)	9 (<1%)	416 (31%)	9 (<1%)
Injection Site Reactions*	333 (25%)	17 (1%)	327 (25%)	15 (1%)
Weight Gain	106 (11%)	1 (<1%)	64 (5%)	1 (<1%)
Increase in Hepatic Transaminases and/or GGT	104 (8%)	5 (<1%)	66 (5%)	5 (<1%)
Fatigue	95 (6%)	5 (<1%)	68 (5%)	3 (<1%)
Hypertension	72 (5%)	2 (<1%)	8 (1%)	0
* Mainly include injection site pain, erythema, swelling, nodule, indurations or inflammation. GGT: gamma-glutamyltransferase				

7.2 Adequacy of Safety Assessments

Of all the 1325 patients who had received at least one treatment or monthly treatment at various doses as shown in Table 18; 78% of patients had exposure over 6 months and 64% had more than 12 months. In the key study CS21, 84% of patients had completed the 12 months of the study. As such, the safety information generated from Study CS21, as shown in the rest of the section for safety, would be adequate for assessing one-month dosing regimens for a year. However, the information would not be able to predict safety for long-terms, e.g. 2 years or longer, of degarelix in the population

intended. In addition, frequency of some important adverse reactions may not be revealed from CS21 as in the study degarelix was compared to leuprolide, another agent causing androgen deprivation, instead of to placebo.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The exposure of patients to study agents in the three arms of CS21 is summarized in Table 19. Despite the differences in total dose, which are related to the design of the study, durations of exposure are basically same in the three arms. A majority of the patients (82-83%) completed the whole 12 months of treatment with degarelix, comparable to the percentage of patients treated with leuprolide monthly.

Table 19: Extent of Exposure to Degarelix in Study CS21

	Degarelix (240/160 mg) N=202	Degarelix (240/80 mg) N=207	Leuprolide (7.5 mg) N=201
Duration of Exposure (months*) Median (range)	12.0 (0.03-12.3)	12.0 (0.03-12.4)	12.0 (0-12.9)
Total dose (mg) Median (range)	2160 (240-2160)	1200 (240-1200)	97.5 (7.5-97.5)
Patient (%)			
≥Median Dose	168 (83%)	170 (82%)	173 (86%)
<Median Dose	34 (17%)	37 (18%)	28 (14%)
* Calculated with every 28 days as a month for the study.			

7.2.2 Explorations for Dose Response

The difference in the total dose between the two degarelix arms is due to the difference in maintenance dose. Despite the difference, the duration of treatment with degarelix and the percentage of patients who completed the study are similar between the two degarelix arms, suggesting that the administered doses had not reached a threshold where different dose responses in safety may occur. This notion will be further examined in the analysis of adverse reactions in the next section.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable to the study.

7.2.4 Routine Clinical Testing

All patients enrolled in the study had pre-study, monthly, and post-study physical and laboratory examinations. ECG's were also obtained 8 times during the study. The results of these tests are adequate for determining if some of the tests are needed for safe use of degarelix in regular practice.

7.2.5 Metabolic, Clearance, and Interaction Workup

Cholesterol was monitored monthly in the study due to the known effects of androgen deprivation on metabolism. No drug interaction collections were planned due to the known metabolic nature of the drug, which was shown to have no suspected interactions through CYP450 or p-glycoprotein.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The known adverse reactions of GnRH receptor agonists or antagonists are generally due to medical castration, which has short-term and long-term manifestation. Concerns about changes in metabolism and cardiac health have been recently raised regarding the safety of androgen deprivation. Therefore, special attention was paid to adverse reactions related to these changes in the review. In addition, the first GnRH antagonist, approved initially in 2003 under restricted distribution but withdrawn from marketing in 2006, was associated with severe anaphylactic or anaphylatoid reactions. It was not clear whether the reaction was related to the GnRH receptor antagonist itself or the formulation used for the antagonist. In this review, special attention is also paid to hypersensitivity reactions.

Reviewer's Comments

The current exposure information and analyses have not necessarily provided a safety basis for long-term (>1 year) use of degarelix monthly. Although some of the patients in Study CS21 continued to an extension phase after completion of the initial 12 months study, the safety information from the patients enrolled in the extension are not complete at present nor submitted, as the extension phase is still ongoing. As stated above, adverse reactions secondary to androgen deprivation may occur with longer term treatment and follow-up. The results of the extension study may provide additional safety information, e.g. whether there could be further increases in hepatic transaminases and/or gamma-glutamyltransferase with continued treatment. Completion of the study and submission of a complete report on the extension phase should be a Phase 4 commitment or requirement.

7.3 Major Safety Results

Major safety parameters and the safety profile were evaluated based on the data on the 610 patients in Study CS 21 who received at least one dose of study medication. A total

of 10 patients who did not receive any study treatment after randomization are not included in these analyses.

7.3.1 Deaths and Serious Adverse Events

A total of 19 patients died during the course of the study. Their distribution in the three arms is summarized in Table 20, along with percentages of SAEs. The incidence rates are similar across the arms. With the increased concerns about cardiac toxicity of longer-term androgen deprivation, patients who died of cardiac disorders are examined based on the information provided in their CRFs and narratives of death. The number of these cases appears to be similar in the three arms and no cases are found to be related to study agent in causality. Other causes of the deaths were associated with gastrointestinal disorders, infections, tumor, and renal and urinary disorders. None of them were reported to be related to study drug. In addition, treatment-emergent SAEs are also similar across the three arms.

Table 20: Overview of Adverse Reactions, Serious Adverse Events, and Death in CS21

	Degarelix (240/160 mg) N=202	Degarelix (240/80 mg) N=207	Leuprolide (7.5 mg) N=201
All Grade TEAEs (%)	168 (83%)	163 (79%)	156 (78%)
All Grade DRARs (%)	120 (59%)	118 (57%)	84 (42%)
SAEs (%)	25 (12%)	21 (10%)	29 (14%)
Non-fatal (%)	14 (7%)	10 (5%)	12 (6%)
Death (%)	5 (2%)	5 (2%)	9 (5%)
Disease	1	0	1
Others	4	5	8
Cardiac*	2	3	4
*including cardiac arrest, myocardial infarction, heart failure, cardiac arrhythmias.			

7.3.2 Dropouts and/or Discontinuations

Patients who dropped out of the study are summarized in Table 21. There are approximately 10 more patients in each of the degarelix arms who stopped due to adverse events as compared to the patients in the leuprolide arm. Examination of the adverse events, as presented in Table 22, does not show or suggest a clear pattern or trend of any particular degarelix associated or related toxicities. However, injection site reactions, related to degarelix but not to leuprolide, might be an issue in few patients.

Table 21: Patients Discontinued or Withdrawn during Study of CS21

Withdrawn/ Discontinuation (%)	Degarelix (240/160 mg) N=202	Degarelix (240/80 mg) N=207	Leuprolide (7.5 mg) N=201
Due to AE*	15 (7%)	10 (5%)	3 (2%)
Voluntary**	11 (5%)	11 (5%)	10 (5%)
Others***	9 (4%)	12 (6%)	7 (4%)
*adverse reaction or event ** including withdrawal of consent and lost to follow-up *** including disease progression, other therapies for prostate cancer, relocation, etc.			

Table 22: Adverse Events Leading to Withdrawal in Study CS21

Adverse Event Causing Withdrawal (Number of Patient)	Degarelix (240/160 mg) N=202	Degarelix (240/80 mg) N=207	Leuprolide (7.5 mg) N=201
Cardiovascular	3	1	1
Injection Site Reaction	3	2	0
Increases in liver enzymes	0	1	0
Other Tumors	2	0	0
Others*	7	6	2
* including events related with infection, bleeding, or disease progression. No trends of safety suggested by the events leading to withdrawal.			

7.3.3 Significant Adverse Events

Based on the results of the commonly observed adverse events, as shown in Section 7.4.1, and the known important toxicities of other approved GnRH agents used for androgen deprivation, the adverse reactions shown in Table 23 are considered important and evaluated with no preset incidence rates for inclusion.

Table 23: Important DRARs Observed in Study CS21

DRAR (%)	Degarelix (240/160 mg) N=202		Degarelix (240/80 mg) N=207		Leuprolide (7.5 mg) N=201	
Grade	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4

Injection Site Reactions	86 (43%)	5 (2%)	72 (36%)	5 (2%)	1 (<1%)	0
Hot Flush	53 (26%)	1 (<1%)	52 (26%)	4 (2%)	42 (21%)	1 (<1%)
Weight Gain	13 (6%)	1 (<1%)	14 (7%)	0	14 (7%)	0
Increase in Hepatic Transaminases and/or GGT	12 (6%)	1 (<1%)	14 (7%)	0	4 (2%)	0
Hypersensitivity*	0	0	1 (<1%)	1 (<1%)	0	0
* Generalized itching 3 weeks after the loading dose/. The patient was discontinued and the reaction resolved about 90 days thereafter.						

Injection site reactions represent the most commonly reported adverse reactions to degarelix. Few patients as shown above discontinued treatment due to the adverse reactions. These reactions were not associated with other clinical signs (e.g. hypotension or dyspnea) to suggest acute systemic allergic reactions. In addition, abnormalities in hepatic laboratory tests appear to be relatively more frequent in the degarelix treatment arms as compared in the leuprolide arm. This may represent a safety signal as the study was open-label and potential bias in classifying causality of adverse findings could be introduced. Further analyses on the hepatic laboratory abnormalities are shown in Section 7.4.2. No patients experienced life-threatening allergic reactions. One patient who developed severe pruritus 3 weeks after the initial loading dose of 240 mg had no other adverse reactions observed. The reaction resolved after discontinuation of treatment.

Reviewer's Comments

Although the deaths secondary to cardiac events were similar in the three arms and assessed as unrelated or unlikely related to study agent, it is necessary to point out that the evidence does not exclude the possibility of study agent's involvement since both agents act through achieving androgen deprivation, which has been recently reported to increase cardiac mortality and morbidity based on the retrospective analyses in large populations of patients with prostate cancer. Therefore, in the absence of a placebo arm in this small sample sized trial, cardiac risks of degarelix or leuprolide could not be adequately assessed.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most frequently reported adverse events with an incidence of 5% or more, regardless of causality, are evaluated as shown in Table 24. Compared to the DRAR results shown in Table 23, the common TEAEs differ mostly in Grade 1/2 non-specific events, including hyperlipidemia, hypertension, fatigue, back pain, antralgia, chills, constipation, and urinary tract infection. The common toxicities between the two tables are similar.

Table 24: TEAEs of $\geq 5\%$ Observed in Study CS21

Adverse Event (%)	Degarelix (240/160 mg) N=202		Degarelix (240/80 mg) N=207		Leuprolide (7.5 mg) N=201	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Injection Site Reactions	89 (44%)	5 (2%)	73 (35%)	5 (2%)	1 (<1%)	0
Hot Flush	53 (26%)	1 (<1%)	53 (26%)	4 (2%)	43 (21%)	1 (<1%)
Weight Gain	22 (11%)	1 (<1%)	18 (9%)	0	24 (12%)	0
Increase in Hepatic Transaminases and/or GGT	20 (10%)	3 (2%)	21 (10%)	0	11 (5%)	0
Hyperlipidemia*	14 (7%)	1 (<1%)	9 (4%)	0	8 (4%)	0
Hypertension	14 (7%)	0	14 (7%)	2 (1%)	11 (5%)	1 (<1%)
Fatigue	13 (6%)	0	7 (3%)	0	13 (6%)	0
Back pain	12 (6%)	0	13 (6%)	1 (<1%)	19 (9%)	1 (<%)
Arthralgia	7 (4%)	1 (<1%)	11 (5%)	0	18 (9%)	1 (<%)
Chills	7 (4%)	1 (<1%)	11 (5%)	1 (<1%)	0	0
Constipation	6 (3%)	0	12 (6%)	0	10	0
Urinary Tract Infection	4 (2%)	0	11 (5%)	0	19 (9%)	1 (<1%)

7.4.2 Laboratory Findings

With the information revealed in Section 7.3.1 about the toxicities of hepatic laboratory tests, the safety in hepatic function is evaluated furthermore for establishing if appropriate monitoring of hepatic function would be needed in routine clinical practice. Table 25 summarizes the abnormalities regardless of causality. In addition, three patients with isolated Grade 1/2 increases in total bilirubin are also presented.

Interestingly, two patients with Grade 3 abnormality continued their maintenance treatment (160 mg monthly) throughout the trial in Romania. The one with abnormal

GGT was reported not recovered, although his ALT/AST had their recovery 6-10 months later. The other with Grade 3 abnormal ALT had a recovery despite continuation of the treatment. Most of patients had Grade 1 or 2 toxicity, which were generally reversible. Nevertheless, one patient with Grade 2 toxicity withdrew.

Table 25: Abnormalities in Hepatic Laboratory Tests in Study CS21

Treatment Related Changes in Hepatic Tests (%)	Degarelix (240/160 mg) or (240/80 mg) N=409				Leuprolide (7.5 mg) N=201			
Grade	All Grades	Grade 1	Grade 2	Grade 3	All Grades	Grade 1	Grade 2	Grade 3
Increase in ALT/AST and/or GGT	42 (10%)	26 (7%)	12 (3%)	2*(<1%)	11 (5%)	4 (2%)	7 (4%)	0
Increase in Bilirubin**	1 (<1%)	1 (<1%)	0	0	2 (1%)	1 (<1%)	1 (<1%)	0
<p>*Both occurred after the loading dose. One case of Grade 3 toxicity in GGT along with Grade 2 toxicity in tansaminases, considered possibly related to study agent, did not recover. The other had increases in ALT, considered as unrelated, and recovered despite continuation of treatment.</p> <p>** isolated increase.</p>								

With the pharmacokinetic information that approximately 20% of degarelix is excreted in urine, laboratory abnormalities in creatinine were also investigated to assess the clinical effects of degarelix on renal function. As shown in Table 26, the incidence rates of the increases, regardless of causality, were very similar in the three arms. The majority of them were transient during the study period, suggesting that the study agents are less likely responsible for the changes.

Table 26: Abnormalities in Creatinine in Study CS21

Adverse Event (%)	Degarelix (240/160 mg) N=202		Degarelix (240/80 mg) N=207		Leuprolide (7.5 mg) N=201	
Grade	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Increases in Creatinine	8 (4%)	3 (2%)	9 (4%)	2 (1%)	12 (6%)	3 (2%)

Other important laboratory findings include anemia and hyperlipidemia. Their incidence rates similar in the three arms, approximately 5%, and their intensities are Grade 2 or less in the majority of the affected patients.

7.4.3 Vital Signs

The percentage of patients who had increases in their weight or blood pressures is presented in Table 24. No immediate hypertension followed by hypotension is detected. The increases appear to be similar in the three arms. No other changes are found different among these arms.

7.4.4 Electrocardiograms (ECGs)

ECGs were obtained at Screening, Day 0, Day 3, Day 84 (± 7 days) and every 84 days (± 7 days) thereafter until the End of Study Visit. At Day 0 three separate ECGs were recorded. ECGs were performed before dosing, if a dosing visit was scheduled.

The submitted ECGs have been evaluated by the Interdisciplinary Review Team for QT studies. For both degarelix and leuprolide, there was no overt prolongation on day 3. However, the reviewers cannot rule out small effects on the QT interval of <10 ms since the study did not include a positive control. The mean change from baseline was approximately 11 ms and 12 ms in patients treated with degarelix and leuprolide by Day 84 and persisted for the remainder of the study (Day 364). Based on the analysis results, the reviewers are uncertain about whether the QT prolongation is directly associated with the degarelix suppression of plasma testosterone levels alone and not due the direct effects of degarelix.

7.4.5 Special Safety Studies

None

7.4.6 Immunogenicity

For Study CS21, samples for monitoring appearances of degarelix antibodies were obtained before the first dose on Day 1 and then on day 168 and 364. Anti-degarelix antibodies were measure using a radioimmunoassay. Positive findings of the antibody were confirmed based on surface Plasmon resonance.

A total of 40 patients (11%) are found having confirmed presence of positive anti-degarelix antibody during the course of treatment. Five patients were detected positive on day 168, but the other 35 patients found positive at the end of the study, suggesting the likelihood of developing antibodies against degarelix increases with duration of the treatment. The distribution of these patients between the two degarelix arms is summarized in Table 27.

Table 27: Patients with Confirmed Positive Tests of Antibodies against Degarelix

Detection of Antibodies against Degarelix (Number of Patient)	Degarelix (240/160 mg) N=202	Degarelix (240/80 mg) N=207	Total N=409
Positive On day 168	3	2	5
Positive On day 364	21	14	35

The impact of the presence of the antibodies on both efficacy and safety are examined. All of these patients remained castrated with testosterone ≤ 0.5 ng/mL from Day 28 to Day 364, and none of them had adverse reactions suggestive of allergic reactions. The patient described in Section 7.3.3 who had severe pruritus did not have post-dose antibody tests as he withdrew after the loading dose. On the other hand, one additional patient with Grade 1 generalized urticaria, occurring after the first dose and considered possibly related to degarelix by the investigator, was tested negative antibodies to degarelix and did not experience a similar event with subsequent doses. Taken together, the evidence suggests that appearance of antibodies against degarelix does not affect efficacy and safety during the 12 month treatment period.

Similar observations are also found from other early clinical trials where appearance of antibodies against degarelix was investigated. However, it is not clear if the known immunogenicity and its effects would remain similar with long term treatment, e.g. >3 years. Given the estimated life span of the population (patients with metastatic prostate cancer) for which this drug would be indicated, this concern may not be an issue, especially in the absence of efficacy or safety signals in relation to the immunogenicity in Study CS21.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The two degarelix arms in Study CS21 differed in maintenance dose, 160 mg vs 80 mg monthly, with a total dose difference of approximately 1000 mg between the two arms as shown in Table 19. Patients in the two arms had similar extents of exposure, with similar percentages of patients receiving their corresponding median dose. However, the adverse events between the two arms, as listed in Tables 23, 24, appear to be comparable, with no trends or signals suggestive of dose-related increases in occurrence of adverse events in the 160 mg maintenance arm as compared in the 80 mg arm. Therefore, it is less likely there could be a dose dependency for adverse events under the current studied doses for one year.

7.5.2 Time Dependency for Adverse Events

Differences in the incidence of adverse reactions between the first 28 days and the period of days 28-364 are examined, since the two degarelix arms had the same starting dose of 240 mg that resulted in medical castration in almost all patients within the 28 days. As shown in Table 28, the main differences between the two time periods in the degarelix arms are focused in the incidence of injection site reactions, which decreased with continued treatment. The decrease appears to be more noticeable in the 240/80 mg arm, suggesting that the lower maintenance dose of 80 mg may have a better local tolerability. This is most likely related to degarelix preparation itself, since the injection volumes of maintenance doses in the two arms were the same, 4 mL. Other common adverse events, except hot flushes, appear increased with time, consistent with the known metabolic changes with androgen deprivation. Hot flushes occurred in similar rates between the two periods, most likely related to the earlier achievement of androgen deprivation with degarelix as compared to the delayed attainment with leuprolide. Hepatic laboratory abnormalities slightly increased with time, but with no signals suggestive of an increase in their severity. The majority of the abnormalities were transient and recovered during the study. One of 13 patients in the first 28 day period and 4 of 27 patients in the post-28 day period were found not recovered in their hepatic abnormalities (including patients lost to follow-up).

Table 28: Occurrences of Adverse Reactions with Time during the CS21 Study

Adverse Event (%)	Degarelix (240/160 mg) N=202		Degarelix (240/80 mg) N=207		Leuprolide (7.5 mg) N=201	
	Day 0-28	Day 28-364	Day 0-28	Day 28-364	Day 0-28	Day 28-364
All Grade						
Injection Site Reactions	64 (32%)	55 (26%)	66 (32%)	31 (16%)	0	1 (<1%)
Hot Flush	29 (15%)	25 (13%)	25 (12%)	32 (15%)	15 (8%)	31 (16%)
Weight Gain	0	22 (11%)	1 (<1%)	17 (8%)	0	24 (12%)
Increase in Hepatic Transaminases and/or GGT	6* (3%)	14 (7%)	7 (3%)	13 (6%)	1 (<1%)	8 (4%)
Hyperlipidemia	0	14 (7%)	1 (<1%)	8 (4%)	0	8 (4%)
Hypertension	2 (1%)	13 (7%)	2 (1%)	10 (5%)	1 (<1%)	7 (4%)
Fatigue	3 (2%)	10 (5%)	1 (<1%)	6 (3%)	3 (2%)	11 (6%)
* two patients had Grade 3 toxicity						

7.5.3 Drug-Demographic Interactions

Not considerable with the current study design and the patient population studied.

7.5.4 Drug-Disease Interactions

Not implicated with the evidence available.

7.5.5 Drug-Drug Interactions

Not planned in the study

7.6 Additional Safety Explorations

7.6.1 Human Carcinogenicity

No preclinical data suggestive of potential carcinogenicity of degarelix.

In Study CS21, eight patients in the degarelix arms were found to have other malignancies, including basal cell carcinoma (the majority of them), lymphoma, melanoma, and squamous cell carcinoma. Similarly, six patients in the leuprolide arm were reported to have malignancies, including basal cell carcinoma, methothelioma, adenocarcinoma of gallbladder. With the few casual cases of malignancies, no relationship could be explored about the carcinogenicity of degarelix.

7.6.2 Human Reproduction and Pregnancy Data

No reports of pregnancy in the study.

7.6.3 Pediatrics and Effect on Growth

Not applicable for the NDA.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No overdoses were reported in the study. The drug has no potential for being abused in the population intended.

8 Postmarketing Experience

None

9 Appendices

9.1 Literature Review/References

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2. Lu-Yao GL, et al. Survival following primary androgen deprivation therapy among men with localized prostate cancer. *JAMA* 2008; 300: 173-181
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4. Alibhai SMH et al. Long-term side effects of androgen deprivation therapy in men with non-metastatic prostate cancer: A systematic literature review. *Critical Review in Oncol. & Hematology* 2006; 60:201-215
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6. Tsai HK et al. Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality. *JNCI* 2007; 99:1516-24
7. Saigal CS et al. Androgen deprivation therapy increases cardiovascular morbidity in men with prostate cancer. *Cancer* 2007; 10: 1493-500
8. Alibi SM et al. Impact of androgen deprivation therapy (ADT) on bone, cardiovascular, and endocrine outcomes: A propensity-matched analysis of 20,000 patients. *J Clin Oncol* 26: 2008 (May 20 suppl; abstr 5012)
9. Pound CR et al. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA* 1999; 281: 1591-1597

9.2 Labeling Recommendations

Considerable changes were recommended to the initial label submitted by the applicant in the highlights, safety, and efficacy sections. To show major clinical recommendations effectively, the areas changed with the recommendation are highlighted in both initial and revised labels. For each section, the initial label information is listed before the revised one. In both efficacy and safety sections, the information was also rearranged considerably for a better presentation with the addition of the results from the 240/160 mg degarelix arm of Study CS21.

11 Page(s) Withheld

 Trade Secret / Confidential (b4)

 ✓ Draft Labeling (b4)

 Draft Labeling (b5)

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Interdisciplinary Review Team for QT Studies Consultation:
QT Study Review

NDA	22-201
Brand Name	FIRMAGON®
Generic Name	Degarelix, FE200486
Sponsor	Ferring Pharmaceuticals
Indication	Treatment of Prostate Cancer
Dosage Form	Depot injection (s.c.)
Drug Class	GnRH antagonist
Therapeutic Dosing Regimen	Starting dose 240@40mg/ml (2 injections) Maintenance dose: 80@20mg/ml every 28 days starting after 28 days
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Not established
Submission Number and Date	N000, 15 September 2008
Clinical Division	DDOP/HFD150

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

The two dosing regimens of degarelix, 240 mg at a concentration of 40 mg/ml (240@40) followed by either an 80mg dose at 20 mg/ml concentration (80@20) or 160 mg/ml at a concentration of 40 mg/ml (160@40), prolonged the QT interval with a similar magnitude and time-course as the active comparator leuprolide 7.5 mg IM every 28 days.

For both degarelix and leuprolide, there was no overt prolongation on day 3. We cannot, however, rule out small effects on the QT interval of <10 ms since the study did not include a positive control. However, the mean change from baseline was approximately 11 ms and 12 ms for degarelix and leuprolide by Day 84 and persisted for the remainder of the study (Day 364).

The time course of QT prolongation is inconsistent with the pharmacokinetics of degarelix. There appears to be a lag time between the time to the maximum concentration of degarelix (T_{max}) and QT prolongation. The highest concentration of degarelix is reached in 1 day after the first dose of degarelix (240 mg). No overt QT prolongation was observed on Day 3.

This was an open-label, Phase 3, three-arm, multi-centre stratified, randomized, controlled, parallel-group study to compare the efficacy and safety of degarelix with leuprolide 7.5 mg in patients with prostate cancer. The summary of changes for QTcF results on Day 3 and End of Study is shown in Table 1.

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Table 1: Summary of QTCF Findings on Day 1 and End of Study

	240/160 mg	Degarelix 240/80 mg	Total	Leuprolide 7.5 mg
Day 3 Corrected QT using Fridericia				
(mMean baseline	403	407	405	404
Mean change	1.02	3.65	2.36	0.836
Mean % change	0.220%	0.875%	0.559%	0.162%
End of Study Corrected QT using Fridericia				
(mMean baseline	403	407	405	404
Mean change	10.3	11.7	11.0	13.0
Mean % change	2.54%	2.86%	2.70%	3.17%
Incidence of Markedly Abnormal Changes in ECG Variables				
Corrected QT using Fridericia (msec)	N (n, %)			
>=450	202 (37, 18%)	204 (44, 22%)	406 (81, 20%)	200 (40, 20%)
>=480	202 (7, 3%)	204 (5, 2%)	406 (12, 3%)	200 (7, 4%)
>=500	202 (1, <1%)	204 (2, <1%)	406 (3, <1%)	200 (4, 2%)

Source: Sponsor's Table 10-16 from the CSR for FE200486CS21.

1.2 QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS

- Although plausible (similar to other androgen inhibitors), we are uncertain about whether the QT prolongation is directly associated with the plasma testosterone level suppression alone and not due the direct effects of degarelix to based on the current observation. Accurate characterization of the relationship between QT prolongation, degarelix concentrations and testosterone inhibition would have required additional ECG observations between Day 3 and Day 84 after degarelix treatment.
- In our opinion, the current QT assessment for degarelix is adequate for the proposed indication of prostate cancer patients _____ and additional characterization of the QT interval is not needed. _____

b(4)

b(5)

- According to the sponsor, the incidence rate estimates for the degarelix treated patients for cardiovascular and cerebrovascular events were smaller and not significantly different compared to the respective background incidence rates in patients with other GnRH antagonist therapy, derived from the [Surveillance Epidemiology and End Results (SEER)] Medicare linked database. The incidence of cardiovascular (including sudden cardiac death) and cerebrovascular events among men with prostate cancer on GnRH antagonist therapy was higher compared to the background incidence in the target population of prostate cancer patients.
- Similar to the increased risk for other cardiovascular and cerebrovascular events risk versus benefits need to weighed with respect to adverse events related to QT prolongation secondary to degarelix or other androgen inhibitors and feasible risk minimization measures need to be instituted.

2 PROPOSED LABEL

2.1 SPONSOR'S PROPOSED LABEL

The sponsor has described the effects on administering degarelix on the QT interval in sections 5 (Warnings and Precautions) and _____. Our recommendations for labeling are shown below. We used red strikeout font to show the proposed text that we recommend deleting and blue font to show text to be included. Our labeling recommendations are suggestions only and we defer all final labeling decisions to the review division.

b(4)

We agree with inclusion of the active comparator (leuprolide) in the label since the QT effects are comparable and leuprolide has no language regarding QT effects included in the current PI.

b(4)

3 BACKGROUND

Ferring Pharmaceuticals is applying for a marketing authorization for FIRMAGON® powder _____ for injection, one-month dosing regimen (degarelix). Degarelix is a third generation gonadotropin releasing hormone (GnRH) antagonist (blocker). FIRMAGON is being developed for treatment of patients with prostate cancer

b(4)

Degarelix is a synthetic decapeptide, which forms a depot following subcutaneous injection; this depot formation results in a sustained release of degarelix.

This application comprises two strengths of FIRMAGON drug product:

- 120 mg - the starting dose of 240 mg is administered as two injections of 120 mg each (40 mg/ml) given simultaneously.

- 80 mg- the monthly maintenance dose is administered as one injection of 80 mg (20 mg/ml)

3.1 MARKET APPROVAL STATUS

Degarelix is not approved for marketing in the USA or elsewhere.

3.2 PRECLINICAL INFORMATION

Source: Pharmacology Written Summary-CTD-2.6.2 dated Dec 21, 2007

“2.6.2.4.4.1 Study No. PHA0204. Effect of FE 200486 on HERG Tail Current Recorded from Stably Transfected HEK293 Cells

The aim of the study was to assess the effect of FE 200486 (20 µg/ml) on HERG tail current recorded from HEK293 cells stably transfected with HERG cDNA. Stock solutions were diluted in bath solution to provide final perfusion solutions of 0.2, 0.7, 2, 7 and 20 µg/ml FE 200486. Reference substance, E-4031, was included. The reference substance, E-4031, inhibited HERG tail current, an effect consistent with its known activity. Treatment with 20 µg/ml FE 200486 produced no inhibition of HERG tail current in HEK293 cells stably transfected with HERG cDNA.

“2.6.2.4.4.2 Study No. PHA0203. Effects of FE 200486 on Action Potential Parameters in Dog Isolated Cardiac Purkinje Fibers

The aim of the study was to evaluate the effects of FE 200486 on intracellularly recorded action potential parameters in the dog isolated Purkinje fiber preparation electrically stimulated at 1 and 0.5 Hz. The effect of FE 200486 on the maximum rate of depolarization at a pacing frequency of 3 Hz was also studied to further assess any effects on sodium channels at the highest concentration. Fibers were exposed to concentrations of 0.2, 2 and 20 µg/ml FE 200486; dl-Sotalol hydrochloride (50 µM), a compound known to prolong action potential duration, was used as a reference substance in this study. The following parameters were measured: action potential duration at 60% and 90% repolarization (APD60 and APD90), maximum rate of depolarization (MRD), upstroke amplitude (UA) and resting membrane potential (RMP). The reference substance, dl-sotalol hydrochloride, caused a prolongation of the action potential duration that was inverse frequency-dependent, an effect consistent with its known activity. In dog isolated cardiac Purkinje fibers, paced at stimulation frequencies of 1 and 0.5 Hz, exposure to 0.2, 2 and 20 µg/ml of FE 200486 had no effect on resting membrane potential, maximum rate of depolarization, upstroke amplitude or action potential duration. These data indicate that plasma concentrations up to 20 µg/ml of FE 200486 are not expected to have direct effects on QRS complex duration or QT interval.

“In conscious and anaesthetized dogs, s.c. administration of a single dose up to 3 mg/kg (maximum dose tested) caused no significant adverse safety pharmacological effects on the cardiovascular and respiratory systems. Intravenous administration in conscious dogs of FE 200486 at 0.03-0.3 mg/kg had

no significant effect on the cardiovascular system, while 1 mg/kg produced a transient increase in blood pressure and heart rate, and 3 mg/kg caused a marked transient hypotension. In conscious cynomolgus monkeys cardiovascular parameters were largely unaffected by 3 consecutive daily s.c. doses of 20 mg/kg.”

3.3 PREVIOUS CLINICAL EXPERIENCE

Source: Summary of Clinical Safety (SCS), CTD 2.7.4 dated Feb 5, 2008

“In the Phase 2/3 degarelix studies for the one-month dosing regimen (n = 1256), most patients received doses of degarelix > 60 to 200 mg as the mean monthly dose (n = 875, 70%) for an exposure of 1514 person years. For patients receiving the recommended therapeutic dose of 240 mg (40 mg/ml) starting dose and 80 mg (20 mg/ml) maintenance dose, there were 171 patients exposed for at least one year. Including the greater maintenance dose of 160 mg (40 mg/ml), there have been 362 patients exposed for at least one year. In the one-month dosing regimen studies, 775 patients (62%) received degarelix for at least one year and 260 (21%) patients for at least two years.

“In the Phase 3 active control study, there were 19 deaths (10 or 2.4% for degarelix and 9 or 4.5% for leuprolide). The causes of death were similar among the treatment groups; most of the deaths were a result of cardiac disorders or due to malignancies. For the five deaths in degarelix 240 mg (40 mg/ml)/160 mg (40 mg/ml) group, the causes of death were prostate cancer, prostate cancer metastatic, cardiopulmonary failure, renal failure acute, and cardiac failure and bronchopneumonia. For the five deaths in degarelix, 240 mg (40 mg/ml)/80 mg (20 mg/ml) group, the causes of death were 2 cardiac arrests, myocardial infarction, bronchopneumonia, and gastric hemorrhage.

“The mortality rate estimate for degarelix in the Phase 2/3 uncontrolled studies for the one-month dosing regimen (40.3) and for the total degarelix group for all Phase 2/3 studies in the one-month dosing regimen (43.0) were slightly higher than that in the Phase 3 active control study (28.2) but still below the mortality estimate for leuprolide (50.7) (Table 24). The mortality estimate for the Phase 2/3 uncontrolled studies in the three-month dosing regimen was 37.5 (95% confidence interval 24.1; 55.9)

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Table 24 Mortality by Treatment Group in Phase 2/3 Studies One-Month Dosing Regimen

	Phase 3 Active Controlled		Phase 2/3 Uncontrolled	Total
	Degarelix	Leuprolide 7.5 mg	Degarelix	Degarelix
N	409	201	1090	1256
Number of Deaths	10	9	55	65
Crude Incidence of Mortality	2%	4%	5%	5%
Person Years Exposure	0.354	0.178	11.36	1.51
Mortality per 1000 Person Years Estimate	28.2	50.7	40.3	43.0
95% Confidence Interval	(13.5; 51.9)	(23.2; 96.2)	(30.4; 52.5)	(33.2; 54.8)

Test for homogeneity of mortality rates: $P=0.3945$ for Phase 3 active control study, $P=7498$ for Total degarelix vs leuprolide 7.5 mg.
Source: [Appendix Table 6.2.1.8], [Appendix Table 6.3.1.12], [Appendix Table 6.6.1.12]

“For the Phase 2/3 uncontrolled studies, ECG heart rate and intervals were measured locally. There were 6% (41/664) of patients who had a clinically significant change in the ECG, i.e. changed from normal or abnormal and not clinically significant at baseline to abnormal and clinically significant after treatment. Similarly, only 5% of patients in the three-month program had clinically significant changes in ECGs ([Appendix Table 11.5.1.1]), SCS).

“Very few patients (<1%) had ECG abnormalities reported as adverse events (Table 40, [Appendix Table 6.5.1.2]-SCS) in either the degarelix group overall or in the leuprolide group. There were no serious adverse events or discontinuations due to ECG QT or other interval changes ([Appendix Table 6.5.1.24] and [Appendix Table 6.5.1.27], SCS). There were two patients in the uncontrolled Phase 2/3 studies (Patient [2794C012, CS12, 5.3.5.2] and Patient [2795D017, CS12A, 5.3.5.2]) for the one month dosing regimen with serious adverse events of ventricular tachycardia (both patients had a cardiovascular history including one patient with a history of ventricular tachycardia). These events were not considered related to degarelix and the patients continued in the study. There was also a patient from a Phase 2 uncontrolled three-month dosing regimen study (Patient [3101C385, CS15, 5.3.5.2]) who developed ventricular fibrillation 4 days after his second dose of degarelix and died 4 days later; this event was not considered related to treatment. Another patient from the three-month dosing regimen (Patient [0703C680, CS15A, 5.3.5.2]), with a history of ischemic heart disease, hypertension, and chronic renal insufficiency, was administered one dose of 240 mg (40 mg/ml) and 4 doses of 240 mg (60 mg/ml) in CS15 and received 3 additional doses in CS15A. He was then switched to a higher dose of 480 mg (60 mg/ml). Two months later, the patient died (coded as sudden death); however, no information was available about causes of the death. His death was not considered related to study drug.

“In the Phase 3 active control study, the treatment groups were comparable in the incidence of serious adverse events (11% degarelix and 14% leuprolide). The most common serious adverse events were cardiac disorders (2% degarelix and 5% leuprolide) and renal and urinary disorders (2% degarelix and 3% leuprolide). Individual serious adverse events by preferred term were experienced by < 1% of patients in any treatment group. None of the serious adverse events were

considered related to study drug except for abnormal prostate examination experienced by one patient in the leuprolide group.

“In the Phase 2/3 one-month degarelix dosing studies, the incidence of serious adverse events of cardiac disorders was 4% and for renal and urinary disorders was 2% with the incidence of any particular serious adverse event of < 1%. The most occurrences for serious adverse events were urinary retention (n = 12), pneumonia (n = 11), myocardial infarction (n = 9), cerebrovascular accident (n = 9), and metastases to bone (n = 8). The incidence rate estimates for the degarelix treated patients for cardiovascular and cerebrovascular events were smaller and not significantly different compared to the respective background incidence rates in patients with GnRH therapy derived from the [Surveillance Epidemiology and End Results (SEER) 5.4] Medicare linked database.”

Reviewer's Comments: According to _____ analysis conducted for the sponsor with data from the Surveillance, Epidemiology and End Results (SEER)-Medicare linked database, the incidence of cardiovascular (including sudden cardiac death) and cerebrovascular events among men with prostate cancer on GnRH therapy was higher compared to the background incidence in the target population of prostate cancer patients. This cohort study consisted of 71,838 men.

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ECG changes and Cardiac adverse events in study FE200486CS 21 are discussed again in section 4.2.8.

3.4 CLINICAL PHARMACOLOGY

The major pharmacokinetic parameters are summarized in Table 2. Please refer to appendix 6.1 for additional pharmacokinetic parameters.

Table 2 Pharmacokinetic Parameters after Subcutaneous Administration of Degarelix 240 mg at a Concentration of 40 mg/ml

Pharmacokinetic parameter	FIRMAGON 240 mg
C _{max} (ng/mL)	53.4
T _{max} (days)	1.4
T _½ (days)	43
AUC (day-ng/mL)	1240

(Source: Table 2 in Section 12.3 Pharmacokinetics from the Label)

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT received and reviewed the following materials:

- Clinical Study Report FE 2000486 CS21
- Waveforms submitted to the ECG warehouse

4.2 QT ASSESSMENT

4.2.1 Title

An Open-label, Multi-Centre, Randomized, Parallel-group Study, Investigating the Efficacy and Safety of Degarelix One Month Dosing Regimens; 160 mg (40 mg/ml) and 80 mg (20mg/ml), in Comparison to LUPRON DEPOTR 7.5 mg in Patients with Prostate Cancer Requiring Androgen Ablation Therapy

4.2.2 Protocol Number

FE 200486 CS21

4.2.3 Study Dates

07 Feb 2006 to 08 Oct 2007

4.2.4 Objectives

4.2.4.1 Primary Objective

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

4.2.4.2 Secondary Objectives

- To compare serum levels of testosterone and PSA using a degarelix dosing regimen versus leuprolide 7.5 mg during the first 28 days of treatment
 - To compare the safety and tolerability using a degarelix dosing regimen versus leuprolide 7.5 mg
 - To compare testosterone, LH, FSH, and PSA response using a degarelix dosing regimen versus leuprolide 7.5 mg during the entire treatment period
-
- To evaluate the pharmacokinetics using a degarelix dosing regimen.
 - Changes in ECGs and vital signs were secondary endpoints.

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4.2.5 Study Description

4.2.5.1 Design

This was an open-label, Phase 3, three-arm, multi-centre (82 sites in 11 countries), stratified, randomized, controlled, parallel-group study to compare the efficacy and safety of degarelix with leuprolide 7.5 mg in patients with prostate cancer. The total duration of the study was 20 months.

4.2.6 Treatment Regimen

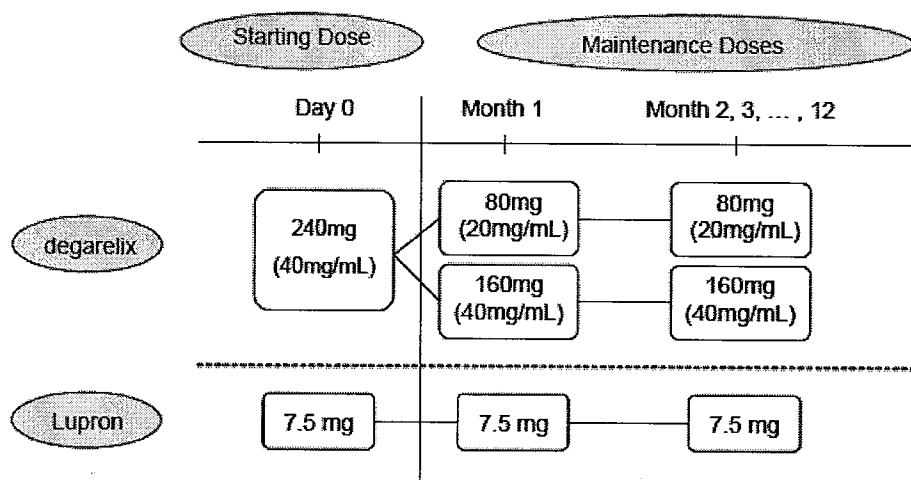
4.2.6.1 Treatment Arms

A total of 620 patients were randomized 1:1:1 to one of three treatment groups. Patients in two treatment groups received a degarelix starting dose of 240 mg at a concentration of

40 mg/ml (240@40) 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 either 80 mg at a concentration of 20 mg/ml (80@20: degarelix 240/80 mg group) or 160 mg at a concentration of 40 mg/ml (160@40: degarelix 240/160 mg group) administered s.c. every 28 days. In the third treatment group, patients received active treatment with leuprolide 7.5 mg on Day 0 and every 28 days administered as a single i.m. injection. For patients receiving treatment with leuprolide 7.5 mg, bicalutamide could be given as clinical flare protection at the Investigator's discretion.

Patients were stratified according to geographic region (Central and Eastern Europe, Western Europe and The Americas) and body weight (<90 kg and ≥90 kg).

Figure 1: Treatment Arms



Source: Sponsor's fig 5-1 from CSR for FE 200486 CS21

4.2.6.2 ECG and PK Assessments

A 12-lead electrocardiogram (ECG) was performed at Screening, Day 0, Day 3, Day 84 (± 7 days) and every 84 days (± 7 days) thereafter until the End of Study Visit. At Day 0 three separate ECGs were recorded. ECGs were performed before dosing, if a dosing visit was scheduled.

Blood samples to measure testosterone, PSA, LH, and FSH, were taken at Screening and before dosing (Day 0), and at Days 1, 3, 7 (± 2 days) and 14 (± 2 days) after the initial dose. Subsequent blood samples were taken on Day 28 (± 2 days), then once every 28 days (± 7 days) before dosing and at the End of Study Visit. Additional blood samples to measure testosterone levels were taken at Visit 15a (Visit 15 +3 days) and Visit 15b (Visit 15 +7 days), respectively.

For patients who received treatment with degarelix, blood samples to measure degarelix concentration were taken before dosing (Day 0), and at Days 1, 3, 7 (± 2 days) and 14 (± 2 days) after the initial dose. Subsequent blood samples to measure degarelix concentration were taken before dosing on Day 28 (± 2 days), Day 308 (± 7 days) and Day

336 (± 7 days). Blood samples for testing for the presence of anti-degarelix antibodies were taken before dosing on Day 0 and Day 168 (± 7 days) and at the End of Study Visit.

4.2.6.3 Baseline

Average of 3 consecutive ECGs on Day 0 (pre-dose) was used as baseline.

Reviewer's Comment: The sponsor does not specify if ECGs were collected at the same timepoint or over 3 time points in the protocol or study report.

4.2.7 ECG Collection

A 12-lead ECG was performed by site personnel at the time points indicated above. The ECGs were acquired digitally and the measurements were performed centrally by

The ECG measurements included heart beat, PR, QRS intervals, QT and QTc, T and U wave. For the baseline ECG assessment, three consecutive ECG measurements were recorded. In addition, each ECG measurement included three consecutive complexes. The Investigator evaluated the overall clinical significance of the ECG abnormalities. The overall clinical significance of the ECG abnormalities was also evaluated centrally at

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4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

- Eight hundred and seven patients were screened for entry into the study. Of these, 620 patients were randomized 1:1:1 into three treatment groups, degarelix 240/160 mg, degarelix 240/80 mg and leuprolide 7.5 mg. A total of 610 patients actually received study medication including 202, 207 and 201 patients in the degarelix 240/160 mg, degarelix 240/80 mg and leuprolide 7.5 mg treatment groups, respectively.
- Relevant inclusion criteria were adult patients with a histologically confirmed (Gleason graded) adenocarcinoma of the prostate (all stages), in whom androgen ablation treatment, except for neoadjuvant hormonal therapy, was indicated and a life expectancy of at-least 12 months.
- Relevant exclusion criteria were a marked baseline prolongation of QT/QTcF interval (e.g., repeated demonstration of a QTcF interval >450 ms), history of additional risk factors for Torsade de Pointes ventricular arrhythmias (e.g., heart failure, hypokalemia, family history of Long QT Syndrome) and use of concomitant medications¹ that may prolong the QT/QTcF interval.
- In total, 116 (19%) patients discontinued from the study: 43 (21%), 41 (20%) and 32 (16%) patients in the degarelix 240/160 mg, degarelix 240/80 mg and leuprolide 7.5 mg treatment groups, respectively. In total, there were reports for 27 patient's non-fatal adverse events which led to withdrawal. Eighteen patients died during treatment. Two patients who received treatment with degarelix were withdrawn due to lack of PSA suppression. The majority of patient withdrawals were for other reasons including 20 patients who withdrew consent.

4.2.8.2 Statistical Analyses

In total, 81 (20%) patients who received degarelix and 40 (19%) patients treated with leuprolide 7.5 mg had a post-baseline QTcF \geq 450 ms. A further 19 patients had QTcF \geq 480 ms: 12 (3%) in the pooled degarelix group and seven (4%) patients in the leuprolide 7.5 mg group. Only seven patients, three (<1%) in the pooled degarelix group and four (2%) patients in the leuprolide 7.5 mg group, had a markedly abnormal QTcF \geq 500 ms (Table 6). It is of note that cardiac repolarization has been shown to be slower and longer in castrated men and in women, compared to men with normal testosterone levels. Therefore, a greater increase in QTcF may be related to prolonged testosterone suppression.

At the end of the study the QTcF had increased by 10-13 ms from baseline. In comparison, on Day 3 when blood levels of study drug were relatively high, only small changes in QTcF (<5 ms) were reported. This also suggests that the increase in QTcF interval may be due to testosterone suppression rather than direct effects of the study drugs.

A significantly greater mean change in QRS axis from baseline for patients treated with leuprolide 7.5 mg (-0.731 degrees) compared to those treated with degarelix (-0.195 degrees) was also observed at End of Study ($p < 0.05$: Wilcoxon test). For all other ECG variables, mean changes from baseline to End of Study were not statistically significant between the treatment groups (Table 4 and Table 5).

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Table 3: Summary of QTcF Results (ms)-ITT Analysis set

	Degarelix							
	Degarelix 240/160 mg		Degarelix 240/80 mg		Total		LUFKON DEPOTS 7.5 mg	
	Abs Value	Change from BL	Abs Value	Change from BL	Abs Value	Change from BL	Abs Value	Change from BL
ITT analysis set	202		207		409		201	
Baseline								
N	202		207		409		201	
Mean	403		407		405		404	
SD	20.2		21.6		21.0		19.4	
Median	401		406		402		404	
Minimum	351		361		351		356	
Maximum	455		486		486		469	
Visit 3 (Day 1)								
N			1	1	1	1		
Mean			418	4.33	418	4.33		
SD								
Median			418	4.33	418	4.33		
Minimum			418	4.33	418	4.33		
Maximum			418	4.33	418	4.33		
Visit 4 (Day 3)								
N	195	195	204	204	399	399	197	197
Mean	404	1.02	411	3.65	407	2.36	405	0.836
SD	22.1	17.3	23.5	16.2	23.1	16.8	23.0	17.8
Median	403	-1.00	409	3.32	405	2.00	404	0.333
Minimum	361	-43.0	363	-44.3	361	-44.2	349	-69.7
Maximum	495	98.3	499	56.0	499	98.3	486	70.7
Visit 7 (Day 28)								
N	1	1	1	1	2	2	1	1
Mean	401	-3.00	398	27.0	400	12.0	353	-26.0
SD					2.12	21.2		
Median	401	-3.00	398	27.0	400	12.0	353	-26.0
Minimum	401	-3.00	398	27.0	398	-3.00	353	-26.0
Maximum	401	-3.00	398	27.0	401	27.0	353	-26.0
Visit 9 (Day 84)								
N	192	192	190	190	382	382	186	186
Mean	415	12.5	416	9.94	416	11.2	416	12.2
SD	20.9	16.4	23.5	19.7	22.2	15.1	23.2	19.8
Median	415	14.0	413	10.0	415	12.0	415	12.2
Minimum	351	-39.3	343	-76.3	343	-76.3	320	-61.7
Maximum	472	55.3	490	52.7	490	55.3	485	72.3
Visit 10 (Day 112)								
N							2	2
Mean							433	50.3
SD							24.7	29.2
Median							433	50.3
Minimum							415	29.7
Maximum							450	71.0

BL = Baseline

End of study = Last visit with available data

FE200486/PROSTATE/CB21/06DEC2007- ECG.3AS

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	Degarelix							
	Degarelix 240/160 mg		Degarelix 240/80 mg		Total		LUPRON DEPOT® 7.5 mg	
	Abs Value	Change from BL	Abs Value	Change from BL	Abs Value	Change from BL	Abs Value	Change from BL
Visit 12 (Day 168)								
N	184	184	184	184	368	368	184	184
Mean	416	13.1	419	13.5	417	13.3	420	16.1
SD	22.7	19.0	24.1	21.7	23.4	20.4	23.9	20.0
Median	414	13.0	418	15.0	416	13.8	419	13.8
Minimum	351	-87.0	353	-58.3	351	-87.0	351	-34.3
Maximum	472	64.3	530	105	530	105	503	89.0
Visit 15 (Day 252)								
N	175	175	176	176	351	351	180	180
Mean	418	15.2	415	8.97	416	12.1	420	15.5
SD	24.5	20.3	24.3	22.0	24.4	21.4	22.7	19.7
Median	417	15.7	412	9.00	415	13.0	418	14.8
Minimum	349	-52.0	363	-75.7	349	-75.7	365	-70.7
Maximum	497	74.3	543	102	543	102	506	70.7
Visit 18 (Day 336)								
N	165	165	169	169	334	334	169	169
Mean	418	15.1	422	16.0	420	15.6	419	15.0
SD	23.2	19.7	20.8	18.4	22.1	19.0	24.5	19.0
Median	414	16.0	420	18.0	418	16.3	417	14.7
Minimum	362	-78.0	374	-36.0	362	-78.0	344	-38.3
Maximum	502	98.7	521	80.0	521	98.7	516	83.7
End of study (Day 364)								
N	161	161	166	166	327	327	168	168
Mean	414	11.6	421	14.7	418	13.1	419	15.2
SD	20.6	16.1	22.1	19.2	21.6	17.8	23.1	20.7
Median	413	11.7	420	14.7	417	12.7	419	17.8
Minimum	358	-27.0	353	-47.7	353	-47.7	351	-63.3
Maximum	483	64.7	536	95.0	536	95.0	511	95.0
End of Study								
N	202	202	207	207	409	409	201	201
Mean	415	11.5	420	13.1	417	12.3	419	14.3
SD	21.7	17.0	22.3	18.9	22.2	18.0	23.3	20.8
Median	413	11.2	420	12.3	417	12.0	418	16.7
Minimum	358	-38.7	353	-47.7	353	-47.7	351	-63.3
Maximum	483	74.3	536	95.0	536	95.0	511	95.0
Mean % Change		2.83		3.21		3.02		3.50

BL = Baseline

End of study = Last visit with available data

FE200486/PROSTATE/CS21/06DEC2007- ECG.SAS

Source: Sponsor's Table 123 from the CSR for FE200486CS21.

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Table 4: Change in ECG Variables From Baseline to Day 3-ITT Analysis Set

	Treatment Group			
	Degarelix 240/160 mg	Degarelix 240/80 mg	Total	Leuprolide 7.5 mg
ITT analysis set	202	207	409	201
PR interval (msec)				
Mean baseline	177	176	176	172
Mean change	-2.98	-2.64	-3.22	-0.650
Mean % change	-1.98%	-2.00%	-1.99%	-0.623%
QRS interval (msec)				
Mean baseline	95.4	96.7	96.1	95.0
Mean change	-0.244	0.493	0.133	1.47
Mean % change	-0.726%	0.188%	-0.260%	1.35%
QRS axis (degrees)				
Mean baseline	10.4	9.50	9.94	7.40
Mean change (*)	-1.26	1.21	-0.044	0.474
Mean % change	-8.16%	0.117%	-4.13%	-11.1%
Uncorrected QT interval (msec)				
Mean baseline	386	397	392	391
Mean change	1.19	1.88	1.54	0.107
Mean % change	0.309%	0.469%	0.391%	-0.010%
Corrected QT using Bazett (msec)				
Mean baseline	412	413	412	412
Mean change (*)	0.914	4.50	2.75	1.11
Mean % change	0.197%	1.07%	0.641%	0.228%
Corrected QT using Fridericia (msec)				
Mean baseline	403	407	405	404
Mean change	1.02	3.65	2.36	0.836
Mean % change	0.230%	0.875%	0.559%	0.162%
Corrected QT using Sagie (msec)				
Mean baseline	404	407	405	404
Mean change	1.06	3.76	2.44	0.981
Mean % change	0.238%	0.903%	0.578%	0.203%
RR interval (msec)				
Mean baseline	857	937	913	914
Mean change	0.500	-12.3	-5.89	-5.93
Mean % change	0.164%	-1.24%	-0.555%	-0.564%
Ventricular rate (Beats/min)				
Mean baseline	69.9	65.9	67.8	67.5
Mean change	-0.343	0.679	0.180	0.253
Mean % change	-0.301%	1.12%	0.424%	0.465%

A "*" indicates significance ($p < 0.05$) between degarelix (total) versus leuprolide 7.5 mg, based on Wilcoxon test

Data source: FE200486/FROSTATE/CS21/06DEC2007 — ECG_CHG_D3.SAS (Table 118)

Source: Sponsor's Table 10-17 from the CSR for FE200486CS21.

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Table 5: Change from baseline in ECG variables at end of study - ITT analysis set

	Degarelix		Total	LUPRON DEPOT® 7.5 mg
	Degarelix 240/160 mg	Degarelix 240/80 mg		
ITT analysis set	202	207	409	201
PR interval (msec)				
Mean baseline	177	176	177	172
Mean change	-3.22	-3.29	-3.26	-2.56
Mean % change	-1.93%	-1.93%	-1.93%	-1.86%
QRS interval (msec)				
Mean baseline	95.9	96.7	96.3	95.0
Mean change	0.499	1.59	1.05	1.77
Mean % change	0.502%	1.67%	1.09%	1.51%
QRS axis (degrees)				
Mean baseline	10.1	9.12	9.60	7.66
Mean change (*)	-2.50	2.05	-0.195	-0.731
Mean % change	-7.43%	4.53%	-1.55%	-4.59%
Uncorrected QT interval (msec)				
Mean baseline	386	398	392	391
Mean change	9.57	8.14	8.85	12.1
Mean % change	2.50%	1.99%	2.24%	3.04%
Corrected QT using Bazett (msec)				
Mean baseline	412	413	413	412
Mean change	10.7	13.6	12.1	13.4
Mean % change	2.56%	3.29%	2.93%	3.21%
Corrected QT using Fridericia (msec)				
Mean baseline	403	407	405	404
Mean change	10.3	11.7	11.0	13.0
Mean % change	2.54%	2.86%	2.70%	3.17%
Corrected QT using Sagie (msec)				
Mean baseline	404	407	405	404
Mean change	9.89	11.6	10.8	12.7
Mean % change	2.43%	2.84%	2.64%	3.10%
RR interval (msec)				
Mean baseline	886	938	912	914
Mean change	-2.14	-22.2	-12.2	-3.32
Mean % change	-0.175%	-2.55%	-1.38%	-0.397%
Ventricular rate (Beats/min)				
Mean baseline	70.0	65.8	67.9	67.5
Mean change	-0.012	1.76	0.884	0.223
Mean % change	0.090%	2.53%	1.32%	0.264%

End of study = Last visit with available data

A '*' indicates significance (p<0.05) between treatment groups based on Wilcoxon test

FE200486/PROSTATE/CS21/06DEC2007 ECG_CHG_EOS.SAS

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Source: Sponsor's Table 119 from the CSR for FE200486CS21.

**Table 6: Incidence of patients with abnormal ECG variables compared to baseline:
ITT dataset**

	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		
Corrected QT using Bazett (msec)												
>=450	198	80	(40%)	198	65	(33%)	396	145	(37%)	195	70	(36%)
>=480	198	16	(8%)	198	11	(6%)	396	27	(7%)	195	15	(8%)
>=500	198	2	(1%)	198	2	(1%)	396	4	(1%)	195	5	(3%)
Corrected QT using Fridericia (msec)												
>=450	202	37	(18%)	204	44	(22%)	406	81	(20%)	200	40	(20%)
>=480	202	7	(3%)	204	5	(2%)	406	12	(3%)	200	7	(4%)
>=500	202	1	(<1%)	204	2	(<1%)	406	3	(<1%)	200	4	(2%)
Corrected QT using Sagie (msec)												
>=450	202	37	(18%)	205	43	(21%)	407	80	(20%)	200	38	(19%)
>=480	202	7	(3%)	205	4	(2%)	407	11	(3%)	200	6	(3%)
>=500	202	1	(<1%)	205	2	(<1%)	407	3	(<1%)	200	2	(1%)
PR interval (msec)												
>=220	175	10	(6%)	180	12	(7%)	355	22	(6%)	186	16	(9%)
QRS interval (msec)												
>=120	187	10	(5%)	191	12	(6%)	378	22	(6%)	185	15	(8%)
Ventricular rate (Beats/min)												
<= 50 and decrease of >= 15 from baseline	202	4	(2%)	207	6	(3%)	409	10	(2%)	201	9	(4%)
>= 120 and increase of >= 15 from baseline	202	1	(<1%)	207			409	1	(<1%)	201	1	(<1%)
N = Number of patients with normal value at baseline and with at least one post-baseline value recorded												
n = Number of patients with normal baseline and post-baseline markedly abnormal value												
% = n/N x 100												
A Fridericia's corrected QT value (QTcF) >= 500 msec is considered a markedly abnormal value												
Data source: FE200486/PROSTATE/CS21/06DEC2007- ECG_ABN.SAS (Table 122)												

b(4)

Source: Sponsor's Table 10-18 from the CSR for FE200486CS21.

Reviewer's Comment: Only absolute values for categoricals were reported, changes in QT interval > 30 ms or > 60 ms were not reported by the sponsor.

4.2.8.3 Safety Analysis

Nineteen patients died during the course of the study, as a result of 21 treatment-emergent SAEs, with relatively equal incidence across treatment groups; ten (2%) patients receiving the degarelix and nine (4%) patients receiving leuprolide. There were no marked trends. No AEs leading to deaths in this study were related to study drug.

One patient, included within the nineteen patient deaths, died post-study: Patient 42065174(degarelix 240/160 mg group) was hospitalized due to metastatic prostate cancer, and was withdrawn from the study due to this SAE. He died the following day.

As discussed earlier, For the five deaths in degarelix 240 mg (40 mg/ml)/160 mg (40 mg/ml) group, the causes of death were prostate cancer, prostate cancer metastatic, cardiopulmonary failure, renal failure acute, and cardiac failure and bronchopneumonia. For the five deaths in degarelix, 240 mg (40 mg/ml)/80 mg (20 mg/ml) group, the causes of death were 2 cardiac arrests, myocardial infarction, bronchopneumonia, and gastric hemorrhage.

There were reports for a total of 73 patients with treatment-emergent SAEs during the study, with relatively equal incidence across treatment groups. There were no marked SAE trends in the ITT analysis set. In total, there were 45 (11%) degarelix-treated patients with AEs that were considered by the Investigator to be SAEs: 24 (12%) patients in the degarelix 240/160 mg group, 21 (10%) patients in the degarelix 240/80 mg group, compared with 28 (14%) patients in the leuprolide 7.5 mg group.

For SAEs, the common SOC were as expected for this elderly group of prostate cancer patients: Cardiac Disorders, in 2% degarelix-treated patients and 5% leuprolide 7.5 mg patients, respectively; Renal and Urinary Disorders, in 2% and 3% patients, respectively; Neoplasms in 2% and 2% patients, respectively; Infections and Infestations, in 2% and <1% patients, respectively. All other SOC were reported by < 2% patients.

The ten degarelix patients with SAEs classed as Cardiac Disorders included three patients with myocardial infarction/acute myocardial infarction/acute coronary syndrome and two patients with cardiac arrest, with the other cardiac disorders being reported as individual events in five different patients (unstable angina, bradycardia, cardiac failure, cardiopulmonary failure, and coronary artery disease).

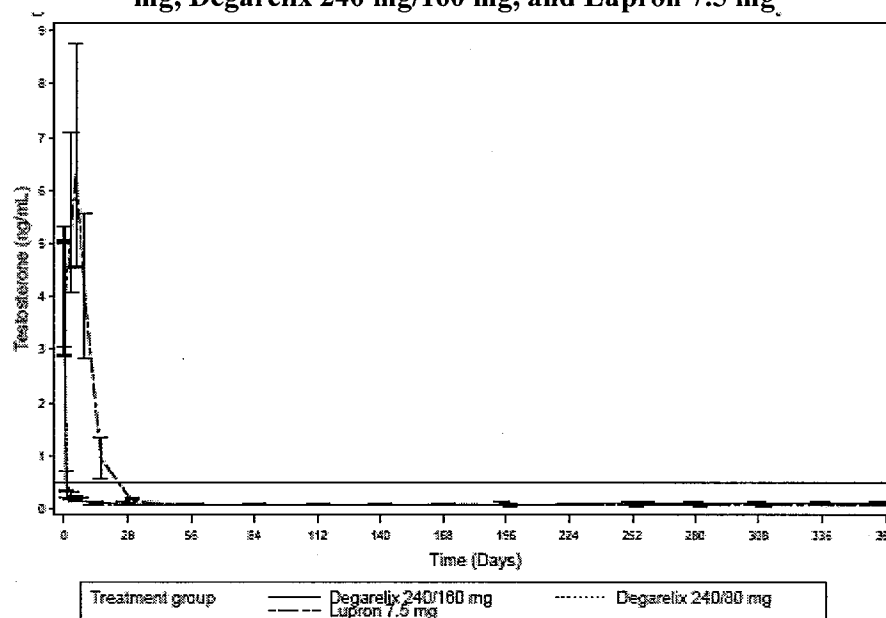
None of the degarelix patients with QTcF \geq 500 ms had outcomes of syncope, torsade de pointes, ventricular fibrillation, or sudden death. There was one leuprolide patient (Patient [01771163, CS21, 5.3.5.1]) with had a cardiovascular history, who reported syncope and cardiac arrhythmia 20 days after a QTc measurement of 503 ms. 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 leuprolide. The patient continued in the study.

5 REVIEWERS' ASSESSMENT

5.1 CLINICAL PHARMACOLOGY ASSESSMENTS

There appears to be a lag time between the time to the maximum concentration of degarelix (T_{max}) and QT prolongation. The highest concentration of degarelix is reached in 1 day (mean) after the first dose of degarelix 240 mg (Source: P109 Clinical Study Report CS-21, Section 9.2.6). Given the half-life of 43 days (Table 2) and a dosing interval of 28 days, the peak concentration in the maintenance phase (80 mg) should be less than or approximately equal to the first peak concentration (with the accumulation factor of 2.7). However, it appears that there is no major change in QT interval on Day 3. Remarkable (11-15 ms) change in mean QT interval is seen after Day 84 post degarelix treatment. Therefore, it is possible that QT prolongation is not directly linked to plasma degarelix concentration. However, adequate ECG observation is necessary between Day 3 to Day 84 in order to fully understand the potential relationship between the QT prolongation and plasma degarelix concentration.

Figure 2 Median Testosterone Levels from Day 0 to 364 for Degarelix 240 mg / 80 mg, Degarelix 240 mg/160 mg, and Lupron 7.5 mg



b(4)

Data source: FE200486/PROSTATE/CS21/12/7/2007 (Figure 11.1.1)

(Source: Figure 9-6, P-94 Clinical Study Report for CS-21, section 9.2.1.6)

Whether the QT prolongation is directly associated with the reduction of plasma testosterone level is unclear based on current data. Plasma testosterone level is reduced by 10-fold following long term therapy of degarelix (240 mg / 80 mg). As shown in Figure 2, the mean baseline plasma testosterone level is above 5 ng/ml. After 1-2 weeks of degarelix treatment, the testosterone level is suppressed well below the castration level of 0.5 ng/ml and is maintained thereafter. Because the only ECG monitoring in patients with adequate sample size was conducted after Day 84 post dose and no adequate ECG observations were obtained between Day 7 to Day 84, with only 1-2 observations on Day 28), it is difficult to establish the direct link between plasma testosterone level and QT interval change.

Reviewer's Comments: In the current trial, the sponsor had ECG observations in only 1-2 subjects between Day 3 and Day 84 (not inclusive) after degarelix treatment. Based on current observations, we are uncertain about whether the QT prolongation is directly associated with the plasma testosterone level. Additional ECG monitoring between Day 3 and Day 84 is useful to further determine or rule out the existence of plasma degarelix concentration and QT prolongation relationship.

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5.2 CLINICAL ASSESSMENTS

5.2.1 Safety Assessments

QTcF > 500 ms was reported on 3 (<1%) patients who had received degarelix. These patients did not experience clinically important adverse events per the ICH E14 guidelines.

On review of the narratives for deaths, SAEs and other significant AEs, the two cases of death due to cardiac arrest in the degarelix group had no reported QT prolongation. There were no reports of seizures. Syncopal episodes were not associated with any reports of QT prolongation. Ventricular fibrillation was reported in the setting of an acute MI. It is hard to come to definitive conclusions regarding these events since there is significant confounding due to patient co-morbidities and lack of ECG reports immediately prior to event.

5.2.2 ECG Acquisition and Interpretation

Waveforms submitted to the ECG warehouse were reviewed:

- Similar to other studies read by the — ECG core-lab baseline and on-treatment QT measurements were not based on the same lead but were read on the lead with the longest QT interval per the — algorithm.
- Several patients had some baseline ECG abnormalities.
- On review of a subset of the ECGs it appears that they were read in the most optimal lead.
- QT analysis scores could not be computed possibly because consecutive waveforms were not annotated all the time.
- However since this is an ECG assessment in patients with co-morbidities with no positive control, we are not going to exclude effects less than 10 ms. These ECGs appears adequate to detect large effects.

b(4)

5.2.3 PR and QRS Interpretation

According to the sponsors analysis (Table 4 and Table 5) there were no significant effects on the PR and QRS intervals. The reported change in the QRS axis is not clinically significant (absolute values remain between -30 to 90 degrees).

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6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Highlights of Clinical Pharmacology submitted by Sponsor

Therapeutic dose	Include maximum proposed clinical dosing regimen. Starting dose 240@40 Maintenance dose: 80@20 every 28 days starting after 28 days	
Maximum tolerated dose	Include if studied or NOAEL dose NOAEL: 50 mg/kg [2.6.6.1.9] in monkeys A maximum tolerated dose has not been established in humans.	
Principal adverse events	Include most common adverse events; dose limiting adverse events Most common AEs >5% Injection site adverse events*, Weight increase, Fatigue, Chills, Hypertension, Back Pain, Arthralgia, Urinary tract infection, Constipation (*injection site pain, injections site erythema, injection site swelling) Dose limiting: None identified	
Maximum dose tested	Single Dose	Specify dose 240@40 (s.c.), i.e. 240 mg at dose concentration 40 mg/ml [CS21] 30 ug/kg (i.v.) [CS05]
	Multiple Dose	Specify dosing interval and duration 160@40 every 28 days for 1 year [CS21]
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC 240@40 Cmax: 66 ng/ml (3.8) [CS21] 240@40 AUC: 1318 days*ng/ml (1.9) [pop PK phase 3] 30 ug/kg i.v. Cmax: 160 ng/ml (5.7) [CS05]
	Multiple Dose	Mean (%CV) Cmax and AUC [pop PK phase 3] 80@20 Cmax: 74 ng/ml (1.6) 160@40 Cmax: 61 ng/ml (2.1) 80@20 AUC _{day 336-364} : 703 days*ng/ml (1.8) 160@40 AUC _{day 336-364} : 1092 days*ng/ml (1.8)
Range of linear PK	Specify dosing regimen i.v.: 6-30 ug/kg (mean Cmax 38-160 ng/ml) [CS05] S.c.: Not formally studied but population PK suggest that linearity is valid within the same dose concentration for doses 160-240 mg at 40 mg/ml at least [pop PK phase 3]. At dosing concentration 60 mg/ml linearity is valid up to 480 mg ——— For ——— material linearity is valid for 80-120@20 and 80-240@40 at least.	
Accumulation at steady state	Mean (%CV); specify dosing regimen 80@20: Ratio between 28 day AUC after single dose and at steady state: 1.6 (0.9) [pop PK phase 3]	
Metabolites	Include listing of all metabolites and activity No active metabolites.	
Absorption	Absolute/Relative Bioavailability	Mean (%CV): 240@40: 36 (5) % [pop PK phase 3] 80@20: 58 (21) % [pop PK phase 3]
	Tmax	<ul style="list-style-type: none"> Median (range) for parent: 1 (0.6-7) days [CS21] Median (range) for metabolites:
Distribution	Vd/F or Vd	Mean (%CV)

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Elimination		Vd: 0.61 L/kg (9.4) [CS05, 15 ug/kg]
	% bound	Mean (%CV) 90.0 (0.4) [CS05, Appendix A13]
	Route	<ul style="list-style-type: none"> Primary route; percent dose eliminated Hepatic elimination: 70-80% Other routes Renal excretion, 20-30 %
	Terminal t _{1/2}	<ul style="list-style-type: none"> Mean (%CV) for parent: [Pop PK phase 3] 240@40: 46 days (1.9) 80@20: 30 days (1.8) Mean (%CV) for metabolites:
	CL/F or CL	Mean (%CV) CL: 50 ml/h/kg (9.0) [CS05, 15 ug/kg]
Intrinsic Factors	Age	Specify mean changes in C _{max} and AUC [pop PK phase 3] Increase for a 90 year old subject compared to median age in CS21 (71 years of age): C _{max} : 5 ng/ml increase AUC: 75 days*ng/ml increase
	Sex	Specify mean changes in C _{max} and AUC NA
	Race	Specify mean changes in C _{max} and AUC Not specifically studied
	Hepatic & Renal Impairment	Specify mean changes in C _{max} and AUC [pop PK phase 3] Severe renal impairment: C _{max} 13 ng/ml increase AUC 189 days*ng/ml increase Mild-moderate hepatic impairment: No increase [CS23]
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in C _{max} and AUC No effect on cytochrome P450 activity has been observed and thus no DDI studies were considered necessary.
	Food Effects	Specify mean changes in C _{max} and AUC and meal type (i.e., high-fat, standard, low-fat) NA
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in C _{max} and AUC. The increase in exposure should be covered by the supra-therapeutic dose. [pop PK phase 3] Worst case subject: 50 kg, 90 years old with no renal function (Renal CL is set to 30% of total CL): C _{max} increase at steady state of clinical dosing: 1.5 fold (Covered by 30 ug/kg i.v., CS05) AUC increase at steady state of clinical dosing: 1.7 fold (10% higher than 160@40)	

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6.2 TABLE OF STUDY ASSESSMENTS

Visit	1 ^a	2	3	4	5	6	7	8	9	10	11	12	13	14	15	15a	15b	16	17	18	End of Study ^e
Day	Max. 21 days prior to Visit 2	0	1	3	7 ±2 d	14 ±2 d	28 ±2 d	56 ±7 d	84 ±7 d	112 ±7 d	140 ±7 d	168 ±7 d	196 ±7 d	224 ±7 d	252 ±7 d	V15 ±3 d	V15 ±7 d	280 ±7 d	308 ±7 d	336 ±7 d	364 ±7 d
Informed consent	x ^b																				
Inclusion/ exclusion criteria	x																				
Demographics	x																				
Medical history	x																				
Alcohol and smoking	x																				
Body weight	x																				
Height	x																				x
History/stage/ histology of PC ^c	x																				
ECOG	x																				
Physical examination	x	x							x			x			x					x	x
12-lead ECG ^d	x	x		x					x			x			x					x	x
Vital signs ^e	x	x						x	x	x	x	x	x	x	x				x	x	x
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Randomisation		x																			
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Quality of Life Questionnaire		x																			
Hot flashes ^f		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Clinical observation ^g		x																			
Blood sampling ^h		x																			
- Clinical chemistry	x	x ⁱ						x	x	x	x	x	x	x	x						x ^j
- Haematology	x	x ⁱ						x	x	x	x	x	x	x	x						x ^j
- Testosterone / PSA/LH/FSH	x	x ⁱ	x	x	x	x	x	x	x	x	x	x	x	x	x	x ^k	x ^k	x	x	x	x ^k
- Degarelix ^l		x ^l	x	x	x	x	x														
- Degarelix antibodies ^m		x ^l																			
Urinalysis ⁿ	x	x						x	x	x	x	x	x	x	x						x ^o
Administration of study drug	x	x						x	x	x	x	x	x	x	x						
MRI scan (sub study only)		x					x ^p														x ^q

a) Visit 1 was the Screening Visit

b) Degarelix groups only

c) Patients were called in for the End of Study Visit after 364 days of treatment. Patients, who were withdrawn from the study prematurely, were called in for the End of Study Visit as soon as possible after the decision to withdraw had been taken.

d) Written informed consent was obtained before any study-related procedure was performed.

e) Stage of prostate cancer was based on the most recent digital rectal examination and bone scan. The bone scan and a current T staging had to be within the last 12 weeks before treatment start.

f) ECG, vital signs, urine and blood sampling were performed before dosing, if a dosing visit was scheduled.

g) If taken within 4 days before the End of Study Visit, new sampling did not need to be repeated.

h) A hot flashes questionnaire was completed at Day 0, and every day until day End of Study (USA, Canada, Germany, Netherlands, UK, Czech Republic, and Hungary).

i) The patient was observed clinically for at least 1 hour after each dosing. During the observation period diastolic and systolic blood pressure (mmHg) and pulse (beats/minutes) were measured at 5, 10, 30 and 60 minutes after dosing.

j) Only samples for testosterone were taken at Visits 15a and 15b.

k) If Digital Rectal Examination was performed on Day 0, blood samples had to be drawn before the Digital Rectal Examination.

l) At Visit 7 (Day 28) a visit window of ±4 days was allowed in relation to the actual study visit.

m) At Visit 13 (Day 196) and End of Study Visit a window of ±10 days was allowed in relation to the actual study visit.

Source: Sponsor's table 5-4 (Study Flow of Scheduled Assessments) from CSR page 39

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