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*APPLICATION NUMBER:*

**22-201**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

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## Clinical Pharmacology Review

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<b>NDA</b>	22-201
<b>Submission Date:</b>	14 February 2008
<b>Proposed Brand Name:</b>	FIRMAGON®
<b>Generic Name:</b>	degarelix
<b>Formulation:</b>	80 mg and 120 mg injectable
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<b>ORM Division:</b>	Division of Drug Oncology Products
<b>Sponsor:</b>	Ferring
<b>Submission Type; Code:</b>	Original NDA; 000
<b>Dosing regimen:</b>	Loading dose of 240 mg followed by monthly (Q28 Day) maintenance doses of 80 mg.
<b>Indication:</b>	Treatment of patients with prostate cancer

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OCP Briefing held on October 23, 2008 attended by: Jeanne Fourie, Lillian Zhang, Gene Williams, Ramana Uppoor, Young-Moon Choi, Qi Liu, Sophia Abraham, Pengfei Song, Sandhya Apparaju, Young-Jin Moon, Shiew-Mei Huang, Jun Yang, Jain Wang, Brian Booth, Atik Rahman, Joga Gobburu, Bahru Habtemariam, Larry Lesko, Mike Pacanowski, Sarah Schrieber, Hae-Young Ahn, Gil Burckart, Aakanksha Khandelwal, Joe Grillo, & Christoffer Tornoe

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## 1 EXECUTIVE SUMMARY

Degarelix is a gonadotropin releasing hormone antagonist. The current submission is the original NDA for degarelix for the treatment of patients with prostate cancer. \_\_\_\_\_

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To support the approval in prostate cancer, the sponsor conducted three phase 2 and one phase 3 study. Patients in the phase 2 studies were randomized to receive various loading doses (40 to 240 mg) followed by various maintenance doses (20 to 160 mg) of degarelix. Testosterone response rate  $\leq 0.5$  ng/mL was the primary endpoint for all the phase 2 trials. The results from these studies were used to identify a dose which maintained testosterone castration from Day 28 through Day 364 to investigate in phase 3 trials.

In the phase 3 study, patients were randomly assigned to receive degarelix or leuprolide. Two degarelix doses were studied. Both degarelix arms used the 240 mg (40 mg/mL) loading dose and patients received either a 80 mg (20 mg/mL) or 160 mg (40 mg/mL) maintenance dose. Results indicate that the probability of maintaining testosterone levels (T)  $\leq 0.5$  ng/mL from Day 28 through Day 364 was 97% for the 80 mg maintenance dose group and 98.3% for the 160 mg maintenance dose group (both groups received 240 mg loading doses). In addition, for both degarelix dosing groups, the 95% confidence intervals for the cumulative probability of T  $\leq 0.5$  ng/mL from Day 28 to Day 364 were  $> 90\%$  which fits the efficacy criterion pre-specified by the Agency.

Based on the in-vitro studies there are no suspected CYP450 or p-glycoprotein based drug-drug interactions with degarelix. There were no significant degarelix metabolites detected in plasma after subcutaneous administration. There will be no drug-drug interaction information reported in the label.

A study in patients with mild and moderate hepatic impairment was conducted and indicated that patients with hepatic impairment obtained exposures lower than that seen in patients with normal hepatic function. However, this exposure difference was not significant enough to warrant a contraindication or dose modification.

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## 1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 5 has reviewed the information contained in NDA 22-201. This NDA is considered acceptable from a clinical pharmacology perspective.

### Phase IV commitments

None.

### Labeling Recommendations

Please refer to Section 3 - Detailed Labeling Recommendations

### Signatures

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## 1.2 CLINICAL PHARMACOLOGY SUMMARY

Degarelix is a selective GnRH receptor antagonist (blocker) that competitively and reversibly binds to the pituitary GnRH receptors and is being developed for use in patients with prostate cancer

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The applicant has conducted seven phase 1 studies in healthy volunteers and patients with prostate cancer to evaluate the safety, pharmacokinetics and pharmacodynamics of degarelix in order to establish a dose that maintains castrate levels of testosterone. In these early studies, much like what was seen in early preclinical studies, differences in pharmacokinetic profiles for the same dose at different concentrations were seen, and therefore multiple doses (mg) and injection concentrations (mg/mL) were studied in the clinical development of degarelix. In addition during an EOP2a meeting held in 2005 it was suggested by the pharmacometrics group that a target trough level > 9-10 ng/mL of degarelix would result in maintenance of testosterone castration in >90% of subjects. These assumptions were all used to guide dose finding for phase 3 evaluation. The sponsor intends to market a 240 mg (40 mg/mL) loading dose with 80 mg (20 mg/mL) maintenance doses.

Degarelix is given as a subcutaneous injection. After injection a depot is formed, from which degarelix is slowly released into the circulation. The formation of this depot allows for once monthly (every 28 days) administration. Results from the dose finding studies established a need for a loading dose to be given for each patient beginning degarelix. Following administration of a 240 mg (40 mg/mL) loading dose, C<sub>max</sub> is reached after 1.4 days and concentrations slowly decreased in a biphasic manner with a median terminal half-life of approximately 43 days. The pharmacokinetics of degarelix are proportional over the dose range of 120-240 mg at a concentration of 40 mg/mL. There are no significant differences between the pharmacokinetics in healthy volunteers and patients.

No radiolabeled mass-balance study was conducted, however analysis of urine collections from multiple studies indicate that approximately 20% of degarelix is excreted in the urine. Peptide fragments of degarelix were mainly excreted in the feces. *In vitro* studies suggest that degarelix is not a substrate, inhibitor or inducer of the cytochrome P450 enzyme system or p-glycoprotein. No drug-drug interaction studies were conducted but based on *in vitro* studies no *in vivo* interaction studies were requested.

A study in patients with mild or moderate hepatic impairment was conducted using an IV formulation of degarelix. Compared to their healthy counterparts, the exposures in patients with hepatic impairment were on average 16 to 30% lower. Testosterone concentrations in the patients with hepatic impairment were similar to those in healthy volunteers, therefore the clinical implications of the lower degarelix exposures should not be significant. As with all patients, testosterone levels should be monitored in patients with mild and moderate hepatic impairment and if efficacy is compromised the patient should stop taking degarelix.

The pharmacometric review suggests no impact of age, body weight, race, or renal function on degarelix trough levels or testosterone concentrations.

## 2 QUESTION BASED REVIEW

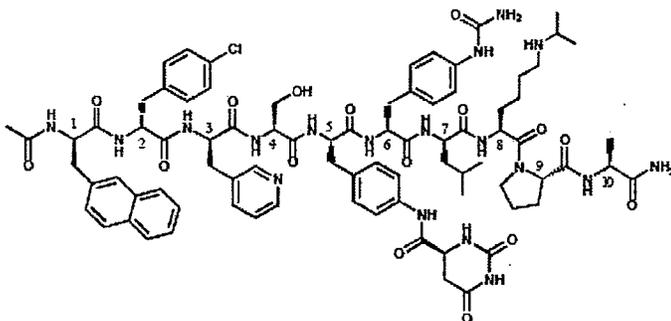
### 2.1 GENERAL ATTRIBUTES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

#### Physico-chemical properties

1. Structural formula:

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2. Established name: degarelix

3. Molecular Weight: 1632.3 g/mol

4. Molecular Formula:  $C_{82}H_{103}N_{18}O_{16}Cl$

5. Chemical Name: 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

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Degarelix is a selective GnRH receptor antagonist (blocker) that competitively and reversibly binds to the pituitary GnRH receptors, thereby rapidly reducing the release of gonadotrophins and consequently testosterone.

2.1.3 What are the proposed dosage and route of administration?

The recommending dose of degarelix is a 240 mg loading dose (given as two injections of 120 mg) followed one month later by 80 mg monthly maintenance doses. Degarelix is given as a subcutaneous injection in the abdominal region. The injection site should vary periodically. Injections should be given in areas where the patient will not be exposed to pressure, e.g. not close to waistband/belt or not close to the ribs.

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## 2.2 GENERAL CLINICAL PHARMACOLOGY

### 2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Four studies in non-prostate cancer subjects and eight studies in patients with prostate cancer were completed to support the NDA. Below in TABLE 1 is the list of studies in non-cancer patients and TABLE 2 & TABLE 3 contain the studies in patients with prostate cancer.

TABLE 1. Studies supporting the clinical pharmacology of degarelix in non-cancer patients.

Study	Design	Doses	number enrolled
CS01	single dose, randomized, placebo controlled, double-blind, dose escalation in men aged 19-69 years.	0.5 mg (5 mg/mL), 2 mg (5 mg/mL), 5 mg (10 mg/mL), 10 mg (10 mg/mL), 20 mg (20 mg/mL), 40 mg (20 mg/mL), 40 mg (10 mg/mL), 40 mg (20 mg/mL), 30 mg (15 mg/mL), 30 mg (30 mg/mL)	6 subjects at each dose.
CS05	single dose, open-label, dose escalation in men aged 19-46 years.	1.5, 6, 15, or 30 µg/kg IV over 15 or 45 min. 20 mg (5 mg/mL) SC 20 mg (5 mg/mL) IM	6 subjects at each dose
CS08	single dose, open-label, randomized, placebo-controlled, dose-response, in elderly subjects (≥ 65 years)	0.864, 1.73, 3.70, 9.87, 24.7 or 49.4 µg/kg IV over 48 hours	48
CS23	single dose, open-label, parallel study in patients with mild or moderate hepatic impairment and healthy subjects	1 mg IV over 1-hour	24

TABLE 2. Studies supporting the clinical pharmacology of degarelix in patients with prostate cancer.

Study	Design	Doses	Number of subjects
CS06	single dose, open-label, dose escalation	40 mg (10 mg/mL), 80 mg (20 mg/mL), 120 mg (30 mg/mL), 160 mg (40 mg/mL)	82
CS07	single dose, open-label, dose escalation	120 mg (20 mg/mL), 120 mg (40 mg/mL), 160 mg (40 mg/mL), 200 mg (40 mg/mL), 200 (60 mg/mL), 240 mg (40 mg/mL), 240 mg (60 mg/mL), 320 mg (60 mg/mL)	172
CS11	single-dose, open-label, dose escalation study in Japanese subjects	160 mg (40 mg/mL), 200 mg (40 mg/mL), 240 mg (40 mg/mL)	18

TABLE 3. Studies supporting the efficacy of degarelix in patients with prostate cancer

Study	Design	Doses	Number of subjects
CS02	randomized, open-label, parallel group, uncontrolled study 6-month study	40 mg (20 mg/mL) loading dose x 2 + 40 mg (20 mg/mL) Q28D 80 mg (20 mg/mL) loading dose x 2 + 40 mg (20 mg/mL) Q28D 80 mg (20 mg/mL) loading dose x 1 + 20 mg (10 mg/mL) Q28D	129
CS12	open-label, randomized, parallel, uncontrolled 12-month study.	200 mg Loading dose + 80 mg Q28D 200 mg Loading dose + 120 mg Q28D 200 mg Loading dose + 160 mg Q28D 240 mg Loading dose + 80 mg Q28D 240 mg Loading dose + 120 mg Q28D 240 mg Loading dose + 160 mg Q28D <i>All doses used the 40 mg/mL concentration</i>	187
CS14	open-label, randomized, parallel group, uncontrolled 12 month study	200 mg loading dose + 40 mg (60 mg/mL) Q28D 200 mg loading dose + 40 mg (80 mg/mL) Q28D	127
CS15	open-label, randomized, parallel group, uncontrolled 12 month study with 3-month depot	<i>3-month depot study will not be reviewed by Clin Pharm.</i>	n/a
CS21	randomized, parallel, groups, open-label active controlled study	240 mg (40 mg/mL) loading dose + 80 mg (20 mg/mL) Q28D 240 mg (40 mg/mL) loading dose + 160 mg (40 mg/mL) Q28D	409

### **Pivotal study**

Study CS21 was an open-label, multi-centre, randomized, parallel-group study of degarelix one Month Dosing Regimens (160 mg (40 mg/mL) and 80 mg (20 mg/mL)) in comparison to Lupron Depot® (7.5 mg) in patients with prostate cancer.

620 patients were enrolled and randomly assigned to receive one of the following treatments:

- Degarelix 240/160 – 240 mg loading dose with 160 mg maintenance doses Q28 days.
- Degarelix 240/80 – 240 mg loading dose with 80 mg maintenance doses Q28 days
- Leuprolide 7.5 mg once every 28 days.

The primary efficacy endpoint was the probability of testosterone  $\leq 0.5$  ng/mL from Day 28 through Day 364. If the lower bound of the 95% confidence interval (CI) for the cumulative probability of testosterone  $\leq 0.5$  ng/ml from Day 28 to Day 364 was no lower than 90% then the efficacy of degarelix would be confirmed.

Of the 620 patients randomized to treatment with degarelix/leuprolide, 610 patients received at least one dose and 504 patients completed the study. For all three treatment groups the lower bound of the 95% CI was above the pre-specified 90% threshold. The secondary efficacy endpoints included the proportion of patients with testosterone surge during the first 2 weeks of treatment, the proportion of patients with testosterone levels  $\leq 0.5$  ng/mL at Day 3, the percentage change in PSA from baseline to Day 28, the probability of testosterone  $\leq 0.5$  ng/mL from Day 56 through Day 364, time to PSA failure, and frequency and size of testosterone increases at Day 255 and/or 259 compared to the testosterone level at Day 252.

#### **2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?**

Degarelix is a GnRH antagonist indicated for prostate cancer. It causes rapid reduction of the circulating levels of androgens, hence, suppression of T is the primary biomarker. In addition, the drug is also expected to suppress the levels of DHT, FSH, LH and PSA. Achievement and maintenance of castration is the primary goal for clinical benefit.

The sponsor has determined T levels as the primary biomarker. The primary efficacy endpoint was the cumulative probability of a testosterone level  $\leq 0.5$  ng/mL from Day 28 through Day 364.

#### **2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?**

Based on in-vitro assessments there are six metabolites formed in human liver microsomes. Small amounts (<10%) of one of the metabolites, FE 200486(1-9), were detected in plasma from two studies (CS11 and CS23). However since the presence was <10% the contribution of FE 200486(1-9) is of low clinical relevance and was not measured in future trials.

#### **2.2.4 Exposure-response**

##### **2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?**

### End of Phase 2a meeting

The correlation between degarelix trough concentration and drug response was previously presented at the EOP2a meeting held in March of 2005. For the EOP2a analysis, data from phase 1 and 2 studies were binned into 4 time ranges (1-1.5, 1.5-2, 3-6 and 6-12 months). The correlation between plasma concentration and percentage of responses were combined and shown in FIGURE 1.

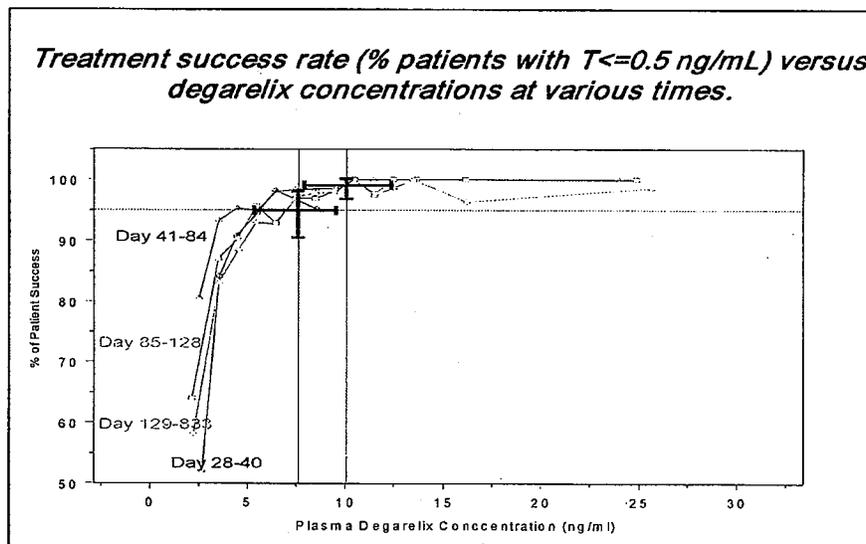


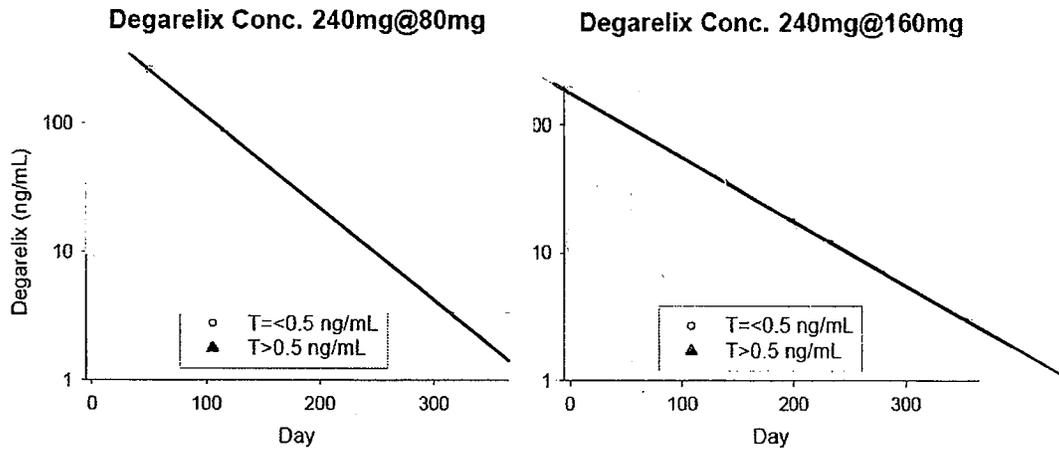
FIGURE 1. Degarelix trough concentration-response relationship at various times (1-1.5, 1.5-2, 3-6 and 6-12 months)

This analysis suggested that a trough degarelix plasma concentration of 7.5 and 9.5 ng/ml correspond to a success rate of 70% to 97% (mean 94%), and 92% to 97% (mean 96.4%), respectively. Based on this analysis the main conclusion communicated at the EOP2a meeting was that the sponsor should evaluate doses for future trials that maintained a target degarelix trough level  $> 9$ -10 ng/mL since this would result in maintenance of castrate levels for testosterone  $> 90\%$  of subjects.

### Pivotal Study CS21

Study CS21 was the pivotal phase 3 trial which evaluating two degarelix dosing regimens compared to Lupron Depot. For further details on the study design please see Section 2.2.1.

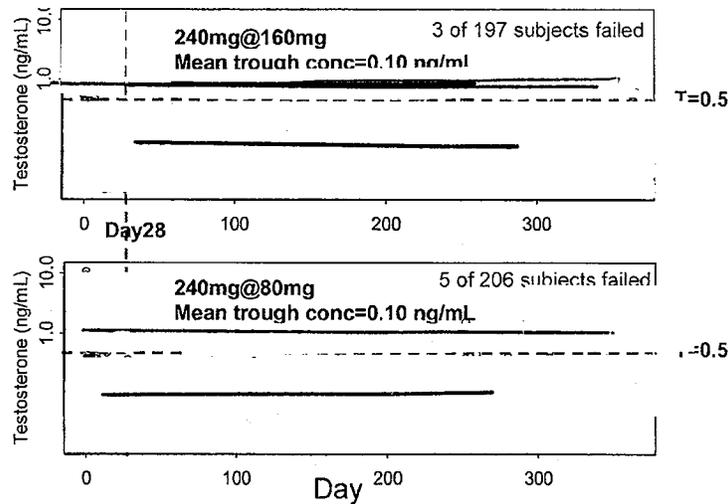
The plasma degarelix concentrations vs. time are shown in FIGURE 2. The mean degarelix concentrations in both degarelix treatment arms are higher than 10 ng/mL. The degarelix concentrations in failed subjects (FIGURE 2, red triangle) are in the average range and therefore the main reason for the failure could be the lack of sensitivity of these patients to degarelix.



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FIGURE 2. Study CS21 Observed degarelix concentrations by time for one year.

The results from this study indicate that the probability of maintaining  $T \leq 0.5$  ng/mL from Day 28 through Day 364 was 98.5%, 97.6% and 96.5% for degarelix 240/160, degarelix 240/80, and Lupron, respectively. As seen in FIGURE 3 by Day 28 all subjects in both degarelix treatment groups had attained castrate levels of testosterone. The 95% confidence intervals for the cumulative probability of  $T \leq 0.5$  ng/mL for both degarelix treatment arms from Day 28 to Day 364 were greater than 90% which fits the efficacy criterion pre-specified by the agency.



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FIGURE 3. Testosterone concentration vs. time for CS21 degarelix arms

In conclusion, both degarelix maintenance dosing regimens (80 mg and 160 mg) are effective in attaining and maintaining testosterone castration. The sponsor chose the 80 mg (20 mg/mL) maintenance dose because it was the lowest effective dose in the pivotal phase 3 trial.

#### **2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?**

Overall, the majority of adverse events were mild to moderate in intensity. The most frequently reported adverse reactions were expected reactions occurring from androgen deprivation and a subcutaneous injection. From the combined phase 2/3 one-month dosing regimen studies there were 14 adverse events that occurred with an incidence of > 5%: hot flush (31%), injection site pain (18%), injection site erythema (11%), back pain (7%), fatigue (7%), nasopharyngitis (7%), weight increased (7%), urinary tract infection (6%), arthralgia (6%), ALT increased (6%), dizziness (6%), constipation (5.5%), hypertension (5.3%), and diarrhea (5.3%). In the Phase 3 active control study, injection site pain and injection site erythema, occurred in 29% and 21%, respectively of degarelix treated patients.

Hot flushes and weight increase are expected adverse events associated with testosterone suppression or androgen deprivation. Hot flush had a decrease in incidence over time; however, the consistency in the prevalence over time suggests that the duration of the event was long for most patients who experienced this event. Weight increase occurred later in treatment and had an increased incidence and prevalence after one year of treatment.

##### **Injection site reactions**

Injection site reactions were the most common adverse event not related to androgen deprivation in the phase 2/3 studies. The prevalence and incidence of injection site reactions decreased over time, with a marked decrease seen when switching to the maintenance dose. Most injection site reactions occurred following the starting dose, were of short duration, and did not re-occur with the maintenance dosing. In addition the reactions were either mild or moderate in intensity, including those with induration or node/nodules present.

The data from the phase 3 study confirmed this finding (see TABLE 4). The number of patients with injection site reactions were higher following the loading dose (dosing interval 1) and decreased with the maintenance doses (dosing intervals 2 through 13). Patients receiving the 160 mg maintenance injection had on average higher rates of reactions compared to the 80 mg injection but this difference is negligible. The incidence of injection site reactions for the leuprolide arm were significantly decreased as this is given as an IM injection which is typically not associated with injection site reactions.

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TABLE 4. Incidence of treatment emergent injection site reactions by monthly intervals (sponsors table)

	Treatment Group			
	Degarelix		Total	Leuprolide 7.5 mg
	240/160 mg	240/80 mg		
N (%)	N (%)	N (%)	N (%)	
ITT analysis set	202 (100%)	207 (100%)	409 (100%)	201 (100%)
All Injection Site Reactions	89 (44%)	73 (35%)	162 (40%)	1 (<1%)
Dosing interval 1	58 (29%)	66 (32%)	124 (31%)	
Dosing interval 2	16 (8%)	7 (3%)	23 (6%)	
Dosing interval 3	7 (3%)	5 (2%)	12 (3%)	
Dosing interval 4	13 (6%)	7 (3%)	20 (5%)	
Dosing interval 5	11 (5%)	6 (3%)	17 (4%)	
Dosing interval 6	5 (2%)	10 (5%)	15 (4%)	
Dosing interval 7	3 (1%)	7 (3%)	10 (3%)	
Dosing interval 8	6 (3%)	5 (2%)	11 (3%)	
Dosing interval 9	5 (2%)	7 (3%)	12 (3%)	
Dosing interval 10	12 (6%)	11 (5%)	23 (6%)	1 (<1%)
Dosing interval 11	4 (2%)	7 (3%)	11 (3%)	
Dosing interval 12	6 (3%)	6 (3%)	12 (3%)	
Dosing interval 13	2 (<1%)	3 (1%)	5 (1%)	

N = number of patients with adverse events  
 % = percentage of patients with adverse events  
 Dosing intervals are true dosing intervals observed on a per-patient basis. Intervals were not fixed at 28 days.

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In an analysis completed by the sponsor using the combined Phase 2/3 studies (degarelix only) confirmed that the starting dose and starting dose concentration (mg/mL) do contribute significantly to the probability of having an injection site reaction.

TABLE 5. Dependencies on injection site reactions

	Hazard Ratio (HR)		
	estimate	95% CI	P value
Initial Loading Dose (mg)	1.01	[1.01;1.02]	<.0001
Initial Loading Dose Concentration (mg/ml)	0.967	[0.938;0.996]	0.0271
Initial Maintenance Dose (mg per month)	1.01	[1.00;1.01]	<.0001
Initial Maintenance Dose Concentration (mg/ml)	0.991	[0.978;1.00]	0.1642

### 2.2.4.3 Does this drug prolong the QT or QTc interval?

The sponsor collected electrocardiogram (ECG) measurements in the phase 3 study to investigate the effect of degarelix on cardiac repolarization.

The IRT was consulted to review the ECG data submitted from the phase 3 trial (CS21). All patients had 12-lead ECGs taken at screening, Day 0, Day 3, Day 84 ( $\pm 7$  days) and every 84 days ( $\pm 7$  days) thereafter until the End of Study Visit. At Day 0 three separate ECGs were recorded (for baseline assessment). ECGs were performed before dosing, if a dosing visit was scheduled. The ECG measurements included heart beat, PR, QRS intervals, QT and QTc, T and U wave. The highlights from the conclusion of the IRT review are as follows:

- 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<sub>max</sub>) 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.

For more details please see the full IRT review posted in DFS by Dr. Suchitra Balakrishnan. In addition, the IRT recommended changes to the sponsors proposed labeling text. The IRT changes to the label can be seen in Section 3 – Detailed Labeling Recommendations.

**2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?**

The dose of degarelix was evaluated in multiple phase 1 and phase 2 trials in patients with cancer.

Results from early phase 2 dose escalation studies CS02 (20 mg to 80 mg @ 10 or 20 mg/mL), CS06 (40 mg to 160 mg @ 10, 20, 30 or 40 mg/mL) and CS07 (120 mg to 320 mg @ 20, 40 or 60 mg/mL) were used to find the appropriate combination of dose and concentration to give a response rate (T ≤ 0.5 ng/mL) of 95% or more for at least 28 days. This was achieved in study CS07 which evaluated the highest doses of the three studies. Two doses, the 240 mg (40 mg/mL) and 200 mg (40 mg/mL) both achieved at least a 95% response rate in the subjects studied (TABLE 6).

In addition, in CS07 it was noted that responses for the same doses at higher concentrations were considerably less. The patients who received lower injection concentrations also had testosterone at castrate levels longer than those patients who received the same dose but at a lower concentration.

TABLE 6: Percent of patients with testosterone ≤ 0.5 ng/mL at Day 28 following a single SC dose of degarelix (CS07).

	N	Patients with T ≤ 0.05 @ Day 28 (%)	median time to escape <sup>a</sup> (days)
120 mg (20 mg/mL)	25	88	84
120 mg (40 mg/mL)	12	67	63
160 mg (40 mg/mL)	12	55	49
200 mg (40 mg/mL)	24	100	140
200 mg (60 mg/mL)	24	75	84
240 mg (40 mg/mL)	24	96	140
240 mg (60 mg/mL)	24	63	84
320 mg (60 mg/mL)	27	89	133

a – escape = T > 0.5 ng/mL

The results of these three phase 2 dose escalation trials supported the starting dosing regimen of 200 mg (40 mg/mL) or 240 mg (40 mg/mL) followed by maintenance dosing regimens of 60 mg (20 mg/mL), 80 mg (40 mg/mL), 120 mg (40 mg/mL) or 160 mg (40 mg/mL) administered every 28 days.

These doses were further investigated in study CS12, which had the primary objective of finding

the dose regimen that maintained T suppression after 196 days (7 cycles) and 364 days (12 cycles) in prostate cancer patients. There were higher responses in the groups treated with the initial 240 mg loading dose in addition to higher responses with increasing maintenance doses (TABLE 7). In addition, the 240 mg (40 mg/mL) loading dose had a higher proportion of patients with castration (95%) at Day 28 compared with the 200 mg (40 mg/mL) loading dose (86%).

TABLE 7: Patients with T ≤ 0.5 ng/mL from Day 29-196 and Day 28-364

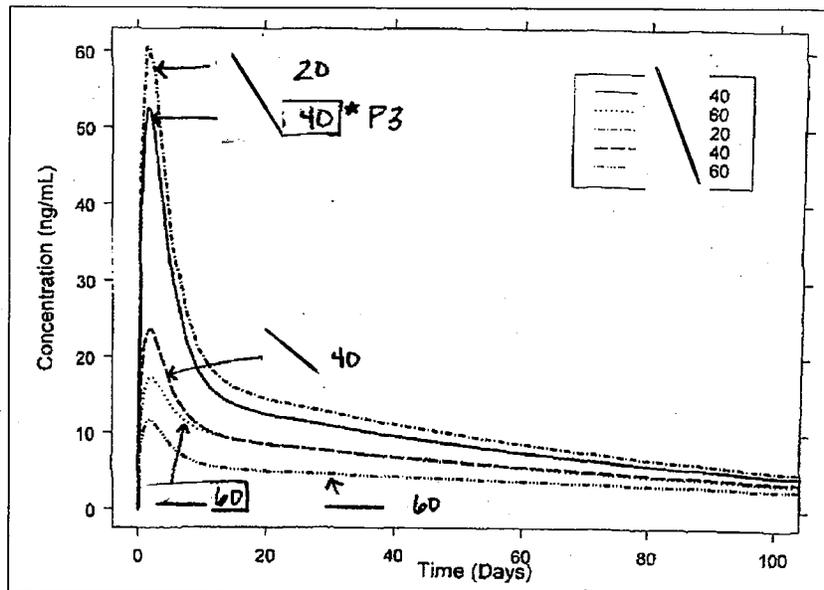
Initial Dose	Maintenance dose					
	80 (40 mg/mL)		120 mg (40 mg/mL)		160 mg (40 mg/mL)	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
<b>Day 28-196</b>						
200 mg (40 mg/mL)	29	66% (46-82%)	28	89% (72-98%)	30	97% (83-100%)
240 mg (40 mg/mL)	30	93% (78-99%)	32	94% (79-99%)	27	93% (76-99%)
<b>Day 28-364</b>						
200 mg (40 mg/mL)	28	61% (41-78%)	25	84% (64-95%)	27	96% (81-100%)
240 mg (40 mg/mL)	30	90% (73-98%)	30	90% (73-98%)	25	92% (74-99%)

N = # of patens in the analysis set

The results of CS12 supported the use of the 240 mg (40 mg/mL) loading dose and the use of a 160 mg (40 mg/mL) maintenance dose. The choice for the 80 mg (20 mg/mL) maintenance dose in phase 3 was supported by study CS14. In study CS14 a loading dose of 200 mg (40 mg/mL) with maintenance doses of either 60 mg (20 mg/mL) or 80 mg (20 mg/mL). From Day 56 onward the 80 mg (20 mg/mL) maintenance dose showed a slightly higher suppression rate (98%) than the 60 mg (20 mg/mL) dose (95%).

In addition to the above studies a population pharmacokinetic model was developed to predict the exposures that would be achieved with the phase 3 formulation. The formulation used in phase 3 was manufactured using a \_\_\_\_\_ compared to a \_\_\_\_\_ which was used for the dose finding and other clinical pharmacology studies (for more information on formulation development please see Section 2.5.2). The population pharmacokinetic model of degarelix model took into account differences between these two formulations employed during the development of degarelix. The model predicted that at all time-points during the first month after administration (and beyond) the plasma concentration of degarelix would be higher for the phase 3 \_\_\_\_\_ drug product than for the \_\_\_\_\_ drug product at the same dose and injection suspension concentration (FIGURE 4). This supports that in phase 3 when using the \_\_\_\_\_ drug product the chosen doses of 240 mg (40 mg/mL), 80 mg (20 mg/mL) and 160 mg (40 mg/mL) will be expected have higher exposures than what was seen in the corresponding dose finding studies and thus ensuring that the degarelix concentration sustains above the critical 9-10 mg/mL for at least as long as with the \_\_\_\_\_ product.

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b(4)

FIGURE 4. Simulated population mean degarelix concentration profiles after single dosing with 240 mg \_\_\_\_\_ formulations at dosing concentrations of 20 \_\_\_\_\_, 40 and 60 mg/mL (Sponsor's figure).

In conclusion, the combined results from the above dose finding studies and the population PK modeling, along with the EOP2a meeting discussion were used to choose the 240 mg (40 mg/mL) loading dose followed by maintenance doses of 80 (20 mg/mL) or 160 mg (40 mg/mL) for phase 3 evaluation.

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In the phase 3 study both regimens (240/80 and 240/160) were efficacious. The sponsor chose the 240/80 dose for marketing as this was the lowest effective dose.

## 2.2.5 Pharmacokinetic characteristics of the drug and its major metabolites

### 2.2.5.1 What are the single dose and multiple dose PK parameters?

Single dose PK parameters have been characterized after IV, IM and SC administration in both healthy volunteers (CS01, CS05, CS08) and patients with cancer (CS06, CS07, CS11). The doses from each of these studies ranged in concentration (5 mg/mL to 60 mg/mL) and strength (0.5 to 320 mg/mL) because non-clinical studies showed that dose and also the concentration of the suspension influenced the pharmacokinetic and pharmacodynamic parameters of degarelix. Therefore, in the Phase 1/2 development program, both doses (mg) and concentrations (mg/mL) were evaluated in various combinations.

#### IV infusion – healthy volunteers

The pharmacokinetics of degarelix after an IV infusion were investigated in healthy adult men in study CS05 (TABLE 8). The AUC following IV infusion was dose proportional. The mean volume of distribution was approximately 0.6 L/kg for the three doses tested and clearance ranged from 36-50 mL/h/kg.

TABLE 8: Single dose PK parameters (mean  $\pm$ SD) of degarelix after a 15-45 minute IV infusion to healthy adult men (CS05).

	AUC (ng hr/mL)	Cmax (ng/mL)	Thalf (hr)
6 $\mu$ g/kg over 15 min (n = 6)	141 $\pm$ 34	38.2 $\pm$ 6.2	11.6 $\pm$ 5.2
15 $\mu$ g/kg over 45 min (n = 6)	296 $\pm$ 82	58 $\pm$ 8.7	13.2 $\pm$ 1.7
30 $\mu$ g/kg over 45 min (n = 6)	747 $\pm$ 120	160 $\pm$ 22	16.5 $\pm$ 1.8

### IM injection – healthy volunteers

The pharmacokinetics of degarelix after a 20 mg (5 mg/mL) IM and SC administration was investigated in healthy adult subjects in study CS05 (see TABLE 9). Twelve subjects received either a single 20 mg (5 mg/mL) subcutaneous or intramuscular injection of degarelix.

The AUC and Cmax and half-life were similar after IM and SC injection, however the time to Cmax was shorter for the SC administration.

TABLE 9: Single dose PK parameters of degarelix following a single SC or IM dose to healthy men (CS05).

	AUC <sup>a</sup> (ng hr/mL)	Cmax <sup>b</sup> (ng/mL)	Tmax <sup>c</sup> (hr)	Thalf <sup>d</sup> (days)
20 mg SC (n = 6)	2270 (32)	6.7 $\pm$ 1.8	5 (3-36)	23 (19-32)
20 mg IM (n = 6)	2451 (31)	7.7 $\pm$ 2.0	18 (3-24)	26 (11-40)

a – geo.mean (CV)

b – mean  $\pm$  SD

c – mean (range)

d – harmonic mean (range)

### SC administration - Patients

The pharmacokinetics of degarelix administered as a SC injection was investigated in three studies (CA06, CA07, and CS11) in prostate cancer patients. The two most relevant studies were CA06 and CS07, as these used the doses at a range close to what is being proposed for approval (240 mg/80 mg). CS11 was conducted in Japanese patients at the indicated loading dose of 240 mg and will be discussed in more detail in Section 2.3.

In patients with cancer, increasing the injection suspension concentration at a constant dose caused a decrease in Cmax and AUC (FIGURE 5). AUC and Cmax were dose proportional to the dose when the degarelix concentration in the injection suspension was the same).

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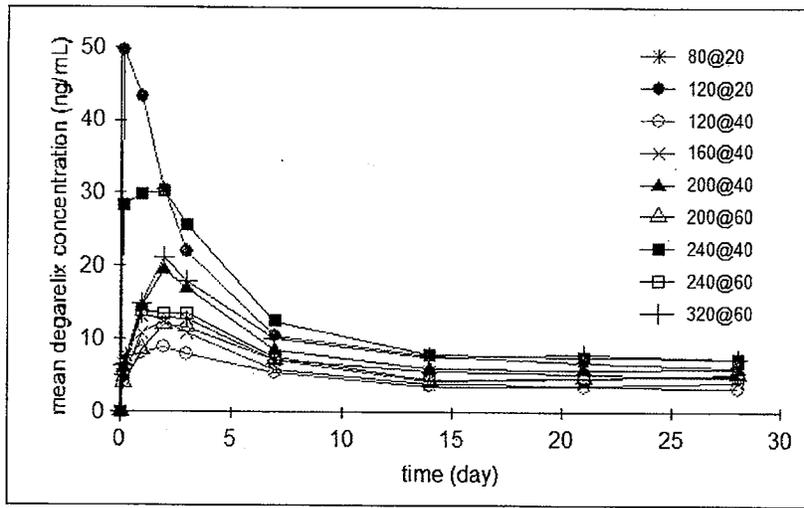


FIGURE 5: Degarelix concentration vs. time following a single subcutaneous dose in patients with prostate cancer (Studies CA06 and CA07).

TABLE 10: Single dose pharmacokinetic parameters of degarelix in prostate cancer patients (Study CA06 and CA07).

	AUC <sup>a</sup> (day ng/mL)	Cmax <sup>a</sup> (ng/mL)	Tmax <sup>b</sup> (hr)	Thalf <sup>c</sup> (days)
<b>20 mg/mL</b>				
80 (n = 24) <sup>d</sup>	479 (34)	14.5 (22)	44 ± 23	21 (25-61)
120 (n = 25)	788 (34)	33.5 (92)	34 ± 17	41 (15-105)
<b>40 mg/mL</b>				
120 (n = 12)	520 (15)	9.0 (28)	46 ± 18	73 (55-116)
160 (n = 12)	641 (29)	11.8 (44)	52 ± 15	71 (54-102)
200 (n = 24)	829 (30)	18.7 (38)	49 ± 12	50 (20-110)
240 (n = 24)	1054 (35)	26.2 (83)	47 ± 17	53 (29-104)
<b>60 mg/mL</b>				
200 (n = 24)	708 (45)	11.8 (46)	49 ± 12	65 (42-422)
240 (n = 24)	951 (44)	14.3 (75)	52 ± 18	75 (25-196)
320 (n = 27)	1079 (40)	19.3 (52)	52 ± 12	45 (17-98)

a - Geo.mean (CV%)  
b - mean ± SD  
c - harmonic mean (range)  
d - from study CS06

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### Multiple dose - patients

The PK after multiple dose administration of degarelix was gathered from two studies (CS12 and CS14). In both of these studies subjects were randomized to receive a loading dose and multiple cycles of every 28 day maintenance therapy. PK samples were taken 'intensively' following the loading dose (Day 0 (dose administered), 1, 3, 7, 14) and predose 'troughs' before each 28 day maintenance injection (Day 28, 56, 84 etc, up to 364) for both studies. Study CS14 added additional 'intensive' sampling following the last dose given on day 366.

In study CS12 maximum plasma concentrations were reached 1-3 days after the initial dose. For the 160 mg maintenance dose the accumulation was notable with degarelix concentrations increasing over time (see FIGURE 6). Steady state levels were on average achieved after 8-10 maintenance doses.

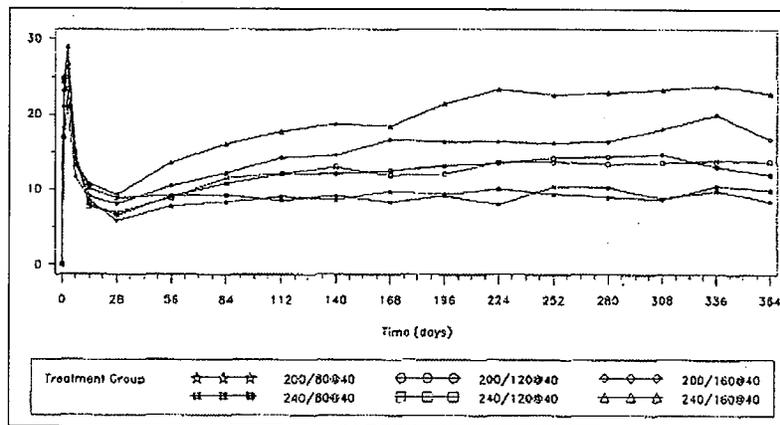


FIGURE 6: Sponsors figure of median degarelix concentration over time for study CS12.

For study CS14 the accumulation was less than that seen in study CS12. Compared to CS12 a more consistent steady degarelix concentration profile is seen (see FIGURE 7) during the maintenance dose phase starting on Day 28.

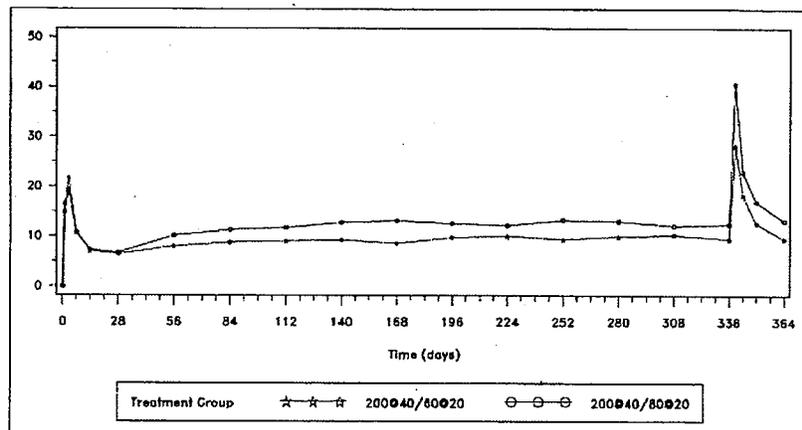


FIGURE 7: Sponsors figure of median degarelix concentration over time for study CS14.

In conclusion, the degree of accumulation for monthly degarelix maintenance doses is dependant on the dose and concentration of the maintenance injection.

**2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?**

Although multiple doses and concentrations of degarelix were studied in both healthy volunteers and patients with prostate cancer there is little data available on the PK of the same dose/concentration combination in both populations. Since the PK of degarelix is dependant not only on the dose, but also on the concentration of the injection, one cannot directly compare the same dose between healthy subjects and patients unless it was also administered using the same injection concentration.

The 40 mg (10 mg/mL) dose from study CS01 (healthy subjects) and CS06 (patients with cancer) is the only data that overlaps between these two groups. The results from these studies are below in TABLE 11.

There are many limitations to this cross-study comparison. First, the number of subjects in both studies are very low. Only five of ten subjects had adequate data for the patients with prostate cancer to calculate AUC, half-life, volume of distribution and clearance. In addition, the data is highly variable in patients with CV%'s ranging from 30-80% and only 2 subjects had data gathered past Day 28. There was no reason for lack of data provided by the sponsor.

TABLE 11: Comparison (geo.mean (CV%)) of single dose PK following a 40 mg (10 mg/mL) SC injection to patients (CS06) and healthy subjects (CS01).

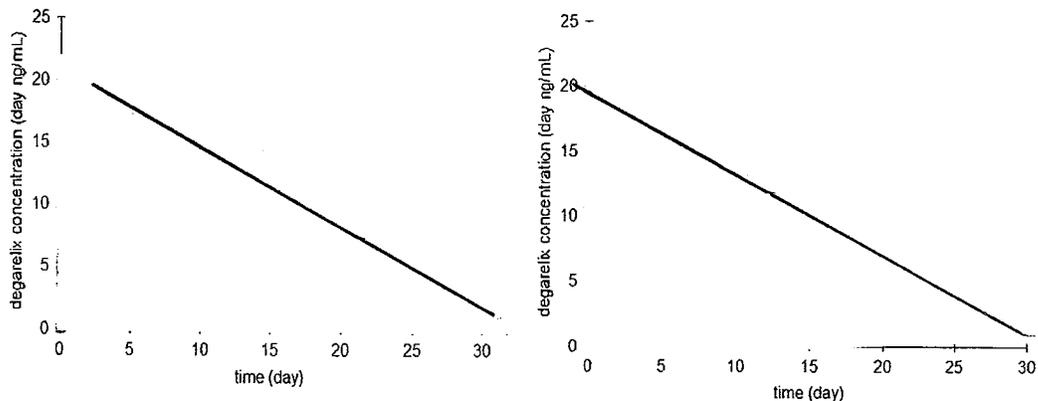
	<b>AUC</b> (day ng/mL)	<b>Cmax</b> (ng/mL)	<b>Tmax<sup>a</sup></b> (hr)	<b>Thalf</b> (days)	<b>Vz/F</b> (L)	<b>CL/F</b> (L/hr)
<b>Patients (n = 10)</b>	149 (59) <sup>b</sup>	6.0 (79)	25 (21, 73)	23 (54) <sup>b</sup>	9010 (30) <sup>b</sup>	11.1 (59) <sup>b</sup>
<b>Healthy subjects (n = 6)</b>	299 (22)	14.2 (37)	18 (4, 48)	962 (16)	7723 (25)	5.6 (22)

a – median (range)

b – n = 5

When looking at individual data there is a fair amount of overlap between healthy volunteers and patients with prostate cancer, but on average healthy subjects had higher exposures (Cmax and AUC) than patients with prostate cancer (FIGURE 8).

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FIGURE 8: Concentration vs. time curves for a single 40 mg (10 mg/mL) degarelix dose in prostate cancer patients (left; study CS06) and healthy subjects (right; study CS01).

There was no explanation given by the sponsor as to why exposures were different in patients and healthy volunteers. The healthy volunteers were on average younger (median age 35) than the patients in study CS06 (median age 73) however this doesn't explain the discrepancy as the population PK model concluded that clearance was found to decrease with increasing age (1 % per year). There was no significant difference in the mean body weight or BMI between the two groups. In conclusion, it appears that there are minor differences between healthy volunteers and prostate cancer patients, however the data is limited.

#### 2.2.5.3 What are the characteristics of drug absorption?

After subcutaneous administration, degarelix forms a hydrogel depot which results in a sustained release of degarelix. Following a 240 mg (40 mg/mL) subcutaneous loading dose of degarelix the median T<sub>max</sub> was 1.95 days (range: 0.125, 2.98 days) in patients with cancer.

#### 2.2.5.4 What are the characteristics of drug distribution?

##### Protein Binding

The *in vitro* protein binding of degarelix to human plasma, serum albumin,  $\alpha_1$ -acid glycoprotein, gamma globulin and high density lipoproteins was determined using human plasma (report 1475/094). Concentrations of 20, 60 and 160 ng/mL of degarelix were added to pooled human plasma and solutions of purified human plasma proteins.

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TABLE 12: Binding of degarelix to human plasma proteins

Protein	Nominal FE200486 concentration (ng/mL)	Total concentration (C <sub>t</sub> ) of FE200486 (ng/mL)	binding (%)
Serum albumin	20	17.1	78.1
	60	50.3	77.9
	120	109	72.7
		<b>Overall Mean</b>	<b>76.3</b>
Gamma globulin	20	18.2	48.6
	60	46.7	46.6
	120	114	24.8
		<b>Overall Mean</b>	<b>48.0</b>
$\alpha_1$ acid glycoprotein	20	19.6	82.5
	60	59.6	79.1
	120	116	73.0
		<b>Overall Mean</b>	<b>78.2</b>
High density lipoprotein	20	18.0	60.6
	60	55.1	56.9
	120	119	56.2
		<b>Overall Mean</b>	<b>57.9</b>
Human plasma	20	17.7	90.7
	60	54.7	90.3
	120	140	90.5
		<b>Overall Mean</b>	<b>90.5</b>

The mean binding of degarelix to human plasma varied between 90.7 and 90.3% with no apparent concentration dependent effects. Binding to purified plasma proteins such as serum albumin,  $\alpha_1$ -acid glycoprotein, gamma globulins and high density lipoproteins were not of significance and showed no concentration dependence.

Protein binding of degarelix in human ex-vivo plasma was also investigated using samples from six healthy volunteers receiving 30  $\mu$ g/kg IV degarelix in study CS05. Samples for protein binding analysis were collected at 1, 12 and 24 hours after completion of the 45-minute infusion. The samples were measured using a validated LC-MS bioanalytical assay. The binding of degarelix in these human samples ranged from 88.1 to 92.4% at 1-hour post infusion did not show significant decline 12 hours after infusion but was slightly lower at 24 hours post infusion (see TABLE 13)

TABLE 13: Binding of degarelix to plasma proteins of human subjects ex-vivo after a single IV infusion of 30  $\mu$ g/kg degarelix.

Subject number	Time after end of infusion (hours)								
	1			12			24		
	Total concentration in plasma <sup>1</sup> (ng/ml)	Unbound concentration (ng/ml)	% bound	Total concentration in plasma <sup>1</sup> (ng/ml)	Unbound concentration (ng/ml)	% bound	Total concentration in plasma <sup>1</sup> (ng/ml)	Unbound concentration (ng/ml)	% bound
D001									
D002									
D003									
D004									
D005									
D006									
Mean	77.90	7.19	90.7	14.63	1.37	90.5	6.68	0.74	88.6

<sup>1</sup> Measured after ultracentrifugation and corrected for FE 200486 present in protein-free plasma supernatant. These concentrations were not corrected for the extent of non-specific binding to the ultracentrifuge tubes, which was not determined

All values are mean of duplicate determinations

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#### **2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?**

No mass balance study was conducted.

The renally excreted fraction of degarelix was calculated using urinary data from Study CS05 where twenty-four healthy male subjects received single IV degarelix doses of 1.5 to 30 µg/kg. Urine was collected for 48 hours in fractions of 0-2, 2-4, 4-8, 8-12, 12-24 and 24-48 hours after dosing. Urine samples were analyzed by a validated LC-MS/MS assay and the amount excreted in the urine and the derived urinary pharmacokinetic parameters were calculated using WinNonlin. The mean fraction of the administered dose excreted unchanged in urine during this study was  $18.5 \pm 5.1\%$ .

Urinary excretion was also evaluated in Study CS23. In this study all 24 subjects, 8 of which were healthy and 16 with hepatic impairment, received 1 mg degarelix IV and urine was collected for 72 hours in fractions of 0-3, 3-6, 6-12, 12-24, 24-48 and 48-72 hours after dosing.

The results from the 8 healthy subjects in study CS23 show an excretion of  $30.7\% \pm 4.3\%$ , after 48 hours, and  $31.2\% \pm 4.2\%$  after 72 hours. There was no significant difference in urinary excretion of degarelix between the healthy subjects and subjects with moderate hepatic impairment (urinary excretion at 48 hours = 29.3%) in this hepatic impairment study.

In conclusion, in the absence of an ADME study, urine excretion data from these two studies suggest that approximately 20-30% of the degarelix dose is excreted renally, suggesting that approximately 70-80% is excreted via other mechanisms.

#### **2.2.5.6 What are the characteristics of drug metabolism?**

##### **In-vitro**

The *in vitro* metabolism (IAP-0193) of FE 200486 was studied in human liver microsomes (HLM) at a concentration of 40.4 µM (65945 ng/mL; C<sub>max</sub> after 240 mg SC injection = 54.5 ng/mL). Six metabolites were detected in the HLM samples after an incubation time of 60 minutes. Five of these metabolites were oxidative metabolites of FE 200486. The total amounts of the oxidative metabolites formed were very low (approximately 350 nM, <1 % of the initial amount of FE 200486 in the incubation samples) indicating that FE 200486 is a poor substrate of human CYP450 activity considering the concentration of degarelix tested in this study is magnitudes higher than the C<sub>max</sub> of a 240 mg SC injection. The sixth metabolite was identified as FE 200486(1-9). This metabolite is not a product formed by cytochrome P450 activity but probably due to protease enzyme activity in the human liver microsomes. It was the most abundant metabolite detected in HLM samples.

Possible *in vitro* glucuronidation of FE200486 in human liver microsomes treated with alamethicin and with NADPH and uridine diphosphoglucuronic acid as cofactors, was also investigated (AR-DCB-0010). The test substrate 7-ethoxycoumarin was used as a positive control, and after incubation for 60 mins two glucuronides were formed, 3-(hydroxy)-7-ethoxycoumarin and 7-hydroxycoumarin. No glucuronic acid conjugates of FE200486, mono-hydroxylated FE200486 or truncated metabolites of FE200486 were formed by *in vitro* metabolism in HLM. Based on the present results, it is unlikely that FE200486 has the propensity to form conjugated metabolites *in vivo*.

### In-vivo

The human plasma, urine and fecal samples were analyzed for metabolic characterization from three clinical studies which enrolled healthy volunteers with hepatic impairment (CS23), Japanese subjects with prostate cancer (CS11), and patients with prostate cancer (CS06). Six different cleavage products have been identified, five common for urine and feces, and one, unique, in blood (see TABLE 14, FIGURE 9)

TABLE 14: Degarelix fragments identified in human blood, urine and feces

Blood	Urine	Feces
FE 200486 (1-9)	FE 200486 (1-4)	FE 200486 (1-4)
	FE 200486 (1-5)	FE 200486 (1-5)
	FE 200486 (1-6)	FE 200486 (1-6)
	FE 200486 (1-7)	FE 200486 (1-7)
	FE 200486 (1-10)OH	FE 200486 (1-10)OH

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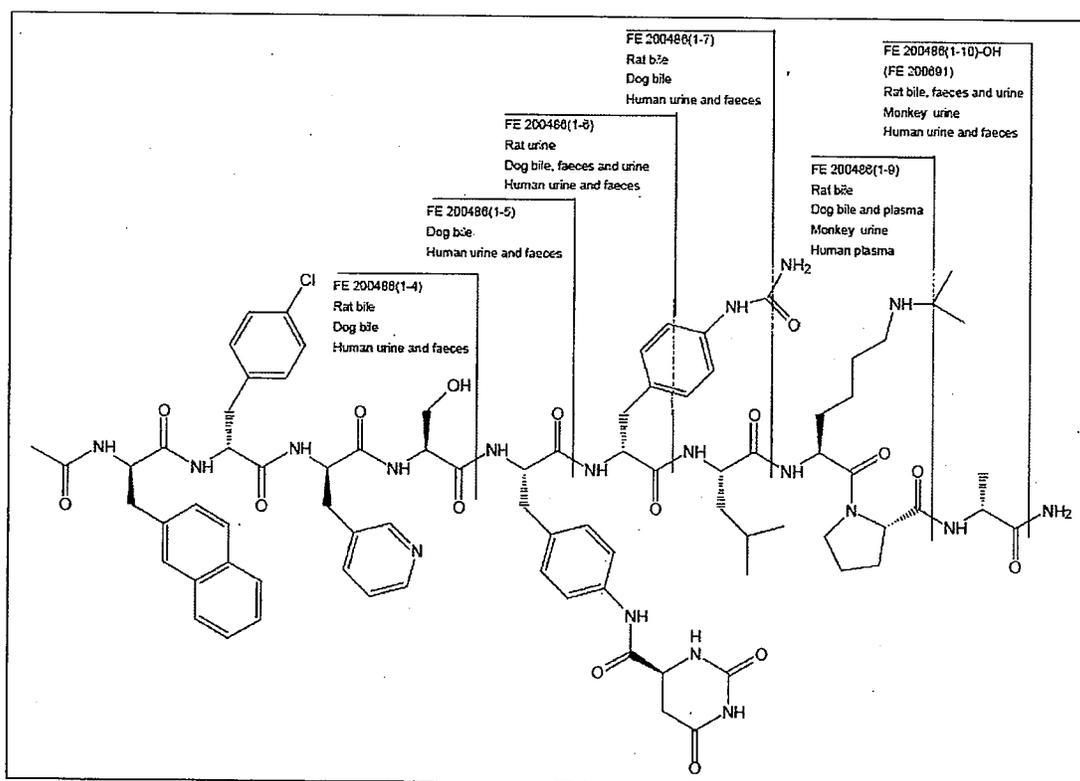


FIGURE 9: Cleavage positions of degarelix

Small amounts (<10%) of FE 200486(1-9) were detected in plasma in the Japanese and hepatic impairment studies (CS11 and CS23). However since the presence was <10% the contribution of FE 200486(1-9) is of no clinical relevance.

Intact compound was found in urine samples from studies CS06, CS11 and CS23 including healthy subjects, Caucasian and Japanese prostate cancer patients, and hepatically impaired

subjects. In these studies degarelix accounted for 70-100% of the degarelix related material. Small amounts (2-15%) of truncated peptides were detected in urine from Japanese subjects and healthy and hepatically impaired subjects from the hepatic impairment trial. All truncated peptides detected in urine were known metabolites of degarelix and had previously been detected in excreta from animals.

Only small amounts of intact degarelix was detected in feces whereas most of the degarelix related material were identified as the truncated peptides FE 200486 (1-4), FE 200486 (1-5), FE 200486(1-6), FE200486 (1-7) and FE200486 (1-9) (Figure 5). This pattern is in agreement with results from animal excreta.

In conclusion, the results from the urine and feces analysis confirm the results from animal studies. Degarelix is excreted mainly unchanged via the urine, but it is also subject to sequential proteolytic degradation during its elimination via the hepato-biliary pathway. There were no differences seen in the metabolism pattern between healthy subjects and prostate cancer patients.

#### **2.2.5.7 What are the characteristics of drug excretion?**

##### **Route of Elimination**

Urinary excretion of degarelix was evaluated in two studies for up to 72 hours: Urine excretion data from these two studies suggest that approximately 20-30% of the degarelix dose is excreted renally, suggesting that approximately 79-80% is excreted via non-renal mechanisms.

##### **Half-life**

The mean (range) half-life of degarelix following a single 240 mg (40 mg/mL) subcutaneous injection in cancer patients was 53(29-104) days.

#### **2.2.5.8 Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?**

To assess dose linearity, single dose PK data from four doses using a 40 mg/mL concentration injection were extracted from study CS07 in patients with prostate cancer. The concentration of 40 mg/mL was chosen for analysis because it composed the largest dose range of all the concentrations studied. The results are below (see FIGURE 10 and TABLE 15 ) and indicate that over the dose range of 120-240 mg at a concentration of 40 mg/mL, both AUC and Cmax increased in proportion to dose.

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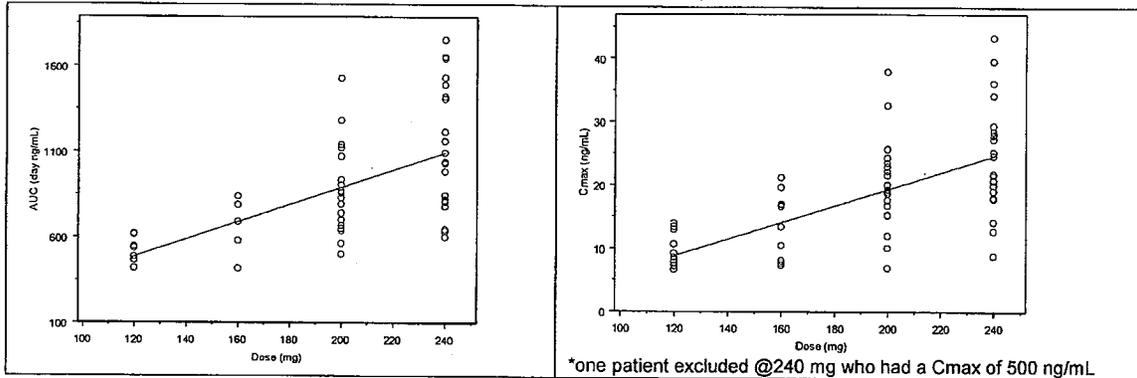


FIGURE 10: Degarelix AUC (left) and Cmax (right) versus dose in patients with prostate cancer receiving a 40 mg/mL concentration of degarelix.

TABLE 15: Single dose geometric mean (CV%) AUC and Cmax following a single SC dose of degarelix using a concentration of 40 mg/mL.

	AUC (day ng/mL)	Cmax (ng/mL)
120 (n = 12)	520 (15)	9.0 (28)
160 (n = 12)	641 (29)	11.8 (44)
200 (n = 24)	829 (30)	18.7 (38)
240 (n = 24)	1054 (35)	26.2 (83)

**2.2.5.9 How do the PK parameters change with time following chronic dosing?**

Degarelix is administered as a loading dose followed by monthly (every 28 day) maintenance injections. The goal of therapy is to maintain a constant amount of degarelix to attain castrate levels of testosterone. During the maintenance phase no accumulation of degarelix is seen. Please see Section 2.2.5.1 for more information on the pharmacokinetics of degarelix following multiple doses.

**2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?**

Variability between patients with cancer ranged between 34-83% for pharmacokinetic measures of exposure. For healthy volunteers the CV% for Cmax and AUC ranged from 20-48%. The increase in variability seen in patients for measures of exposure could be to decreased sampling schemes used in the trials that enrolled prostate cancer patients. The Cmax with these decreased sampling schemes may not have been adequately characterized. In addition obtaining sampling in the terminal phase which was days after the initial injection may not have been as closely followed in patients in later development stages as it was in healthy volunteers during the dose ranging studies.

## 2.3 INTRINSIC FACTORS

### 2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Based on the pharmacometric review, it is concluded that there was no effect of age, body weight or race on degarelix exposure or testosterone response. For more details please see the pharmacometric review in Section 4.2.

#### Race

A study conducted in Japan (CS11) enrolled 18 Japanese subjects into three dose groups (160, 200 and 240 mg; all 40 mg/mL). After a single dose of degarelix subjects were followed until treatment was no longer suppressing testosterone sufficiently. Blood samples for degarelix analysis were taken on day 0 (prior to dosing and 3 hours post-dosing), 1, 2, 3, 7, 14, 21 and 28, then weekly for 8 weeks and then every-other-week until a decision had been made to discontinue. Samples for testosterone and other related hormones were taken at the same time.

The pharmacokinetic results were similar from other studies following single doses SC degarelix (see TABLE 16). A cross study comparison of the twenty-four Caucasian prostate cancer subjects who received 240 mg (40 mg/mL) in study CS07 show that the Japanese subjects had on average higher exposures (see FIGURE 11). The clinical significance of this has not been established. The main differences were seen early in the injection interval and by Day 20 the degarelix concentrations were similar between the two patient populations.

TABLE 16: Pharmacokinetic parameters of degarelix following a range of doses (all 40 mg/mL) in Japanese subjects from study CS11.

	AUC <sup>a</sup> (day ng/mL)	Cmax <sup>a</sup> (ng/mL)	Thalf <sup>b</sup> (day)
160 mg (n = 6)	593 (31)	17.0 (58)	28 (16, 85)
200 mg (n = 6)	1061 (18)	26.0 (40)	51 (24, 92)
240 mg (n = 6)	1517 (28)	52.7 (160)	41 (18, 143)

a - geo.mean (CV)  
b - median (range)

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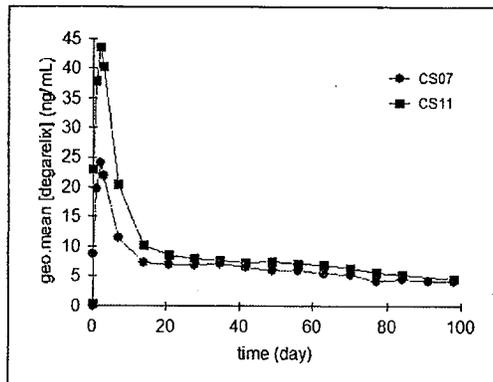


FIGURE 11: Concentration vs. Time for Japanese (n = 6; CS11) and Caucasian subjects (n = 24; CS07) who received single SC dose of 240 mg (40 mg/mL) degarelix.

The reason for the difference in AUC and Cmax between the two populations is unclear, but are not likely to affect efficacy since efficacy is related to steady state trough concentrations. No dose changes will be recommended for Japanese patients receiving degarelix.

**2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.**

**2.3.2.1 Pediatric patients**

There were no pediatric studies included in the current submission.

**2.3.2.2 Renal impairment**

At the EOP1 meeting on January 26, 2004 the agency agreed that no renal impairment study would need to be conducted. Below is the excerpt from the meeting minutes:

**Question 1:** The mean (+/-SD) renal excretion of degarelix was determined at 18% (+/- 5%) after intravenous administration to healthy men in the FE200486 CS05 study. On this basis, Ferring does not intend to perform a study in renally impaired patients. Does the Agency concur?

**Division response:** We concur. No renal impairment studies are required.

A population PK analysis of data from the phase 3 study was conducted to discern exposure or efficacy differences in patients with renal impairment and included the following patients:

- 240/80 group: 52 Mild; 155 Normal
- 240/160 group: 1 Moderate; 57 Mild; 144 Normal

The results indicated that there was no apparent difference in degarelix trough concentration or testosterone response between mild (CrCL 50-80 mL/min) and normal (CrCL > 80 mL/min) groups. For more details please see the Pharmacometric Review in Section 4.2.

Appropriate caution statements for patients with moderate and severe renal impairment will be included in the label as an adequate number of subjects with this degree of renal impairment

were not studied.

### 2.3.2.3 Hepatic impairment

A study (CS23) investigating the effect of hepatic impairment on the PK of degarelix and its metabolites was completed in male patients with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment with a healthy control group. All subjects were administered a single dose of 1 mg degarelix IV over 1-hour. Blood samples for analysis of degarelix, testosterone, and LH were collected up to 72-hours after dosing.

Patients with hepatic impairment had on average lower AUC and Cmax mean values compared to the healthy subjects. In addition, the volume of distribution was noticeably higher in patients with hepatic impairment while the values for clearance and half-life did not differ considerably.

TABLE 17: Degarelix pharmacokinetic parameters in healthy subjects and patients with hepatic impairment.

Parameter	Mild hepatic impairment N=8	Moderate hepatic impairment N=8	Healthy Parameter N=8
AUC (h ng/mL) <sup>a</sup>	289 (14%)	267 (22%)	319 (14%)
AUCt (h ng/mL) <sup>a</sup>	271 (15%)	247 (21%)	303 (15%)
Cmax (ng/mL) <sup>a</sup>	47.9 (21%)	39.7 (13%)	57.2 (8%)
Tmax (h) <sup>b</sup>	0.969 ± 0.088	1.00 ± 0.00	1.01 ± 0.02
Thalf (hr) <sup>c</sup>	18.9	17.9	16.6
Vz (L) <sup>b</sup>	95.9 ± 13.2	99.4 ± 15.4	78.9 ± 16.9
CL (L/hr) <sup>b</sup>	3.49 ± 0.48	3.84 ± 0.89	3.17 ± 0.47

a – geo. Mean (CV%)  
b – mean ± SD  
c – harmonic mean

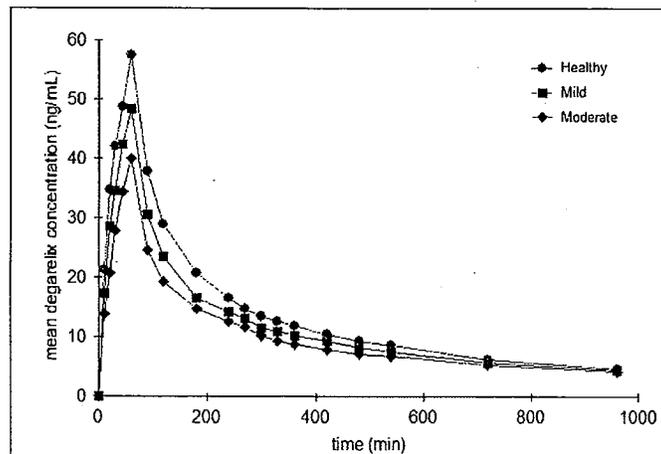


FIGURE 12: Degarelix concentration vs. time for healthy subjects and patients with mild or moderate hepatic impairment.

A standard 90% confidence interval approach (0.8-1.25) for the ratio of geometric means of AUC, AUCt, and Cmax between the test groups (hepatic impairment) and the control group (healthy subjects) was used to conclude no effect. The sponsor's results are below in TABLE 18.

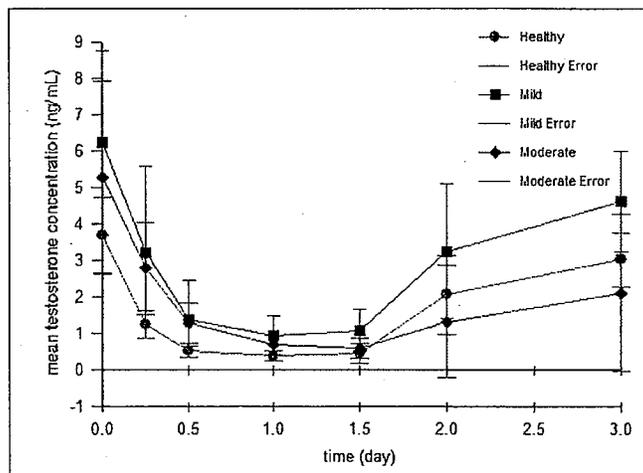
TABLE 18: Statistical analysis of degarelix C<sub>max</sub> and AUC following treatment in healthy subjects or patients with hepatic impairment.

	N	Comparison	Estimate (90% CI)
AUC [h*ng/mL]	8	Mild vs Healthy	90.7 (78.0, 105)
	8	Moderate vs Healthy	83.6 (71.9, 97.2)
AUC <sub>t</sub> [h*ng/mL]	8	Mild vs Healthy	89.6 (77.2, 104)
	8	Moderate vs Healthy	81.5 (70.3, 94.6)
C <sub>max</sub> [ng/mL]	8	Mild vs Healthy	83.7 (73.6, 95.3)
	8	Moderate vs Healthy	69.4 (61.0, 79.0)

Source: EOT-Table 10  
 N = number of subjects; CI = confidence interval.  
 Estimates for AUC, AUC<sub>t</sub>, and C<sub>max</sub> are based on a linear model of the ln-transformed variables including period, treatment condition, and sequence as fixed effects and subject within sequence as random effect.

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Based on the differences in exposure in patients with hepatic impairment one would expect the testosterone concentrations in this group to be higher than those seen in the healthy volunteers. The sponsors data confirmed this (FIGURE 13). After dosing, the healthy subjects had greater decreases in their testosterone concentrations compared to subjects with mild or moderate hepatic impairment. This was consistent for approximately 1.5 days after dosing. However, by this time, there was no meaningful difference in degarelix concentrations between the groups (see FIGURE 12).



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FIGURE 13: Testosterone mean concentration vs time in healthy subjects and patients with hepatic impairment.

In addition, urine and fecal samples from this study were screened for degarelix metabolites (DCB-A-0019). For the most part hepatic impairment did not effect results of the urine and fecal analysis and only two minor differences in metabolite profiles of degarelix were observed between excreta samples from healthy subjects and samples from hepatically impaired subjects. The minor metabolite FE 200486 (1-7) was only detected in post-dose urine samples from hepatically impaired subjects, and the major metabolite FE 200486 (1-4) in post-dose feces samples was found in higher relative amounts in feces samples from hepatically impaired subjects than from healthy subjects.

In conclusion, the decrease in exposures seen in hepatic impairment is not a cause for safety

concern. However, since efficacy is dependant on degarelix trough concentrations and since the C<sub>min</sub> between patients with hepatic impairment compared to normal hepatic function did not differ, no dosage adjustment will be recommended for patients with hepatic impairment. However, like all patients, patients with hepatic impairment should be followed adequately for efficacy and should be taken off degarelix if testosterone castration cannot be maintained.

#### **2.3.2.4 What pregnancy and lactation use information is there in the application?**

Not applicable.

### **2.3.3 Immunogenicity**

Antibodies in pre-and post-dose blood samples taken from 1283 prostate cancer patients enrolled in a wide range of phase 2 (CS02, CS12, CS14, CS15 and extension studies) and phase 3 (CS21) clinical studies have been analyzed using a sensitive (lower limit of quantitation 50 ng/mL using

#### **2.3.3.1 What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?**

Using all RIA screening data from all studies, 14% of the patients had one or more positive post-treatment anti-degarelix antibody measurements. Overall, 11% of patients became antibody positive after one year of treatment. For patients receiving the 80 mg (20 mg/mL) maintenance dose 10% were positive after 1 year.

Although there was a tendency towards increased prevalence of anti-degarelix antibodies with longer treatment time, the levels of anti-degarelix antibodies were low in the vast majority of the patients throughout. At all time-periods approximately 80% of all the patients that showed anti-degarelix antibodies had a concentration of <250 ng/mL, and less than 10% showed concentrations >500 ng/mL. Furthermore, once the anti-degarelix antibodies were developed, the concentration in the individual patient did not seem to increase.

#### **2.3.3.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?**

Evaluation of degarelix levels in patients from the phase 3 trial with positive antibody findings indicated that the levels of non-antibody bound degarelix in the blood were generally above levels targeted for efficacy ( $\geq 9$  ng/mL). Therefore, it is unlikely that the development of anti-degarelix antibodies has an impact on pharmacokinetics or testosterone concentrations.

#### **2.3.3.3 Do the anti-product antibodies have neutralizing activity?**

The sponsor did not provide any information on the neutralizing activity of anti-degarelix antibodies. Because of low levels of antibody found in patients (<1,000 ng/mL) coupled with interfering levels of free degarelix the sponsor concluded that the neutralizing assay which was developed lacks the sensitivity for application to clinical samples.

#### **2.3.3.4 What is the impact of anti-product antibodies on clinical efficacy?**

See Section 2.3.3.2 above. In the phase 3 trials patients maintained degarelix concentrations  $\geq 9$  ng/mL which are needed to maintain testosterone suppression. Since the presence of anti-product antibodies did not affect levels of degarelix there is no reason to expect anti-antibodies to affect efficacy.

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**2.3.3.5 What is the impact of anti-product antibodies on clinical safety? (e.g., infusion-related reactions, hypersensitivity reactions, cross-reactivity to endogenous counterparts, etc.)?**

Standardized MedDRA Queries were used by the sponsor to define important hypersensitivity reactions in terms of anaphylactic reaction, angioedema and severe cutaneous adverse reactions. Only 10 (5 from the phase 3 study CS21) of more than 19,000 dosing occasions (almost 5,000 in CS21) led to patients reporting adverse events that could potentially be hypersensitivity reactions. None of these patients had antibodies at the time of reaction. Only three of these events could have had a timely relationship with dosing of degarelix, and the three patients completed the studies without additional potential hypersensitivity reactions. There were no immediate anaphylactic responses.

**2.4 EXTRINSIC FACTORS**

**2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?**

There were no specific studies or analyses designed to evaluate the effects of factors such as herbal products, diet, smoking or alcohol use on the PK or PD of degarelix.

**2.4.2 Drug-drug interactions**

**2.4.2.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?**

No. Degarelix is neither a substrate, inhibitor or inducer of CYP450 activity.

**2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?**

No. *In vitro*, degarelix was found to be a poor substrate of CYP450 activity following incubation of HLM at concentrations folds higher than the concentrations seen at Tmax following a 240 mg SC dose of degarelix.

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**2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?**

***In vitro* induction**

The potential for degarelix to induce CYP1A2, 3A4 and 2C9 was investigated using cryopreserved human hepatocytes (AR-DCB-0025.01). Degarelix was tested in concentrations of 0.1, 1 and 10  $\mu$ M, and 25 $\mu$ M rifampin was used as a positive control for induction of CYP3A4 and CYP2C9, and 50 $\mu$ M omeprazole as positive control for induction of CYP2C9.

Degarelix did not induce CYP3A4, 1A2 or 2C9 at a concentration of 10  $\mu$ M (16,323 ng/mL) which is magnitudes higher than the mean clinical Cmax, 0.03  $\mu$ M (53.4 ng/mL). The positive controls showed positive induction signals in the same system. Based on the FDA drug-drug interaction guidance if degarelix is not an inducer of CYP3A4 then it can be concluded that it is not an inducer of 2C8, 2C9, or 2C19.

### ***In vitro* inhibition**

The potential for degarelix to act as an inhibitor of CYP enzymes was investigated using human liver microsomes (IAP-0146-01). Four concentrations of FE 200486: 4.2, 42, 420 and 4200 nM. The substrates tested are as follows; phenacetin (CYP1A2), Diclofenac (2C9), omeprazole (2C19), bufuralol (2D6), chlorzoxazone (2E1), and testosterone (3A4/5). The positive control inhibitors used were furafylline for 1A2, sulfaphenazole for 2C9, ketoconazole for 2C19, quinidine for 2D6, disulfiram for 2E1, and miconazole for 3A4/5.

For all the enzymes tested, there were no inhibitory effects of FE 200486 observed on relevant marker enzyme activities in human liver microsomes. The positive controls for all enzymes inhibited their respective enzymes. These results indicate that FE 200486 is unlikely to cause significant inhibition of CYP1A2, CYP3A4/5, CYP2C9, CYP2C19, CYP2D6 & and CYP2E1 activities *in vivo*.

#### **2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?**

The sponsor studied the effect of FE200486 on human Pgp (ABCB1/MDR1) transporters in ATPase assays and Fluorescent dye efflux assays.

ATPase assays are *in vitro* assays, using membrane vesicles isolated from cells over expressing the respective transporter. The ATPase assays are designated to indicate the nature of the interaction between the test compound and the transporter. If a test compound significantly stimulates the basal ATPase activity of the transporter it is probably a good substrate of the transporter. In inhibition assays, the test compound is tested for its ability to reduce the stimulatory effect of the control drugs on the respective ABC transporter.

The fluorescent dye assays are indirect inhibitory-type cellular assays. They provide information on any interaction between the ABC transporter and the test drug that would affect the transport of the reporter compound (precursor of the fluorescent dye).

The degarelix did not show any interaction with Pgp in either of these assays.

#### **2.4.2.5 Are there other metabolic/transporter pathways that may be important?**

The sponsor also studied the effect of degarelix on MXR and MRP2 human ABC efflux transporters in using ATPase assays. Indirect vesicular transport assays were used to investigate interaction of the compounds with human MXR, MRP2 and BSEP. Fluorescent dye efflux assays were used to study the interaction of the compounds with human MDR1 and MXR. Cell based uptake transporter assays were applied to identify interactions with human OATP1B1, OATP1B3 and OATP2B1.

The compound inhibited OATP1B3 mediated fluo-3 transport with an IC<sub>50</sub> value of 10 μM (16323 ng/mL). The clinical relevance of this OATP1B3 transporter inhibition occurring is unlikely given that the C<sub>max</sub> of degarelix after a loading dose of 240 mg is only 26.2 ng/mL which is far less than the IC<sub>50</sub> (16323 ng/mL).

The compound did not show any interaction with BCRP, MRP2, BSEP, OATP1B1 and OATP2B1 in any of the assay used up to 10 μM (16323 ng/mL).

**2.4.2.6 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?**

The label does not specify co-administration of another drug.

**2.4.2.7 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?**

No. There is no reason to suspect *in vivo* drug-drug interactions based on the *in vitro* data.

**2.5 GENERAL BIOPHARMACEUTICS**

**2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?**

Not applicable

**2.5.2 What is the composition of the to-be-marketed formulation?**

The degarelix drug product is formulated with mannitol as \_\_\_\_\_ product for reconstitution with water for injection (WFI) prior to subcutaneous injection. The proposed term for the dosage form is "powder \_\_\_\_\_ for injectable \_\_\_\_\_ (USP)". The composition of both drug products are below.

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- Composition of 80 mg drug product (20 mg/mL)

Raw Material	Amount	Function
Degarelix		Drug substance
Mannitol	_____	_____

- Composition of 120 mg drug product (40 mg/mL)

Raw Material	Amount	Function
Degarelix		Drug substance
Mannitol	_____	_____

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The only alteration in the formulation of degarelix was the synthesis of the degarelix drug substance. \_\_\_\_\_ method was used to provide drug supplies for the phase 1 (CS01, CS05, CS08) and phase 2 (CS02, CS06, CS07, CS11, CS12, CS14 and corresponding extension studies) studies. \_\_\_\_\_

\_\_\_\_\_ method was introduced. This method was used for the pivotal phase 3 study (CS21). \_\_\_\_\_ method will be used to provide the degarelix market supply.

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**2.5.3 What moieties should be assessed in bioequivalence studies?**

Degarelix should be assessed in human plasma.

**2.5.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?**

Degarelix is administered subcutaneously therefore an evaluation of food effect is not necessary.

**2.5.5 Has the applicant developed an appropriate dissolution method and specification that will assure in vivo performance and quality of the product?**

Not applicable.

**2.6 ANALYTICAL SECTION**

**2.6.1 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?**

There are no relevant metabolites of degarelix formed in human plasma. For all studies, degarelix was measured in human plasma.

**2.6.2 Were the analytical procedures used to determine drug concentrations in this NDA acceptable?**

During the degarelix clinical development program, bioanalytical methods based on both radioimmunoassay (RIA) and liquid chromatography with tandem mass spectrometry detection (LC-MS/MS) have been used for the quantification of degarelix in human biological samples (plasma and urine). A summary of the validation report results are below:

- Validation QFD-141: This human plasma radioimmunoassay was used in study CS01. The lower limit of quantitation was determined to 100 pg/mL for human plasma. The between-run precision (total precision) of the assay, expressed as coefficient of variation, at low (=LLOQ) quality control validation samples over three analytical occasions was between 5.9 % and 10.5 %. At the medium concentration the coefficient of variation was between 3.4 % and 5.8 %. At the high concentration level (=ULOQ) the coefficient of variation was between 9.8 % and 21%. The between-run accuracy (mean values) of the method at low (=LLOQ) quality control validation samples over three analytical occasions was between 106 % and 123 %. At the medium concentration the accuracy was between 90.4 % and 117 %. At the high concentration level (=ULOQ) the accuracy was between 88.2% and 111%.
- Validation 0595/027: This human plasma LS/MS/MS method was used in studies CS02, CS05. The lower limit of quantification (LLOQ) for FE200486 in human plasma was 0.5 ng/mL, with linearity demonstrable to 50 ng/mL. All coefficients of determination ( $r^2$ ) were better than or equal to 0.9958. Intra-assay precision values, based upon coefficients of variation (CV%) of QC samples, were less than or equal to 7.5%. Inter-assay precision values, based upon the CV% at the QC levels (LoQC, MeQC, HiQC and DiQC) were less than or equal to 14.1%. The inter-assay accuracy values, based upon the calibration standards across the range, were between 98.2% and 102.6%. The maximum number of freeze/thaw cycles was two, and samples could be stored at room temperature up to 4 hours and stored at 4°C for 2 months.
- Validation 0595/036: This human plasma LC-MS/MS method was used in studies CS02A, CS06, CS06A, CS07, and CS07A. The lower limit of quantification (LLOQ) for FE200486

in human plasma was 0.5 ng/mL, with linearity demonstrable to 50ng/mL. All coefficients of determination ( $r^2$ ) were better than or equal to 0.9980. Intra-assay precision values, based upon coefficients of variation (CV%) of QC samples, were less than or equal to 9.3%. Inter-assay precision values, based upon the CV% were less than or equal to 13.9%. The inter-assay accuracy values, based upon the calibration standards across the range, were between 96.8% and 106.0%.

- Validation MVR-PD-0010.01: This human plasma LC-MS/MS method was used in study CS08. Both intra-assay and inter-assay precision requirements (CVs  $\leq$  15 % (VAL 2-4), whereas CV of VAL 1  $\leq$  20 % which defines LLOQ) were met. Accuracy (both intra-assay and inter-assay) on back-calculated degarelix concentrations required a mean deviation  $\leq$ 15% (VAL 2-4) and  $\leq$  20% (VAL 1) from theoretical and these criteria were also met.
- Validation 0595/046: This human plasma LC-MS/MS method was used in studies CS11, CS11A, CS12, CS12A, CS15, CS15A, — CS21, CS21A, and CS23. The lower limit of quantification (LLOQ) for FE200486 in human plasma was 0.5 ng/mL, with linearity demonstrable to 50 ng/mL. The correlation coefficient ( $r^2$ ) varied between 0.9994 and 0.9996. Intra-assay precision values, based upon coefficients of variation (CV%) of QC samples, were less than or equal to 6.5%. Inter-assay precision values, based upon the CV% at the QC levels (LLOQ QC, LoQC, MeQC and HiQC) were less than or equal to 7.5%. The inter-assay accuracy values, based upon the calibration standards across the range, were between 97.0% and 106.0%.
- Validation 7198-111: This human plasma LC-MS/MS method was used in studies CS14 and CS14A. The lower limit of quantitation (LLOQ) for FE200486 in human plasma was 0.500 ng/mL, with linearity demonstrable to 50.0 ng/mL (upper limit of quantitation, ULOQ). Inter-assay precision and accuracy values based upon data from the calibration standards across the calibration range were  $\leq$  15%. Mean intra-assay precision and accuracy data, based upon percent Relative Standard Deviation (%RSD) and percent Deviation of Mean from Theoretical (%DMT) of quality control (QC) samples were  $\leq$  15%. Similarly, mean inter-assay precision and accuracy data, based upon the %RSD and %DMT at the low, mid, and high QC levels were  $\leq$  15%
- Validation 0595/048: This human plasma LC-MS/MS method was used in studies CS11, and CS11A. The lower limit of quantification (LLOQ) for FE200486 in Japanese human plasma was 0.5 ng/mL, with linearity demonstrable to 50 ng/mL. All correlation coefficients ( $r^2$ ) were better than or equal to 0.9980. Intra-assay precision values, based upon coefficients of variation (CV%) of QC samples, prepared in Japanese plasma, were less than or equal to 2.7%. Precision values, based upon the CV% of the human plasma QC samples were less than or equal to 3.0%. The accuracy values, based upon the calibration standards across the range, were between 95.4% and 110.0%

### Testosterone

Methods based on LC-MS/MS as well as immunoassay were used for the quantification of testosterone in human serum. The accuracy and precision of the LC-MS/MS methods used for the quantification of testosterone in human plasma samples are below

Laboratory	Calibration Range (pg/mL)	Lower Limit of Quantification (pg/mL)	Mean Inter-Occasion Accuracy (%)	Mean Inter-Occasion Precision*
[Redacted]	100—15000	100	91—104	4—12
	50—25000	50	94—108	4—14
	25—50000	30	87—98	4—10

\*Expressed as coefficient of variation  
<sup>b</sup>At lower limit of quantification, mean inter-occasion accuracy was 109% and mean inter-occasion precision was 15%.

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The [Redacted] analyzed testosterone samples from the first clinical study CS01. The method was based on [Redacted]. For this method calibration standards and quality control samples were prepared in horse serum.

[Redacted] solutions tested samples from studies CS02, CS05, CS07, CS08, CS11, and CS12. This method was based [Redacted]

[Redacted]

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The remainder of the studies (CS14, CS14, CS15, — CS21, CS23) were analyzed [Redacted]. This method was based on an [Redacted]. For this method, a water blank, five assay control pools and [Redacted] standard are processed with samples to assess accuracy and precision of the assay. In two studies, CS15 and CS21, to optimize the accuracy of the testosterone results, plasma samples were divided into three aliquots, all of which were analyzed and the median testosterone value was reported.

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       Draft Labeling (b5)

       Deliberative Process (b5)

## 4 APPENDICES

### 4.1 INDIVIDUAL STUDY REVIEWS

Study/ Report	Objectives	Design	Subjects	Doses	Remarks
CS01	to establish the dose and T suppression.	Phase 1 single dose, randomized, placebo controlled, double-blind, dose escalation in men aged 19-69 years.	Healthy Men 19-69 years of age. 6 subjects at each dose.	0.5 mg (5 mg/mL) 2 mg (10 mg/mL) 5 mg (10 mg/mL) 10 mg (20 mg/mL) 20 mg (20 mg/mL) 40 mg (20 mg/mL) 40 mg (10 mg/mL) 40 mg (20 mg/mL) 30 mg (15 mg/mL) 30 mg (30 mg/mL)	Data not helpful as doses are too low and completed in HV's.  Data for 40 mg (10 mg/mL) was used for comparison to cancer patients.
CS05	to assess the safety and tolerability following a single dose administered as IV infusion, IM or SC injections to determine concentration response relationship between degarelix and T in healthy elderly male subjects.	Phase 1 single dose, open-label, dose escalation in men aged 19-46 years.	Healthy Men 19-46 years of age. 6 subjects at each dose	1, 5, 6, 15, or 30 µg/kg IV over 15 or 45 min. 20 mg (5 mg/mL) SC 20 mg (5 mg/mL) IM	IM, and IV data used. Also for protein binding, and urine analysis.  not reviewed.
CS08	to investigate whether the PK of degarelix in patients with mild or moderate hepatic impairment differs from that in healthy subjects.	Phase 1 single dose, open-label, randomized, placebo-controlled, dose-response, in elderly subjects (≥ 65 years)	48 Healthy men ≥65 years of age	0.864, 1.73, 3.70, 9.87, 24.7 or 49.4 µg/kg IV over 48 hours	
CS23	To investigate whether the effect on testosterone suppression of ascending single doses of degarelix administered subcutaneously to prostate cancer patients	Phase 1 single dose, open-label, dose escalation	hepatic impaired; moderate = 16, mild = 16. 16 healthy volunteers	1 mg IV over 1-hour	Used for hepatic impairment analysis. Also for urine analysis and metabolite identification.
CS06	To investigate the effects of ascending single dose on T suppression	Phase 1 single dose, open-label, dose escalation	82 prostate cancer patients, 10 in 40 mg group and 24 in each of the 80, 120 and 160 mg groups. 172 prostate cancer patients	40 mg (10 mg/mL) 80 mg (20 mg/mL) 120 mg (30 mg/mL) 160 mg (40 mg/mL)	Used for basic PK parameters, dose response, metabolite analysis and comparison to healthy PK.
CS07				120 mg (20 mg/mL) 120 mg (40 mg/mL) 160 mg (40 mg/mL) 200 mg (40 mg/mL) 200 mg (60 mg/mL) 240 mg (40 mg/mL) 240 mg (60 mg/mL) 320 mg (60 mg/mL)	Used for basic PK parameters, dose response, and comparison to Japanese data

Study/ Report	Objectives	Design	Subjects	Doses	Remarks
CS11	to evaluate the safety and tolerability.	Phase 1 single-dose, open-label, dose escalation study in Japanese subjects	18 Japanese prostate cancer patients	160 mg (40 mg/mL) 200 mg (40 mg/mL) 240 mg (40 mg/mL)	Japanese PK data, urine analysis, metabolite identification
CS02	to select a dose regimen that would result in T <0.5 ng/mL in at least 70% of patients in at least one week and in at least 90% at 2, 4, 8, 12, 16, 20 and 24 weeks from initial dosing.	Phase 2 randomized, open-label, parallel group, uncontrolled study 6-month study using a loading dose.	129 prostate cancer patients	40 mg (20 mg/mL) x 2 + 40 mg (20 mg/mL) Q28D 80 mg (20 mg/mL) x 2 + 40 mg (20 mg/mL) Q28D 80 mg (20 mg/mL) + 20 mg (10 mg/mL) Q28D	Used for dose response.
CS12	to demonstrate the efficacy of different degarelix dosing regimens by testosterone suppression after 196 days of treatment	open-label, randomized, parallel, uncontrolled 12-month study.	187 prostate cancer patients	200 mg Loading dose + 80 mg Q28D 200 mg Loading dose + 120 mg Q28D 200 mg Loading dose + 160 mg Q28D 240 mg Loading dose + 80 mg Q28D 240 mg Loading dose + 120 mg Q28D 240 mg Loading dose + 160 mg Q28D <i>All doses used the 40 mg/mL concentration</i>	Used for dose response and multiple dose PK.
CS14	To demonstrate the efficacy of two different degarelix dosing regimens by testosterone suppression (< 0.5 ng/mL) after 196 days (7 cycles) of treatment in prostate cancer patients.	Phase 2 open-label, randomized, parallel group, uncontrolled 12 month study	127	200 mg loading dose + 40 mg (60 mg/mL) Q28D 200 mg loading dose + 40 mg (80 mg/mL) Q28D	Used for dose response.
CS15	To demonstrate that the efficacy in achieving and maintaining testosterone castration levels (≤0.5 ng/mL) in prostate cancer patients treated up to either 12 or 13 months is at least 80%.	Phase 2/3 open-label, randomized, parallel group, uncontrolled 12 month study with 3-month depot	n/a	240 mg (40 mg/mL) LD + 240 mg (40 mg/mL) Months 3-6-9 240 mg (40 mg/mL) LD + 240 mg (60 mg/mL) Months 3-6-9 240 mg (40 mg/mL) LD + 240 mg (60 mg/mL) Months 4-7-10	1 <sup>st</sup> month exposure of 240 mg used for population PK and dose finding.
CS21	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.	Phase 3 randomized, parallel, groups, open-label active controlled study	409	240 mg (40 mg/mL) loading dose + 80 mg (20 mg/mL) Q28D 240 mg (40 mg/mL) loading dose + 160 mg (40 mg/mL) Q28D Leuprolide 7.5 mg IM every 28 days.	efficacy data, adverse events

## 4.2 PHARMACOMETRIC REVIEW

### Pharmacometrics Review

<b>NDA</b>	22-201
<b>Submission Date:</b>	14 February 2008
<b>Proposed Brand Name:</b>	FIRMAGON®
<b>Generic Name:</b>	degarelix
<b>Formulation:</b>	80 mg and 120 mg injectable _____
<b>Clinical Pharmacology Reviewer:</b>	Julie M. Bullock, Pharm.D.
<b>Pharmacometrics Reviewer:</b>	Jun Yang, Ph.D.
<b>Clinical Pharmacology Team Leader:</b>	Brian Booth, Ph.D.
<b>Pharmacometrics Team Leader:</b>	Yaning Wang, Ph.D.
<b>OCP Division:</b>	Division of Clinical Pharmacology V
<b>ORM Division:</b>	Division of Drug Oncology Products
<b>Sponsor:</b>	Ferring
<b>Submission Type; Code:</b>	Original NDA; 000
<b>Dosing regimen:</b>	Loading dose of 240 mg followed by monthly (Q28 Day) maintenance doses of 80 mg.
<b>Indication:</b>	Treatment of patients with prostate cancer _____

b(4)

### BACKGROUND

Degarelix is a water-soluble gonadotropin releasing hormone (GnRH) antagonist under development for suppression of testosterone in prostate cancer patients. Ferring conducted seven phase 2 trials with various s.c. injection volume, drug concentration, dose, dose interval, and length of durations. Patients in the phase 2 studies were randomized to receive various loading doses (40 to 240 mg) followed by various maintenance doses (20 to 160 mg) of degarelix. Single doses up to 320 mg were tested. No obvious adverse events were observed in these studies.

An EOP2a meeting was held in 2005, the FDA pharmacometrics group suggested that a target trough level > 9-10 ng/mL of degarelix would result in maintenance of testosterone concentration at castration level in >90% of subjects. These assumptions were used to guide dose finding for phase 3 evaluation (CS21). Two degarelix doses were studied in pivotal CS21 trial. Both arms used the 240 mg (40 mg/mL) loading dose and patients received either a 80 mg (20 mg/mL) (arm1) or 160 mg (40 mg/mL) (arm2) maintenance dose. The sponsor intends to market a 240 mg (40 mg/mL) loading dose (LD) with 80 mg (20 mg/mL) maintenance doses (MD). The clinical efficacy is defined as no testosterone (T) concentration > 0.5 ng/ml from day 28 to 1 year in 90% or more patient during the therapy.

### KEY REVIEW QUESTIONS

The purpose of this review is to address the following key questions;

1. What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?
2. What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response, and what is the impact of any differences in exposure on efficacy?

### RESULTS OF DATA ANALYSIS

#### Correlation Between Plasma Concentration and Response

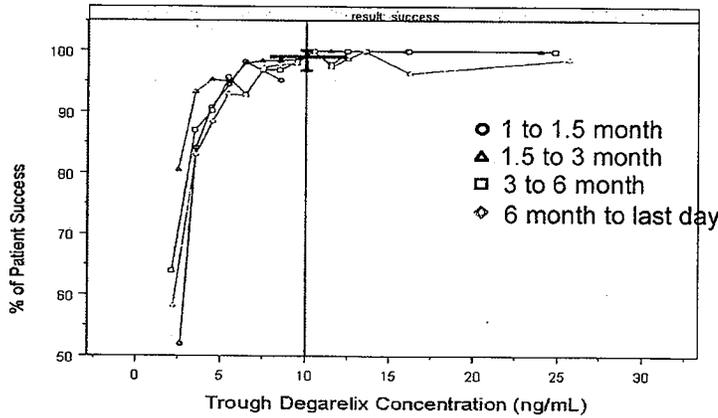
Based on the study of CS02, CS06, CS07, CS12 and CS14 (Table 1), the correlation between degarelix trough concentration and drug response was extensively studied by FDA pharmacometrics group during EOP2 meeting. Data from the above studies were binned into 4 time ranges (1-1.5, 1.5-2, 3-6 and 6-12 months). The correlation between plasma trough concentrations and percentage of responses were combined and shown in Figure 1. The plasma concentration of 7.5 and 9.5 ng/ml correspond to a success rate of 70% to 97% (mean 94%) and 92% to 97% (mean 96.4%), respectively.

Study	Number of individuals	Dose levels
CS05 (5.3.1.1)	24	i.v. 1.5, 6, 15, 30 µg/kg at 5µg/mL
CS06/6A (5.3.5.2)	48	80@20 160@40
CS07/7A (5.3.5.2)	170	120@20 120@40 160@40 200@40 240@40 200@60 240@60 320@60
CS12/12A (5.3.5.2)	129	200/120/160@40 200/160/160@40 200/160@40 200/80/160@40 240/120/160@40 240/160/160@40 240/160@40 240/80/160@40
CS14/14A (5.3.5.2)	63	80@20 80@20/160@40
CS15 (5.3.5.2)	447	240@40/240@40 (3-6-9) 240@40/240@60 (3-6-9) 240@40/240@60 (4-7-10)
<b>Total</b>	<b>881</b>	

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*Table 1. Summary of clinical studies in Phase 1 and 2.*

Treatment Success Rate (% patients with  $T \leq 0.5 \text{ ng/mL}$ ) at Various Degarelix Trough Concentrations

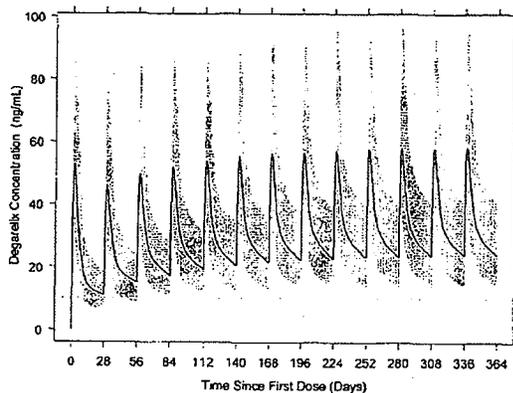


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Figure 1. Degarelix trough concentration–response relationship at various times (1-1.5, 1.5-2, 3-6 and 6-12 months). Treatment Success Rate is calculated as the percentage of patients with  $T \leq 0.5 \text{ ng/mL}$ .

All these studies were based on the  $\curvearrowright$  formulation, which has a bioavailability of 0.23 and 0.37 when the dosing concentration equals to 40 and 20 mg/mL, respectively. The sponsor further conducted CS15 study using a new formulation of  $\curvearrowleft$  with a LD of 240 mg (40 mg/mL) giving every 3 month. Population PK study showed an improved bioavailability (0.32) for formulation  $\curvearrowleft$  when the dosing concentration equals to 40 mg/mL. Further simulation study based on individual PK parameter estimates from CS 15 indicating that a LD of 240 mg and a MD of 160mg would achieve Degarelix trough concentrations well above 10ng/ml (Figure 2). The simulation study on a MD of 80 mg was not submitted, which could be due to a lack of bioavailability data for the dosing solution of 20 mg/mL.

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Figure 2. Simulation of monthly dosing schedule for the  $\curvearrowleft$  formulation with loading dose of 240mg@40 and maintenance dose 160mg@40.

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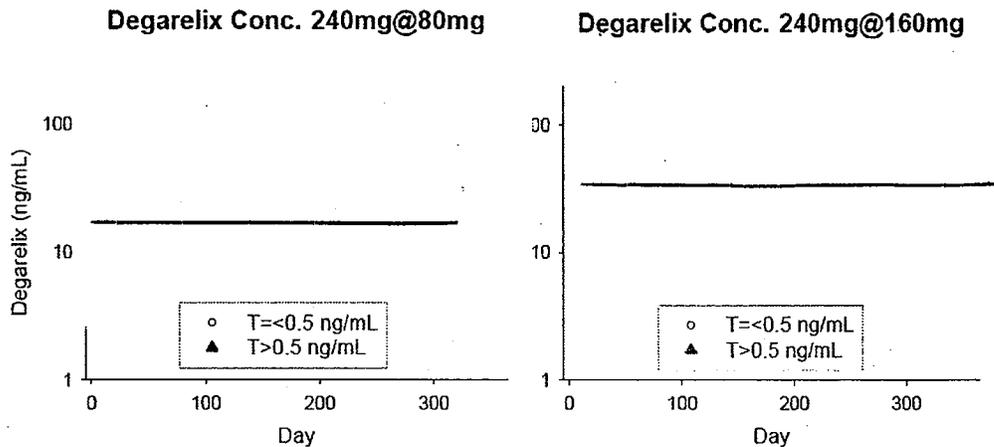
### Study CS21

Study CS21 was an open-label, multi-center, randomized, parallel-group study of degarelix one month dosing regimens (160 mg (40 mg/mL) — and 80 mg (20 mg/mL) — in comparison to Lupron Depot® (7.5 mg) in patients with prostate cancer. 620 patients were enrolled and randomly assigned to receive one of the following treatments:

- Arm 1: Degarelix 240/160 – 240 mg loading dose with 160 mg maintenance doses Q28 days.
- Arm 2: Degarelix 240/80 – 240 mg loading dose with 80 mg maintenance doses Q28 days.
- Leuprolide arm: Leuprolide 7.5 mg once every 28 days.

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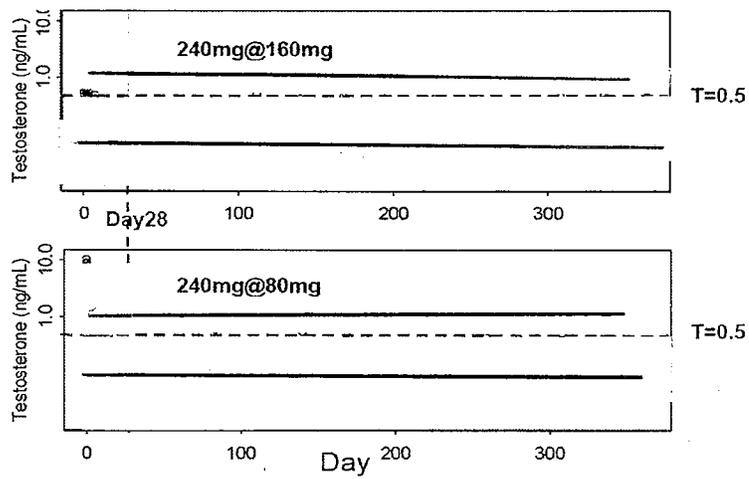
The plasma degarelix concentrations vs. time were shown in Figure 3. The mean degarelix concentrations in both arms are higher than 10 ng/mL. A population PK model on study CS21 showed a bioavailability of 0.38 and 0.60 for the formulation of — when the dosing concentration equals to 40 and 20 mg/mL, respectively.



b(4)

Figure 3. Study CS21: Observed degarelix concentrations by time for one year.

Results indicate that the probability of maintaining  $T \leq 0.5$  ng/mL from Day 28 through Day 364 was 98.5%, 97.6% and 96.5% for arm1, arm2 and the Leuprolide arm, respectively. The 95% confidence intervals for the cumulative probability of  $T \leq 0.5$  ng/mL for arm1 and arm2 from Day 28 to Day 364 were greater than 90% which fits the efficacy criterion pre-specified by the agency. It also appeared that the mean degarelix concentration in arm1 was higher than that of arm2 (20.9 vs. 13.7 ng/mL). Even though the testosterone concentrations are similar between these two arms as shown in Figure 4, the overall response rate is numerically higher for arm1 (98.5%,) than arm2 (97.6%). The degarelix concentrations in failed subjects (Figure 3) are in the average range and therefore the main reason for the failure could be the lack of sensitivity of these patients to degarelix.



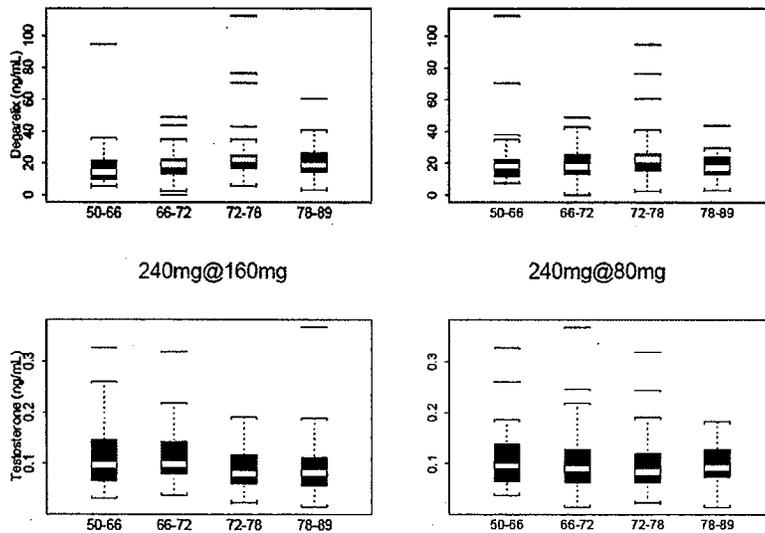
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Figure 4. Testosterone Concentrations vs. time in two degarelix arms.

Age Effect

The patients were evenly assigned into 4 groups (55-66, 66-72, 72-78 and 78-89 years old). No clear relationship between age and degarelix exposure/testosterone response was observed (Figure 5).

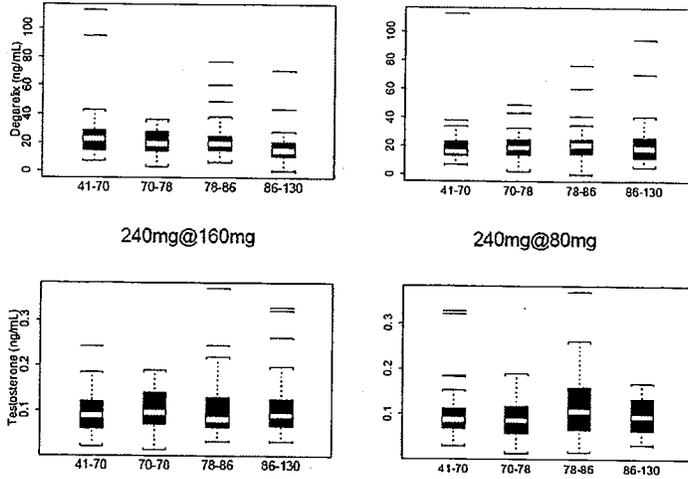


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Figure 5. Age effect on trough concentrations of degarelix and testosterone.

**Body Weight and Race**

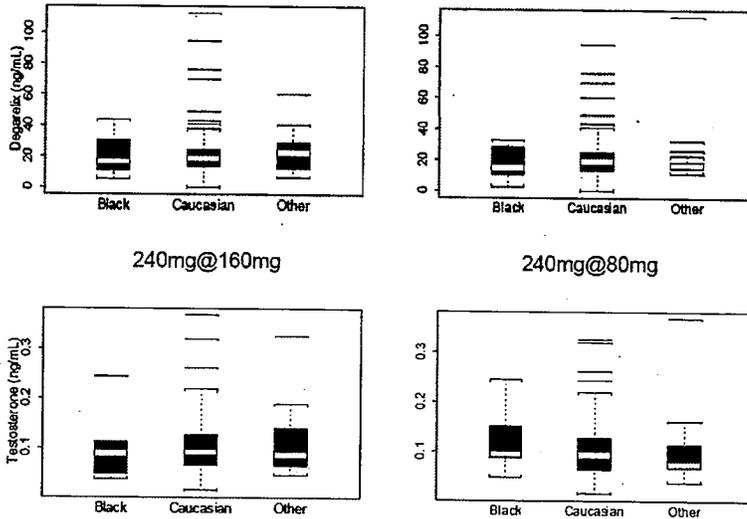
The relationship between response and other demographic variables, body weight and race, was also examined (Figure 6 and 7). The patients were evenly assigned into 4 groups (41-70, 70-78, 78-86 and 86-130 kg). No clear relationship between body weight and degarelix exposure/testosterone response was observed (Figure 6).



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*Figure 6. Body weight effect on trough concentrations of degarelix and testosterone.*

In the pivotal study, about 83% of total subjects are Caucasian, 6.8% are Black and 9.8% are other. No apparent difference in degarelix trough concentration and testosterone concentration among Caucasian, Black and Other (Figure 7) was seen. There was only one Asian in each treatment arm, and therefore the Asian was included in group of other and was not studied separately.

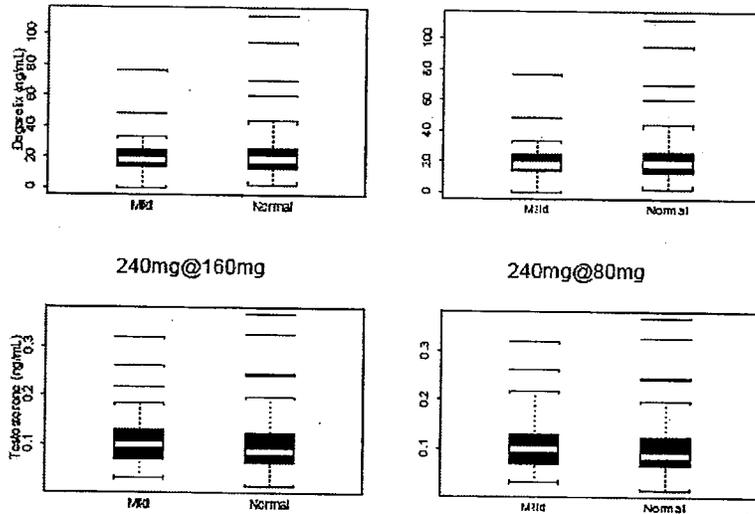


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*Figure 7. Race effect on trough concentrations of degarelix and testosterone.*

### Renal Function

The subjects were classified into mild ( $\leq 80$  mL/min) and normal ( $> 80$  mL/min) groups. There was only one subject in CS21 study with moderate impairment (CRCL 30-50 mL/min). There were no patients with severe renal impairment (CRCL  $< 30$  mL/min) enrolled in this study. The testosterone concentrations for the moderate renal impairment subject from day 28 to one year are all below 0.5 ng/mL. With respect to renal function, there was no apparent difference between mild and normal groups within each treatment arm (Figure 8).



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Figure 8. Renal function on trough concentrations of degarelix and testosterone.

### CONCLUSION

Overall, treatment arm1 tends to have higher mean degarelix concentration than that of arm2. No difference in drug response between arm1 and arm2 was seen. The intrinsic factors (age, body weight, race and renal function) do not seem to affect the mean testosterone response.

\_\_\_\_\_  
Jun Yang, Ph.D.  
Clinical Pharmacology Reviewer  
CDER/OTS/OCP/DCP5

Date: \_\_\_\_\_

\_\_\_\_\_  
Yaning Wang, Ph.D.  
Pharmacometrics Team Leader

Date: \_\_\_\_\_

4.3 FILING MEMO

Office of Clinical Pharmacology <i>New Drug Application Filing and Review Form</i>				
General Information About the Submission				
NDA Number	22-201	Proposed Brand Name	Firmagon®	
DCP Division (I, II, III, IV, V)	V	Generic Name	degarelix	
Medical Division	Oncology	Drug Class	GnRH antagonist	
OCP Reviewer	Julie M. Bullock, Pharm.D.	Indication(s)	prostate cancer	
OCP Team Leader	Brian Booth, Ph.D.	Dosage Form	80 mg, 120 mg injectable: _____	
Date of Submission	Feb 14, 2008	Dosing Regimen	240 mg loading dose, 80 mg monthly	
Due Date of OCP Review	Sept 14, 2008	Route of Administration	subcutaneous	
Standard PDUFA Due Date	Nov 14, 2008	Sponsor	Ferring	
Clinical Pharmacology Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	22		16 Method + Validation for Degarelix 4 method + validation for Testosterone 2 long-term stability reports
<b>I. Clinical Pharmacology</b>				
Mass balance:	X	5		no ADME study blood/feaces/urine from 5 studies
Isozyme characterization:	X	6		2 substrate studies 3 studies for induction/inducer 1 P-gp
Blood/plasma ratio:				
Plasma protein binding:	X	3		2 protein binding studies 1 plasma stability study
<b>Pharmacokinetics (e.g., Phase I) -</b>				
<i>Healthy Volunteers-</i>				
single dose:	X	3		CS01 DE SC CS05 DE IV, SC, IM CS08 DE IV
multiple dose:				
<i>Patients-</i>				
single dose:	X	2		CS06 DE SC CS07 DE SC
multiple dose:	X	5		CS02 Qmonth SC CS12 Qmonth SC CS14 Qmonth SC CS15 Q3month SC CS21 Qmonth SC
<b>Dose proportionality -</b>	X			
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				

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ethnicity:				CS11 DE SC Japanese subjects
gender:				
geriatrics:				
renal impairment:				
hepatic impairment:	X	1		CS23 IV HV study with mild/moderate imp.
pediatrics:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	X	1		
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability:</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies:</b>				
<b>QTC studies:</b>				
<b>In-Vitro Release BE</b>				
<b>(IVVC):</b>				
<b>Bio-wavier request based on BCS</b>				
<b>BCS class</b>				
<b>III. Other CPB Studies</b>				
<b>Biliary Elimination</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>				
<b>Filability and QBR comments</b>				
	"X" if yes	<b>Comments</b>		
Application filable?	X			
Comments sent to firm?	X			
QBR questions (key issues to be considered)				
Other comments or information not included above				
Primary reviewer Signature and Date	Julie M. Bullock, Pharm.D.			
Secondary reviewer Signature and Date	Brian Booth, Ph.D.			

CC: HFD-150 (CSO - C Huntley; MTL - A Farrell; MO - M Ying)  
HFD-860 (Reviewer - J Bullock; DDD & Acting TL - B Booth; DD - A Rahman)

**Clinical Pharmacology - NDA Filing Memo**

**NDA:** 22-201/000 Original Submission **IND:** 51,222  
**Compound:** degarelix for injectable \_\_\_\_\_ 80 mg and 120 mg  
**Sponsor:** Ferring Pharmaceuticals  
**Filing Date:** April 28, 2008  
**Reviewer:** Julie M. Bullock, Pharm.D.

b(4)

**Background and Mechanism of action:** The current submission is the original NDA for degarelix for the treatment of patients with prostate cancer \_\_\_\_\_  
\_\_\_\_\_ Degarelix is a third generation gonadotropin releasing hormone (GnRH) antagonist which binds to the GnRH receptor resulting in the suppression of pituitary gonadotropins with subsequent effects on the gonadal tissue. This leads to decreases in circulating levels of luteinising hormone (LH), follicle-stimulating hormone (FSH) and testosterone (T).

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Degarelix is a synthetic decapeptide which forms a depot following subcutaneous injection. This depot formation results in a sustained release of degarelix. The sponsor is proposing a starting dose of 240 mg, followed by monthly maintenance doses of 80 mg.

**Formulation:** The only alteration in the formulation of degarelix was the synthesis of the degarelix drug substance. \_\_\_\_\_ method provided clinical trial supplies for the phase 1 (CS01, CS05, CS08) and phase 2 (CS02, CS02A, CS06, CS06A, CS07, CS07A, CS11, CS11A, CS12, CS12A, CS14 and CS14A) studies \_\_\_\_\_

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\_\_\_\_\_ method was introduced. This method was used the phase 3 study CS21, the phase 2/3 study CS15, and the phase 2 study \_\_\_\_\_ along with their corresponding extension studies (CS21A and CS15A). \_\_\_\_\_ method will be used to provide the degarelix market supply.

The population PK analysis indicates that \_\_\_\_\_ drug product resulted in higher exposure than the \_\_\_\_\_ drug product during the first month after administration (modelled at a dose level of 240 mg (40 mg/mL)). The model predicted that at all time-points during the first month after administration (and beyond) the plasma concentration of degarelix would be higher for \_\_\_\_\_ drug product than for \_\_\_\_\_ drug product at the same dose and injection suspension concentration, thus ensuring that the degarelix concentration sustains above the critical 9-10 mg/mL for at least as long as with the \_\_\_\_\_ product. The results of the pivotal clinical trial (CS21) in which the \_\_\_\_\_ product was used indicate that the differences observed in the PK profiles between the two formulations had no impact on the efficacy or safety of the compound.

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The sponsor conducted eleven studies with the 1-month degarelix depot. Four of the studies were conducted in healthy volunteers (see Table 1), and the other studies were done in patients with prostate cancer. Four of the studies in patients with prostate cancer were used to support efficacy of degarelix (see Table 3). The other studies in patients were initial tolerability studies and a Japanese patient population study (see Table 2). One study was submitted which used the

3-month depot formulation.

**TABLE 1. Clinical Pharmacology Studies in Healthy Volunteers**

Study	Design	Doses
CS01	single dose, randomized, placebo controlled, double-blind, dose escalation in men aged 19-69 years.	0.5 mg (5 mg/mL), 2 mg (5 mg/mL), 5 mg (10 mg/mL), 10 mg (10 mg/mL), 20 mg (20 mg/mL), 40 mg (20 mg/mL), 40 mg (10 mg/mL), 40 mg (20 mg/mL), 30 mg (15 mg/mL), 30 mg (30 mg/mL)
CS05	single dose, open-label, dose escalation in men aged 19-46 years.	1.5, 6, 15, or 30 µg/kg IV over 15 or 45 min. 20 mg (5 mg/mL) SC 20 mg (5 mg/mL) IM
CS08	single dose, open-label, randomized, placebo-controlled, dose-response, in elderly subjects (≥ 65 years)	0.864, 1.73, 3.70, 9.87, 24.7 or 49.4 µg/kg IV over 48 hours
CS23	single dose, open-label, parallel study in patients with mild or moderate hepatic impairment and healthy subjects	1 mg IV over 1-hour

**TABLE 2. Clinical pharmacology studies in prostate cancer patients**

Study	Design	Doses
CS06	single dose, open-label, dose escalation	40 mg (10 mg/mL), 80 mg (20 mg/mL), 120 mg (30 mg/mL), 160 mg (40 mg/mL)
CS07	single dose, open-label, dose escalation	120 mg (20 mg/mL), 120 mg (40 mg/mL), 160 mg (40 mg/mL), 200 mg (40 mg/mL), 200 (60 mg/mL), 240 mg (40 mg/mL), 240 mg (60 mg/mL), 320 mg (60 mg/mL)
CS11	single-dose, open-label, dose escalation study in Japanese subjects	160 mg (40 mg/mL), 200 mg (40 mg/mL), 240 mg (40 mg/mL)

**TABLE 3. Studies to Support Efficacy**

Study	Design	Doses
CS02	randomized, open-label, parallel group, uncontrolled study 6-month study	40 mg (20 mg/mL) loading dose x 2 + 40 mg (20 mg/mL) Q28D 80 mg (20 mg/mL) loading dose x 2 + 40 mg (20 mg/mL) Q28D 80 mg (20 mg/mL) loading dose x 1 + 20 mg (10 mg/mL) Q28D
CS12	open-label, randomized, parallel, uncontrolled 12-month study.	200 mg Loading dose + 80 mg Q28D 200 mg Loading dose + 120 mg Q28D 200 mg Loading dose + 160 mg Q28D 240 mg Loading dose + 80 mg Q28D 240 mg Loading dose + 120 mg Q28D 240 mg Loading dose + 160 mg Q28D <i>All doses used the 40 mg/mL concentration</i>
CS14	open-label, randomized, parallel group, uncontrolled 12 month study	200 mg loading dose + 40 mg (60 mg/mL) Q28D 200 mg loading dose + 40 mg (80 mg/mL) Q28D
CS15	open-label, randomized, parallel group, uncontrolled 12 month study with 3-month depot	<i>3-month depot study will not be reviewed by Clin Pharm.</i>
CS21	randomized, parallel, groups, open-label active controlled study	240 mg (40 mg/mL) loading dose + 80 mg (20 mg/mL) Q28D 240 mg (40 mg/mL) loading dose + 160 mg (40 mg/mL) Q28D

The sponsor conducted in-vitro studies to evaluate protein binding, in-vitro metabolism, CYP450 inhibition/induction and a study investigating interaction potential with drug transporters. There was no formal evaluation of mass-balance (ADME study) however the sponsor did include degarelix and metabolite analysis of fecal and urine samples from three studies (CS06, CS22 and CS23). Dose proportionality was assessed in the initial tolerability studies in both patients with prostate cancer and healthy volunteers.

Data from phase 1 and 2 studies were compiled to form a population PK model for degarelix. The sponsor used the data from the following studies:

- CS05: IV dose escalation in Healthy Volunteers
- CS06: single SC dose escalation study in prostate cancer patients
- CS07: single SC dose escalation study in prostate cancer patients
- CS12: loading dose + multiple Q28 dose study in prostate cancer patients
- CS14: loading dose + multiple Q28 dose study in prostate cancer patients
- CS15: 3-month depot study

Only one study (CS 15) used the \_\_\_\_\_ drug substance \_\_\_\_\_ and this was the 3-month depot formulation study. The main conclusions from this popPK model were:

- The absorption profile was affected by dosing concentration and formulation \_\_\_\_\_
- Bioavailability and the “fast absorbed dose fraction” decreased with increasing dosing concentration but was higher for \_\_\_\_\_
- Terminal half-life was longer for \_\_\_\_\_ and increased with increasing drug concentration in the dosing solution.
- Clearance was found to decrease with age (1 % per year)
- Weight affected the PK profile by lowering exposure but increasing terminal half-life (0.8% per kg in both cases).

b(4)

In addition, multiple population PK analyses were used to explore the data including:

- High degarelix concentrations (CS12, CS14, CS15, CS21)
- Hepatic impairment (CS23)
- Phase 3 analyses (CS21 and CS08) which investigated effects of weight, age, and renal function on the PK of degarelix.

**Recommendation:** The Office of Clinical Pharmacology/Division of Pharmaceutical Evaluation 5 find that NDA 22-201 is fileable.

**Comments:**

Please submit the following datasets to support your population PK analyses:

- All datasets used for model development and validation should be submitted as a SAS transport files (\*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
- Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with \*.txt extension (e.g.: myfile\_ctl.txt, myfile\_out.txt).

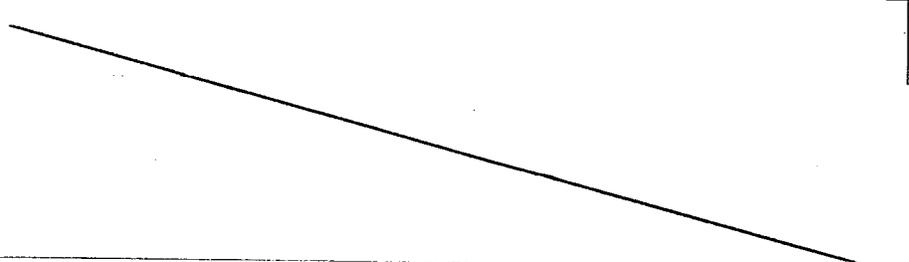
- A model development decision tree and/or table which gives an overview of modeling steps. For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

If any of the above were included with the original submission, please provide detailed instructions on where they can be located in your electronic submission.

**Action**

The above comments need to be sent to the sponsor.

1. An IRT consult needs to be submitted. The sponsor claims the following in their draft label under warnings and precautions:



b(4)

2. A pharmacometrics consult needs to be submitted for the review of the PK models

**Signatures**

---

Julie M. Bullock, Pharm.D.  
Reviewer  
Division of Clinical Pharmacology 5

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Brian Booth, Ph.D.  
Deputy Div Director & Acting Team Leader  
Division of Clinical Pharmacology 5

Cc: DDOP: CSO - **D Woody**; MTL - **A Ibrahim**; MO - **M Ning**  
DCP-5: Reviewer - **J Bullock**; Deputy DD & Acting TL - **B Booth**;  
DD - **A Rahman**

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this page is the manifestation of the electronic signature.**  
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/s/

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Julie Bullock  
11/12/2008 01:16:16 PM  
BIOPHARMACEUTICS

Jun Yang  
11/12/2008 01:45:31 PM  
PHARMACOLOGIST

Yaning Wang  
11/13/2008 11:45:00 AM  
BIOPHARMACEUTICS

Brian Booth  
11/13/2008 12:04:37 PM  
BIOPHARMACEUTICS