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# Efficacy and safety of degarelix in Korean patients with prostate cancer requiring androgen deprivation therapy: Open-label multicenter phase III study

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ABSTRACT

**Purpose:** To assess the noninferiority, efficacy, and safety of degarelix in achieving and maintaining testosterone at castrate levels (≤0.5 ng/mL) in Korean patients (CS42) versus non-Asian patients with prostate cancer (PCa).

**Methods:** A Phase III, open-label, multicenter, single-arm trial was conducted in Korean patients with PCa. Degarelix was administered at a starting dose of 240 mg followed by monthly (28-day intervals) maintenance doses of 80 mg (240/80 mg dose regimen) for 7 months. The results were compared with non-Asian patients receiving degarelix 240/80 mg in the CS21 study.

**Results:** The estimated difference in the cumulative probabilities of testosterone ≤0.5 ng/mL from Day 28 to Day 196 between the trials was −2.3% (96.7% in CS42 vs. 99.0% in CS21). The lower limit of the 95% confidence interval was −5.5%, i.e., above the predefined noninferiority limit of −10% and thus non-inferiority was established. Decreases in serum testosterone, prostate-specific antigen, and luteinizing hormone over time were similar in CS42 and CS21. There were no clinically significant differences in incidence of treatment-emergent adverse events (72% in CS42 vs. 70% in CS21) and changes in clinical chemistry and hematology parameters between the two trials. The most common adverse event was injection-site reaction.

**Conclusions:** Overall, degarelix was effective and well tolerated in Korean patients. Testosterone suppression was noninferior to that in non-Asian patients and safety findings were as would be expected for elderly men with PCa undergoing androgen deprivation therapy.



## 1. Introduction

Androgen deprivation therapy (ADT) is first-line treatment for advanced/metastatic prostate cancer (PCa) and is also recommended in combination with radiotherapy in the management of intermediate and high-risk localized disease.[1] For many years, luteinizing hormone-releasing hormone (LHRH) agonists have formed the mainstay of ADT. However, gonadotrophin-releasing hormone (GnRH) antagonists offer a more recently developed alternative first-line ADT treatment option. The most extensively studied and widely available antagonist worldwide is degarelix. Unlike LHRH agonists, degarelix provides immediate GnRH receptor inhibition resulting in rapid and profound testosterone suppression.[2]

In the pivotal Phase III registration trial (CS21; NCT00295750), conducted in Europe and North America, degarelix displayed similar efficacy to the LHRH agonist leuprolide in suppressing testosterone over 1 year.[3] However, degarelix reduced testosterone and prostate-specific antigen (PSA) more rapidly with no initial testosterone surge or subsequent microsurges, and no requirement for flare protection with antiandrogens. Studies show that response to drug therapy can vary according to ethnicity.[4,5] It is known that racial differences within the androgen/androgen receptor pathway not only exist but also could be causally related to clinically observed differences in the biology of PCa among the ethnicity,

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including responses to ADT.[6] Therefore, clinical pharmacologic drug evaluation should ideally include a population representative of the target therapeutic population. In addition to studies in predominantly non-Asian populations, the efficacy of degarelix has also been studied in Japanese patients.[7]

The aim of the current trial (CS42; NCT01071915) was to establish the efficacy and tolerability of degarelix in Korean patients with PCa and to establish noninferiority of degarelix in Korean patients compared to non-Asian patients treated with the same dose regimen in the pivotal phase III CS21 trial with regard to achieving and maintaining castrate testosterone levels.

## 2. Methods

### 2.1. Study design

CS42 was an open-label, multicenter, single-arm trial in Korean patients with PCa. Patients received subcutaneous injections of degarelix 1-month depot at a starting dose of 240 mg (40 mg/mL) followed by monthly (28-day intervals) maintenance doses of 80 mg (20 mg/mL; 240/80 mg dose regimen) for 7 months. The results were to be bridged to those of the 240/80 mg arm of the CS21 trial in non-Asian patients.[3] Degarelix was supplied as a freeze-dried powder for suspension in water.

The trial was conducted in accordance with the Declaration of Helsinki as well as Good Clinical Practice Guidelines. The Institutional Review Board at all participating institutions approved the protocol. All patients provided written informed consent.

### 2.2. Patients

Korean men aged ≥18 years with histologically confirmed adenocarcinoma of the prostate (all stages), in whom androgen ablation was indicated, except for neoadjuvant hormonal therapy, were recruited. The population included patients with an increasing PSA after having undergone prostatectomy or radiotherapy with curative intent, i.e., those with biochemical failure or metastatic disease (hormone-sensitive). Patients were required to have a screening serum testosterone level >1.5 ng/mL and PSA ≥2 ng/mL, and an Eastern Cooperative Oncology Group score ≤2. Previous or current hormonal management of PCa was not allowed, except in patients who had undergone localized therapy of curative intent in which neoadjuvant or adjuvant hormonal therapy for ≤6 months was accepted (discontinued >6 months before inclusion). Patients considered candidates for curative therapy were excluded.

### 2.3. Assessment

The primary endpoint was the difference in cumulative probability of testosterone suppression to castrate levels (≤0.5 ng/mL) from Day 28 to Day 196 between Korean patients and non-Asian patients treated with the degarelix 240/80 mg dose regimen in the CS21 trial. If noninferiority was established, the secondary objective of showing that 7-month testosterone suppression response rate was significantly >90% in the full analysis set (FAS) in Korean patients was tested; therefore this prioritized secondary endpoint was the cumulative probability of testosterone ≤0.5 ng/mL from Day 28 to Day 196 in Korean patients. Secondary endpoints also included the proportion of patients with testosterone ≤0.5 ng/mL at Day 3, percentage change in PSA from baseline to Day 28, cumulative probability of testosterone ≤0.5 ng/mL from Day 56 to Day 196, serum levels of testosterone, luteinizing hormone (LH) and PSA over time, and cumulative probability of no PSA failure (2 consecutive increases of 50%, and ≥5 ng/mL, compared to nadir). Safety analysis comprised the frequency and severity of adverse events (AEs) and clinically significant changes in laboratory values, electrocardiogram, physical examination, and vital signs. Blood samples for analysis of testosterone, PSA, and LH were collected at each trial visit. At dosing visits, blood sampling was performed predose and, where possible, at the same time of day, preferably in the morning. A central laboratory (SCL, Seoul, Korea) measured serum hormones (testosterone and LH) and PSA in accordance with Good Laboratory Practice, using validated methods.

### 2.4. Determination of sample size

For sample size calculation, the 95% confidence interval (CI) of the testosterone suppression response rate for the CS21 240/80 mg non-Asian reference population was 95.8–99.7%. Assuming a response rate in Korean patients of 97% (lower than observed point-estimate of 99% but still well within the CI) and a 15% annual drop-out rate, 150 patients are required to have sufficient power (≥90%) in the FAS.

### 2.5. Statistical analysis

The primary analysis population was the FAS, defined as patients who received the study drug and in whom ≥1 efficacy variable (primary or secondary) was evaluated after administration. Intention-to-treat (ITT) analysis comprised all patients who were allocated to treatment, the per-protocol (PP) analysis was defined as FAS patients who did not violate specific predefined criteria for major protocol deviations which were in line with the CS21 trial, and the safety analysis set comprised patients who received ≥1 degarelix dose.

The primary efficacy endpoint (noninferiority assessment) measuring the difference in cumulative probability of testosterone ≤0.5 ng/mL between Korean (CS42) and non-Asian (CS21) patients receiving degarelix 240/80 mg, was estimated using the Kaplan–Meier (KM) method using testosterone measurements from Day 28 to Day 196. The standard error of this estimate was based on Greenwood's formula. The corresponding 95% two-sided CI was constructed using the pooled standard errors of these estimates. Noninferiority was established if the lower limit of this CI was >−10%. To determine effectiveness in Korean patients (prioritized secondary endpoint), testosterone suppression was considered statistically significant if the lower limit of the two-sided 95% CI was ≥90%. The two-sided 95% CI was derived in the same manner as the primary endpoint.

The difference in proportion of patients with testosterone ≤0.5 ng/mL at Day 3 was tested using Fisher's Exact test ($\alpha = 0.05$, two-sided). Median (interquartile range) percentage change from baseline to Day 28 in PSA was calculated and groups tested using the two-sample Wilcoxon test ($\alpha = 0.05$, two-sided). Cumulative probability of testosterone ≤0.5 ng/mL from Day 56 to Day 196 was estimated by the KM method. Cumulative probability of no PSA failure was estimated using the KM method; groups were compared using the log-rank test ($\alpha = 0.05$, two-sided).

## 3. Results

### 3.1. Patient disposition

The study was conducted between March 2010 and November 2011. Of 187 patients screened, 157 were allocated to treatment (ITT). Of these, 156 (99%) received one or more degarelix dose (safety population) and 155 (99%) had one or more efficacy assessment after dosing (FAS). Six FAS patients were excluded from the PP analysis, which comprised 149 (95%) patients. The proportions of patients completing CS42 (148/157; 94%) and 7 months