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A Phase III Extension Trial With a 1-Arm Crossover From Leuprolide to Degarelix: Comparison of Gonadotropin-Releasing Hormone Agonist and Antagonist Effect on Prostate Cancer

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Purpose: We investigated the efficacy and safety of degarelix treatment and the effects of switching from leuprolide to degarelix in an ongoing extension study with a median 27.5-month followup of a pivotal 1-year prostate cancer trial.

Materials and Methods: Patients who completed a 1-year pivotal phase III trial continued on the same monthly degarelix maintenance dose (160 or 80 mg in 125 each), or were re-randomized from leuprolide 7.5 mg to degarelix 240/80 mg (69) or 240/160 mg (65). Data are shown on the approved degarelix 240/80 mg dose. The primary end point was safety/tolerability and the secondary end points were testosterone, prostate specific antigen, luteinizing hormone and follicle-stimulating hormone responses, and prostate specific antigen failure and progression-free survival.

Results: During followup testosterone and prostate specific antigen suppression were similar to those in the 1-year trial in patients who continued on degarelix or switched from leuprolide. The prostate specific antigen progression-free survival hazard rate was decreased significantly after the switch in the leuprolide/degarelix group while the rate in those who continued on degarelix was consistent with the rate in treatment year 1. The same hazard rate change pattern occurred in the group with baseline prostate specific antigen greater than 20 ng/ml. Adverse event frequency was similar between the groups and decreased with time.

Conclusions: Data support the statistically significant prostate specific antigen progression-free survival benefit for degarelix over leuprolide seen during year 1 and the use of degarelix as first line androgen deprivation therapy as an alternative to a gonadotropin-releasing hormone agonist.

Key Words: prostate, prostatic neoplasms, progression-free survival, leuprolide, acetyl-2-naphthylalanyl-3-chlorophenylalanyl-1-oxohexadecylseryl-4-aminophenylalanyl(hydroxyrotyl)-4-aminophenylalanyl(carbamoyl)-leucyl-ILys-prolyl-alaninamide

ANDROGEN deprivation therapy for advanced PCa often uses GnRH agonists to achieve castration.¹ However, agonists initially cause an abrupt in-

crease in LH and FSH, and a subsequent testosterone surge.² The same phenomenon may develop at lower amplitudes when agonists are re-in-

Abbreviations and Acronyms

ADT = androgen deprivation therapy
AE = adverse event
ALP = alkaline phosphatase
FSH = follicle-stimulating hormone
GnRH = gonadotropin-releasing hormone
LH = luteinizing hormone
PCa = prostate cancer
PFS = progression-free survival
PSA = prostate specific antigen

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jected (miniflares/microsurges).^{3,4} GnRH agonists also only transiently suppress FSH.⁵ This mode of action delays castration and testosterone surges may exacerbate disease symptoms (clinical flare).¹ Concomitant antiandrogens should be considered to protect against testosterone surge and accelerate castration when using GnRH agonists.

GnRH blockers (antagonists) induce immediate testosterone suppression without an initial testosterone surge.² The GnRH blocker degarelix was as effective as the GnRH agonist leuprolide for suppressing testosterone to castrate levels in patients with PCa in the 1-year phase III CS21 trial (ClinicalTrials.gov Identifier NCT00295750).⁴ In contrast to leuprolide, degarelix rapidly suppressed LH and FSH, and consequently testosterone. Testosterone suppression with degarelix was maintained without the (micro)surges observed with leuprolide. Furthermore, there was no late FSH escape with degarelix.

During the CS21 trial PSA was also suppressed significantly more rapidly by degarelix. For the approved degarelix 240/80 mg dose there was a significantly lower risk of PSA progression or death vs those of leuprolide and better control of the bone formation marker serum ALP in patients with metastatic disease.^{6,7}

While these differences between degarelix and leuprolide are well characterized, long-term efficacy and safety data on degarelix are limited. Thus, patients who successfully completed CS21 had the opportunity to enter extension trial CS21A investigating those continuing to receive degarelix and those who switched from leuprolide to degarelix. CS21A is ongoing and will run for 5 years.

We report efficacy and safety data from the CS21A trial on patients who continued on degarelix 240/80 mg and patients who switched from leuprolide to degarelix at a median followup of 27.5 months.

MATERIALS AND METHODS

Main Trial CS21

This 1-year phase III, multicenter, randomized, open label trial was powered to show the noninferiority of degarelix vs leuprolide for the primary end point, that is the proportion of patients with testosterone suppression 50 ng/dl or less during 12-month treatment in those with all stages of PCa requiring ADT.⁴

During CS21 patients received degarelix 240 mg subcutaneously for 1 month, followed by monthly maintenance doses of 80 mg in 207 or 160 mg in 202, or monthly doses of leuprolide 7.5 mg intramuscularly in 201 with or without bicalutamide at investigator discretion.

Extension Trial CS21A

Patients who completed CS21 were offered the option of entering the open label, multicenter extension trial. Patients who initially received degarelix continued with the

same monthly maintenance dose. Those who previously received leuprolide 7.5 mg were re-randomized (1:1) to a degarelix 240 mg starting dose, followed by monthly doses of 80 or 160 mg. At randomization primary data on CS21 had not been conclusively analyzed and, thus, patients on leuprolide were switched to either maintenance degarelix dose. Upon receiving regulatory approval of degarelix 240/80 mg, patients on the 160 mg dose were switched to the approved dose.

CS21A was initiated in March 2007 and the database was analyzed in March 2010 at a median followup of 27.5 months. The trial complied with the Declaration of Helsinki and was approved by independent ethics committees/institutional review boards. Patients provided written informed consent.

The primary objective of CS21A was to evaluate safety and tolerability during long-term degarelix treatment. Secondary objectives were to evaluate testosterone, PSA, LH and FSH responses in patients who continued on degarelix or switched from leuprolide.

Assessments

All serum hormone and PSA measurements were made at a central laboratory.⁴ Serum LH and FSH were measured at days 0, 1, 3, 7, 14 and 28, and thereafter monthly during CS21 and monthly up to 3 months during CS21A. Serum testosterone and PSA were measured at days 0, 1, 3, 7, 14, 28, monthly until month 15 and at 3-month intervals thereafter. Biomarker level changes are shown as the median and quartiles with time for testosterone and PSA, and as the median percent change from baseline and quartiles for LH and FSH.

PSA failure was defined as 2 consecutive PSA increases of 50% or greater vs nadir and 5 ng/ml or greater on 2 consecutive measurements 2 or more weeks apart with the end point recorded on the date of measurement 2 according to protocol CS21 criteria. PSA PFS was analyzed using the Kaplan-Meier method and assessed by baseline PSA. Time to an event was defined as the number of days from dose 1 to the first of PSA failure or death. Statistical comparisons were performed using the log rank test. PSA PFS hazard rates were calculated before and after switching using a likelihood ratio based procedure to test for a change in the hazard rate of the patient survival distribution. Statistical comparisons were made using the chi-square test.

For patients continuing on degarelix data are shown for the approved degarelix 240/80 mg dose. Data on patients who switched from leuprolide to degarelix 240/160 and 240/80 mg were pooled (leuprolide/degarelix group).

Safety and tolerability were assessed by measuring AEs. The probability of not experiencing musculoskeletal AEs was analyzed using the Kaplan-Meier method and assessed by baseline PSA.

RESULTS

Patients

Of 504 patients who completed CS21 385 entered CS21A, of whom 250 continued to receive the same monthly maintenance dose of degarelix (160 or 80 mg in 125 each) and 135 who switched from leupro-

lide to degarelix 240/160 mg (65) or 240/80 mg (69). One patient in the 240/160 mg group did not receive further treatment. Baseline characteristics were generally comparable between patients who continued on degarelix 240/80 mg and those who switched from leuprolide (table 1).

At a median followup of 27.5 months 51 patients on degarelix and 62 switched from leuprolide had discontinued the study. Similar proportions of patients in the degarelix and leuprolide groups discontinued due to AEs (10% and 16%, respectively) and 6 per group died during treatment (table 2). The AE leading to the single death in the degarelix 240/80 mg arm was bile duct cancer but this was considered unrelated to study drug treatment. At followup 74 and 72 patients in the degarelix and leuprolide groups, respectively, continued in the study.

Testosterone

After year 1 (day 364), median testosterone was 9 and 7 ng/dl in the degarelix and leuprolide groups, respectively. During CS21A median testosterone remained suppressed at less than 20 ng/dl in patients on degarelix and in those who switched to degarelix from leuprolide at all time points measured (fig. 1).

Table 1. Baseline characteristics of patients continuing on degarelix or switched from leuprolide to degarelix

	Degarelix 240/80 mg		Leuprolide 7.5 mg to Degarelix 240/80 or 160 mg	
No. safety analysis set	125		134	
Median yrs age (range)	71.0	(51–89)	73.0	(52–98)
Median ng/dl testosterone (range):				
Main trial	463	(128–1,060)	415	(37–1,250)
Extension trial	10	(2–286)	8	(2–136)
Median ng/ml PSA (range):				
Main trial	22.2	(1.70–3,186.5)	19.2	(1.60–10,952.0)
Extension trial	0.60	(0.0–3,274.0)	0.40	(0.0–2,938.4)
Median IU/l LH (range):				
Main trial	5.80	(2.02–22.0)	5.80	(1.25–37.0)
Extension trial	0.28	(0.04–4.32)	0.04	(0.04–1.12)
Median IU/l FSH (range):				
Main trial	7.40	(1.80–73.6)	8.60	(1.40–66.4)
Extension trial	1.30	(0.15–9.10)	4.5	(1.20–15.80)
No. disease stage at enrolment (%):				
Localized (T1/2, NX or N0 + M0)	39	(31)	39	(29)
Locally advanced (T3/4, NX or N0 + M0 or N1 + M0)	46	(37)	42	(31)
Metastatic	23	(18)	30	(22)
Not classifiable	17	(14)	23	(17)
No. Gleason score (%):*				
2–4	15	(12)	19	(14)
5–6	37	(30)	43	(32)
7–10	73	(58)	72	(54)

* Sum of Gleason grade of primary and secondary patterns.

Table 2. Patient disposition in CS21A

	No. Degarelix 240/80 mg (%)		No. Leuprolide to Degarelix 240/80 or 160 mg (%)	
Ongoing:				
Day 364	125	(100)	134	(100)
Followup*	74	(59)	72	(54)
Discontinued:	51	(41)	62	(46)
AEs	12	(10)	22	(16)
AEs leading to death	1	(less than 1)	—	
Death during treatment	6	(5)	6	(4.5)
Lost to followup	5	(4)	1	(less than 1)
Other	27	(22)	33	(25)

* March 2010.

LH and FSH

In year 1 LH was suppressed in patients on degarelix or leuprolide. During the first 3 months of CS21A LH remained suppressed to low levels in patients continuing on degarelix and those who switched from leuprolide. At day 364 median LH was 0.25 and 0.04 IU/l, respectively ($p < 0.0001$). LH remained significantly different at day 448 (fig. 2, A).

At year 1 (day 364) median FSH was 1.20 and 4.40 IU/l in the degarelix 240/80 mg and leuprolide groups, respectively ($p < 0.0001$). In CS21A at 3 months FSH continued to be suppressed in patients who continued on degarelix 240/80 mg (median 1.30 IU/l at day 448). In contrast, FSH was further suppressed in patients who switched from leuprolide to degarelix until levels were similar to those observed during continuous degarelix treatment (median 1.60 IU/l at day 448) (fig. 2, B).

Prostate Specific Antigen

At year 1 (day 364) median PSA was 0.5 and 0.4 ng/ml in the degarelix and leuprolide groups, respectively. During CS21A PSA remained suppressed (median less than 1 ng/ml) in each group (fig. 3).

PSA PFS in Intent to Treat Population

Up to 1 year the risk of PSA failure or death was significantly lower in patients on degarelix vs leuprolide ($p = 0.05$). Beyond 1 year the risk of PSA failure or death decreased in patients who switched from leuprolide to degarelix (fig. 4, A).

At a median followup of 27.5 months the PSA PFS hazard rate had decreased significantly from 0.20 events annually in year 1 to 0.08 events annually after the switch in the leuprolide/degarelix group (chi-square test $p = 0.003$). The corresponding hazard rate in the continuous degarelix 240/80 mg group was 0.11 and 0.14 events annually ($p = 0.464$), showing a consistent effect of degarelix with time.

In patients with baseline PSA greater than 20 ng/ml time to PSA failure at up to 1 year was significantly longer in patients on degarelix 240/80 mg vs leuprolide (log rank test $p = 0.0436$). At a median

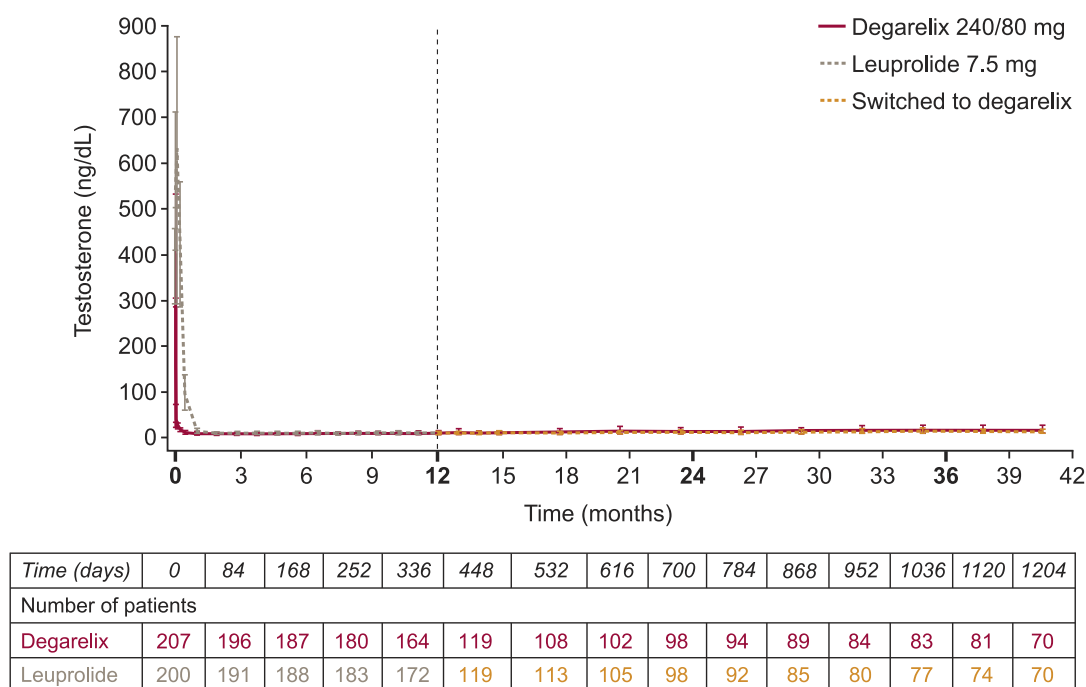


Figure 1. Median serum testosterone and quartiles in patients switched from leuprolide to degarelix and those continuing degarelix in extension trial.

followup of 27.5 months the same PSA PFS hazard change pattern in the overall population also occurred in patients with baseline PSA greater than 20 ng/ml. The PSA PFS hazard rate decreased significantly from 0.38 events annually in year 1 to 0.19 events annually after the switch in patients on leuprolide (chi-square test $p = 0.031$). The hazard rate for degarelix was 0.23 and 0.23 events annually, respectively ($p = 0.988$, *fig. 4, B*).

Safety

The overall incidence of treatment emergent AEs was similar in the 2 treatment groups throughout the 4 study years and it decreased as the extension study progressed. By year 4 the incidence of individual AEs was low in each group with no major between group differences.

Switching from leuprolide to degarelix was accompanied by more injection site reactions in year 2. However, the incidence of these effects decreased in years 3 and 4 to attain similar levels in the 2 groups.

During year 1 (CS21) the proportion of patients reporting musculoskeletal and connective tissue AEs was significantly higher for leuprolide vs degarelix (26% vs 17% of all on degarelix, $p < 0.05$). In CS21A the proportion of patients reporting first time musculoskeletal and connective tissue AEs was similar between the degarelix and leuprolide/degarelix switch groups (17% and 20%, respectively, $p = 0.532$). Probability curves for those without musculoskeletal AEs in the overall popu-

lation and those with baseline PSA greater than 20 ng/ml revealed that the lower probability noted for degarelix 240/80 mg at 1 year persisted during CS21A (*fig. 5*).

DISCUSSION

During CS21 degarelix achieved more rapid suppression of LH, FSH, testosterone and PSA than leuprolide, and it was as effective as leuprolide in inducing and sustaining testosterone suppression to castrate levels (50 ng/dl or less).

The extension trial substantiates the long-term efficacy of the approved dose of degarelix 240/80 mg. Our data show that effective suppression of testosterone and PSA can be maintained for greater than 3 years in patients with PCa receiving degarelix 240/80 mg. In patients switched from leuprolide to degarelix testosterone and PSA suppression were also maintained at consistent levels after 1 year.

In CS21A LH suppression was maintained for at least 3 months in all patients at levels similar to those during year 1. The difference in LH suppression was also maintained during the 3 months of observation after switching. Patients who switched from leuprolide to degarelix experienced further FSH suppression during the initial months of CS21A. Persistent FSH suppression by GnRH antagonists was previously described and its therapeutic advantage is under discussion.⁸ FSH receptors are selectively expressed on blood vessels of many

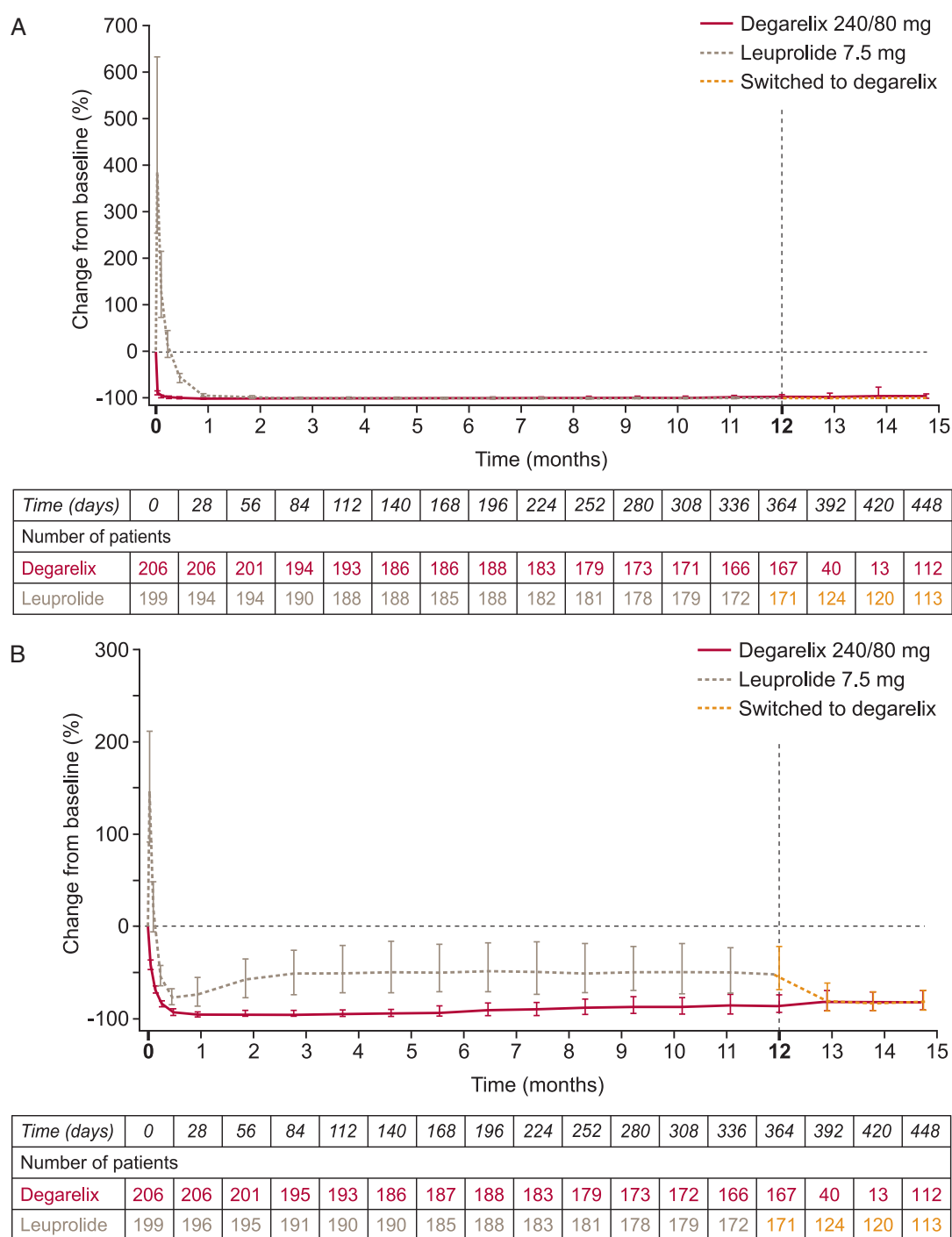


Figure 2. Median percent change from baseline and quartiles in LH (A) and FSH (B) in patients switched from leuprolide to degarelix and those continuing degarelix in extension trial.

tumors, including prostate tumors,⁹ and FSH signaling may contribute to the progression of castration resistant PCa.¹⁰

In PCa cases PSA recurrence often precedes clinically detectable recurrence by years and effective PSA control is associated with improved overall survival.^{11–13} Patients on degarelix 240/80 mg had a significantly lower risk of PSA failure or death than those on leuprolide during treatment

year 1. As expected, PSA failure in year 1 occurred mainly in patients with locally advanced or metastatic disease, and exclusively in patients with baseline PSA greater than 20 ng/ml.⁶ More than half of the patients in CS21A had advanced disease (locally advanced/metastatic disease). After switching from leuprolide to degarelix the PSA PFS hazard rate decreased significantly. Indeed, the patient risk of progression in 1 year was more

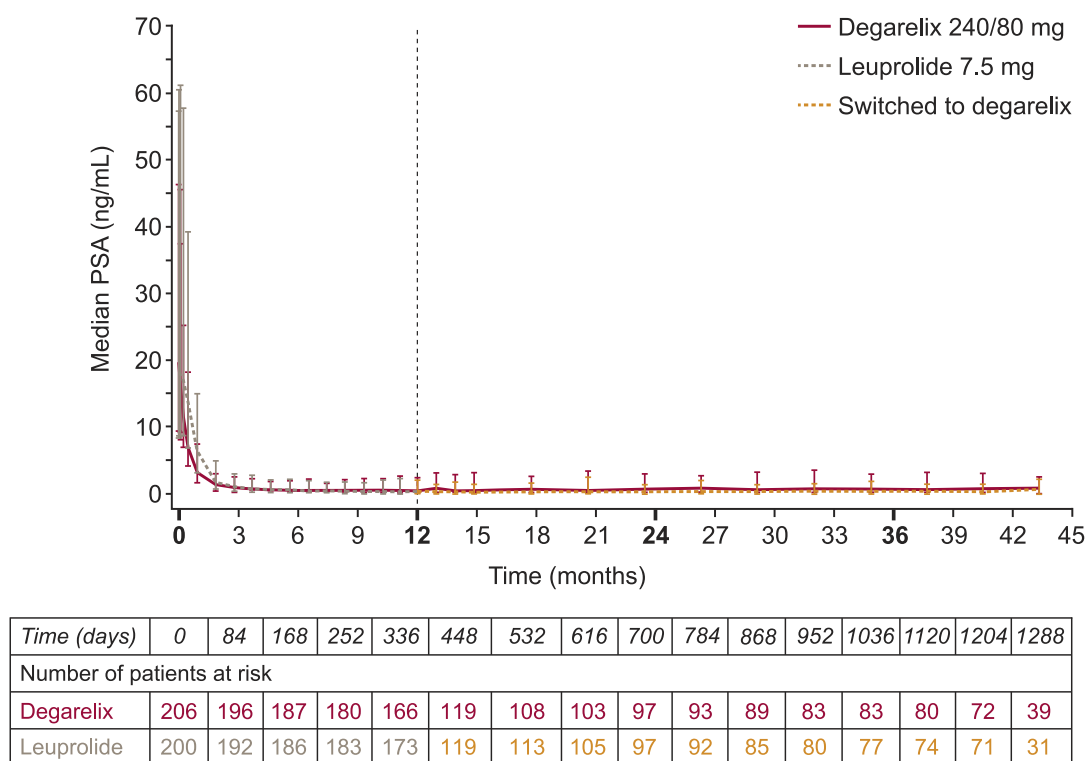


Figure 3. Median PSA and quartiles in patients switched from leuprolide to degarelix and those continuing degarelix in extension trial

than halved. There was no significant change in the hazard rate in patients who continued to receive degarelix.

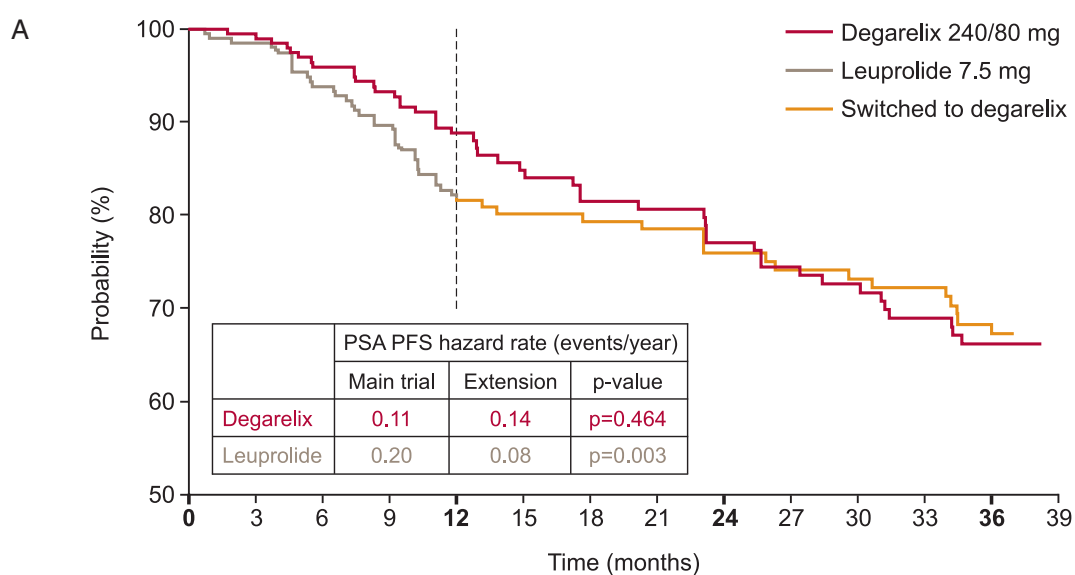
In patients with baseline PSA greater than 20 ng/ml there was a significantly lower risk of PSA failure for degarelix 240/80 mg vs leuprolide during year 1. Patients in this subgroup who switched from leuprolide to degarelix experienced an improvement in the PSA PFS hazard rate similar to that in the overall population.

The hazard rate at 1 year could have been influenced by the change in monitoring frequency at 15 months. However, this would have affected each treatment arm and cannot explain the observed difference in hazard rate change. A control group continuing on leuprolide would also have enabled more robust assessment of the effects on PSA progression of switching to degarelix but this study was primarily designed to investigate the long-term safety of degarelix.

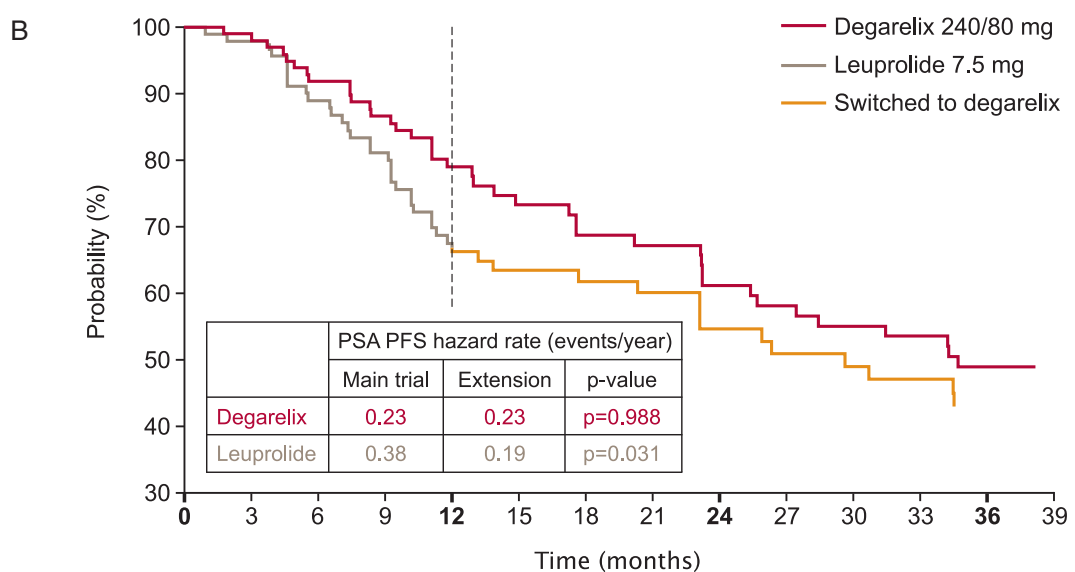
GnRH agonists are associated with an initial testosterone surge and subsequent microsurgues. While to our knowledge the clinical significance of testosterone microsurgues is unknown, ineffective testosterone control may be associated with increased PCa mortality.¹⁴ Indeed, breakthrough testosterone increases predict decreased PFS.¹⁵ Also, about 5% to 17% on GnRH agonists fail to achieve a castrate testosterone of 50 ng/dl or

less.¹⁶ Improved PSA control when patients switched from leuprolide to degarelix after 1 year may reflect improved testosterone control for the antagonist compared with the agonist. PSA PFS in these patients is indicative of time to castration resistance. Thus, the additional improvements in FSH suppression,⁴ the rapid, sustained testosterone suppression and the improved PSA control, which is more indicative of tumor control, achieved with the antagonist degarelix may further delay progression to castration resistant disease.¹⁰ These data support degarelix as first line ADT, as an alternative to a GnRH agonist.

The high incidence of discontinuation in the 2 treatment groups, of which most were unrelated to study drug treatment, may be expected in an extension study of this duration since the pivotal part was completed, and considering patient age and the monthly injection schedule. AEs in the extension trial were primarily related to androgen deprivation or a consequence of the primary disease and they occurred at a similar frequency in the 2 arms. The increase in injection site reactions after switching in year 2 likely reflects the different forms of administration (subcutaneous degarelix vs intramuscular leuprolide) and injection volume.^{17,18} As expected, the incidence of injection site reactions decreased in years 3 and 4 to attain similar low levels in the 2 groups.



Time (days)	0	84	168	252	336	420	504	588	672	756	840	924	1008	1092	1176	
Number of patients at risk																
Degarelix	207	200	187	176	162	109	101	93	91	87	83	79	75	71	67	
Leuprolide	201	193	182	174	157	110	102	98	93	85	81	78	74	68	66	



Time (days)	0	84	168	252	336	420	504	588	672	756	840	924	1008	1092	1176	
Number of patients at risk																
Degarelix	100	97	91	84	77	53	50	45	44	40	37	36	35	32	31	
Leuprolide	93	90	81	75	63	43	40	37	35	29	27	26	23	23	21	

Figure 4. PSA PFS probability in all patients (A), and those with baseline PSA greater than 20 ng/ml switched from leuprolide to degarelix 240/80 mg and those continuing degarelix 240/80 mg (B) in extension trial using original CS21 criteria for PSA progression.

During year 1 patients on degarelix experienced a significantly lower musculoskeletal AE rate vs those on leuprolide. This was unlikely to have been due to concomitant bisphosphonates since similar proportions of each group received bisphosphonates.⁷ Pa-

tients who switched from leuprolide to degarelix experienced an improved musculoskeletal AE rate after switching, similar to that in patients who continued on degarelix. The axial skeleton is involved in a high proportion of men who die of PCa,¹⁹ and the

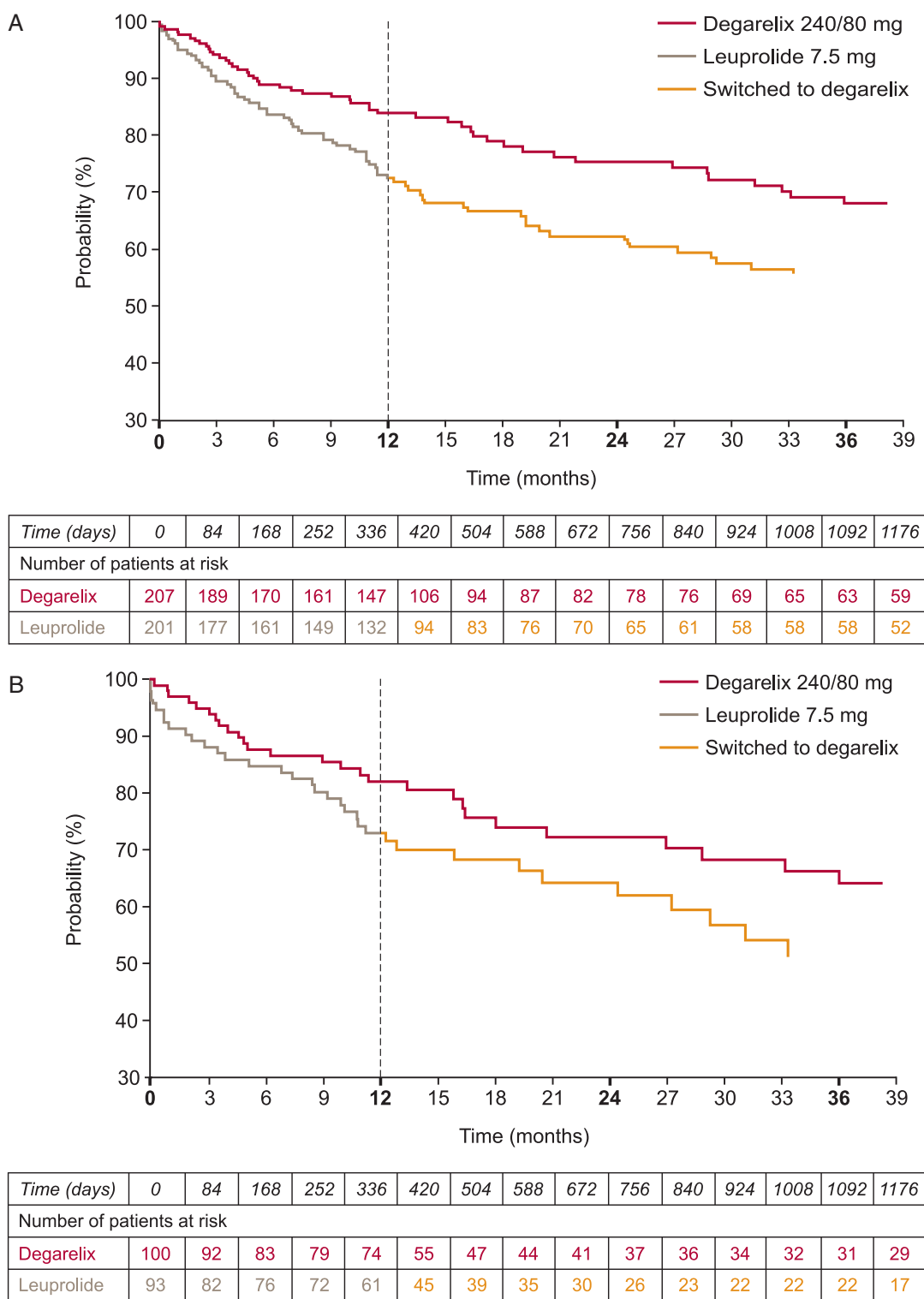


Figure 5. Probability of no musculoskeletal AEs in group switched from leuprolide to degarelix and group that continued degarelix 240/80 mg in extension trial in all patients (A) and those with baseline PSA greater than 20 ng/ml (B).

presence and extent of bone metastases can reflect prognosis.¹ In PCa cases increased serum ALP and bone specific ALP are associated with the progression of skeletal metastasis^{20,21} and may be predictors of early death.^{22–25} Degarelix 240/80 mg may

also provide better serum ALP control compared to leuprolide, especially in patients with metastatic disease or baseline PSA 50 ng/ml or greater.⁷ These observations support the hypothesis that degarelix may further prolong the control of skeletal metasta-

sis compared with GnRH agonists during long-term treatment.

CONCLUSIONS

This extension trial demonstrates the long-term efficacy and safety of degarelix. Data support the durability of the significant PSA PFS benefit for degarelix treatment over monthly leuprolide seen

during treatment year 1 and support degarelix as first line ADT, as an alternative to a GnRH agonist.

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