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Changes in alkaline phosphatase levels in patients with prostate cancer receiving degarelix or leuprolide: results from a 12-month, comparative, phase III study

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OBJECTIVE

To compare the activity of degarelix, a new gonadotrophin-releasing hormone (GnRH) blocker, with leuprolide depot 7.5 mg in the control of total serum alkaline phosphatase (S-ALP) levels in patients with prostate cancer.

PATIENTS AND METHODS

In the randomized, phase III trial (CS21), patients with histologically confirmed prostate cancer (all stages), were randomized to one of three regimens: degarelix subcutaneous 240 mg for 1 month followed by monthly maintenance doses of 80 mg or 160 mg, or intramuscular leuprolide 7.5 mg/month. Patients receiving leuprolide could also receive antiandrogens for flare protection. We report exploratory S-ALP analyses from CS21, focusing on the comparison of degarelix 240/80 mg with leuprolide 7.5 mg, in line with the recent approvals of this dose by the USA Food and Drug Administration and the European Medicines Agency.

RESULTS

Overall, 610 patients were included, with a median age of 73 years and median prostate-specific antigen (PSA) level of 19.0 ng/mL. Baseline S-ALP levels were high in metastatic patients and highest in patients with metastatic disease and a haemoglobin level of <13 g/dL. In metastatic disease, after initial peaks in both groups, S-ALP levels were suppressed below baseline with degarelix but were maintained around baseline with leuprolide. The late rise in S-ALP seen with leuprolide was not apparent with degarelix. The pattern of S-ALP response was similar in patients with a baseline PSA level of ≥50 ng/mL. Between-treatment differences in patients with metastatic disease and those with a PSA level of ≥50 ng/mL were significant at day 364 ($P = 0.014$ and 0.007, respectively).

CONCLUSION

Patients with metastatic disease or those with PSA levels of ≥50 ng/mL at baseline had greater reductions in S-ALP levels with degarelix than with leuprolide. Patients in the degarelix group maintained S-ALP suppression throughout the study, in contrast to those in the leuprolide group. This suggests that degarelix might offer better S-ALP control than leuprolide and might prolong control of skeletal metastases, compared with GnRH agonists, over a 1-year treatment period.

KEYWORDS

alkaline phosphatase, degarelix, disease stage, leuprolide, prostate cancer, prostate-specific antigen

INTRODUCTION

Bone metastases occur with several types of cancer; the skeleton is the most frequent location of metastasis in men with prostate carcinoma [1]. Bone formation and resorption are altered in bone metastases compared with normal bone and two main types of metastasis occur. If there is excessive bone formation, as in bone metastases from prostate cancer, lesions are said to be sclerotic or osteoblastic, whereas osteolytic lesions are characterized by excessive bone resorption. Osteoblastic metastases commonly cause increased serum levels of parathyroid hormone, which promotes the growth and invasiveness of prostate cancer cells in bone. Thus, blastic metastases induce a 'vicious cycle' in which parathyroid hormone induces the resorption of normal bone to support the growth of blastic bone [2]. Furthermore, factors that increase bone resorption independent of the tumour, such as sex hormone deficiency, might contribute to this cycle.

Bone matrix components are released into the systemic circulation during both bone

formation and resorption processes. Serum and urinary markers can be measured as correlates of markers of bone turnover. Markers of bone formation include serum osteocalcin, procollagen I extension peptides, total serum alkaline phosphatase (S-ALP) and bone-specific alkaline phosphatase (B-ALP). Bone resorption markers include serum or urinary C-terminal telopeptide fragment of type I collagen, as well as urinary calcium, hydroxyproline, collagen-pyridinium cross-links, and N-terminal type I collagen telopeptide fragment. Levels of most of these markers have been shown to be elevated in patients with bone metastases from prostate cancer [3], despite their predominantly osteoblastic nature. ALP measurements can be used alongside bone scintigraphy in the diagnosis and follow-up of bone metastases in patients with prostate cancer [4,5]. However, clinical interpretation can be complex because increased S-ALP levels can be reflective of either bone or liver metastases [6], although liver metastases are relatively uncommon in patients with prostate cancer [7]. In addition, as a sign of bone repair, an initial rise in S-ALP can occur [8]. In an attempt to improve the specificity and sensitivity of S-ALP measurements, assays using monoclonal antibodies specific for the bone isoenzyme have been developed [9]. Elevated S-ALP and B-ALP levels have been associated with progression of skeletal metastases in patients with prostate cancer [10,11] and have also been shown to be significant predictors of early death [3,12–14].

Androgen-deprivation therapy (ADT) is commonly used in the management of patients with advanced prostate cancer, especially those with bone metastases. The most commonly used agents for ADT are the GnRH receptor agonists. These achieve castrate testosterone levels (≤0.5 ng/mL) in 90–100% of patients, but only after ≈1 month's treatment [15]. These agents also result in an initial testosterone surge, which can stimulate prostate cancer cells and lead to an exacerbation of clinical symptoms (so-called 'clinical flare') [16]. ADT with GnRH agonists or orchidectomy increases markers of osteoblast and osteoclast activity, decreases bone mineral density and increases the risk of fracture in patients with prostate cancer [17–19]. Concomitant treatment with bisphosphonates, such as zoledronic acid, can preserve bone density and suppress markers of bone turnover in patients receiving ADT for prostate cancer, both in those with and without bone metastases [20].

GnRH receptor blockers are a new class of hormonal therapy that induce a faster suppression of serum testosterone than GnRH receptor agonists, but without a testosterone surge. Degarelix is a GnRH receptor blocker that has been developed as a novel therapy for patients with prostate cancer who require ADT. In a recent phase III trial (CS21), both tested dose regimens of degarelix (240/80 mg and 240/160 mg) and leuprolide 7.5 mg suppressed testosterone to ≤0.5 ng/mL in >95% of patients over a 1-year treatment period [21]. Both degarelix regimens achieved a more rapid reduction of testosterone and PSA than leuprolide, and neither degarelix dose induced testosterone surge or microsurges. Although the effects of GnRH receptor agonists on ALP levels have been reported previously [17,18], the effects of GnRH blockers such as degarelix are not known. Here we report S-ALP analyses from the CS21 study, focusing on the comparison of degarelix 240/80 mg vs leuprolide 7.5 mg, in line with the recent approvals of this degarelix dose by the USA Food and Drug Administration and European Medicines Agency for the treatment of advanced prostate cancer.

PATIENTS AND METHODS

CS21 was a three-arm, randomized (1:1:1), active-controlled, open-label, parallel-group, phase III trial with a 1-year duration [21]. Patients were randomized to receive s.c. injections of degarelix with a starting dose of 240 mg, followed by 12 monthly (every 28 days) maintenance doses of either 80 mg (at 20 mg/mL) or 160 mg (at 40 mg/mL), or 12 monthly (every 28 days) i.m. injections of leuprolide 7.5 mg. In the leuprolide group, antiandrogens could be administered for flare protection at the discretion of the investigator. The trial was conducted in accordance with the Declaration of Helsinki as well Good Clinical Practice Guidelines. Appropriate independent ethics committees and institutional review boards for the participating sites were used throughout the trial.

Men (aged ≥18 years) with histologically confirmed adenocarcinoma of the prostate (all stages), for whom endocrine treatment was indicated (except for neoadjuvant hormonal therapy), were recruited. This included patients with increasing PSA levels after treatment of curative intent (i.e. patients with biochemical failure). Patients were also required to have a screening serum testosterone level of >1.5 ng/mL, an Eastern Cooperative Oncology Group performance status of ≤2, and a PSA level of ≥2 ng/mL. Previous or current hormonal management of prostate cancer was not permitted except in patients who had undergone localized therapy with curative intent, in whom neoadjuvant or adjuvant hormonal therapy for ≤6 months was accepted (this must have been discontinued for >6 months before inclusion). Patients considered to be candidates for curative therapy were excluded.

S-ALP and PSA levels were prospectively measured for all patients in CS21 as part of the laboratory tests included in the overall safety analysis and the secondary efficacy analyses, respectively. An exploratory analysis of S-ALP development over time in relation to baseline disease characteristics is presented here. Effects of treatment on S-ALP levels were analysed by baseline prostate cancer disease stage (localized, locally advanced or metastatic) and PSA level (<10, 10–20, 20–50 or ≥50 ng/mL). The effects of leuprolide on S-ALP levels were also analysed by the presence or absence of concomitant antiandrogen treatment.

Central laboratories were used to measure all S-ALP and PSA levels in the patients' blood samples. S-ALP levels were measured using a standardized colorimetric assay based on the p-nitrophenyl phosphate AMP buffer method. PSA was analysed using a validated immunoassay. An ANOVA, with treatment and day as factors and baseline value as covariate, was used to determine between-treatment differences at day 364. A repeated-measures analysis (incorporating all time points from day 112), with treatment and day as factors and baseline value as covariate, was used to assess between-treatment differences from day 112 to day 364.

RESULTS

The baseline characteristics and demographics were comparable between the degarelix 240/80 mg and leuprolide 7.5 mg treatment groups (Table 1). Overall, about half of the patients had locally advanced or metastatic disease at baseline, the median testosterone level was 3.93 ng/mL and the median PSA level was 19.0 ng/mL. In all, six

TABLE 1 The baseline characteristics of the intent-to-treat population

Median (range) or *n* (%) variable	Degarelix 240/80 mg	Leuprolide 7.5 mg
Intent-to-treat analysis set	207	201
Age, years	72 (51–89)	74 (52–98)
Testosterone, ng/mL*	4.11 (3.05–5.32)	3.84 (2.91–5.01)
PSA, ng/mL	19.8 (9.4–46)	17.4 (8.4–56)
Stage of disease		
Localized†	69 (33)	63 (31)
Locally advanced‡	64 (31)	52 (26)
Metastatic	37 (18)	47 (23)
Incompletely classified¶	37 (18)	39 (19)
PSA subgroup, ng/mL		
<10	55 (27)	64 (32)
10–20	52 (25)	44 (22)
20–50	52 (25)	38 (19)
≥50	48 (23)	55 (27)

**Interquartile range; †Localized, T 1/2, NX or N0, and M0; ‡Locally advanced: T 3/4, NX or N0, and M0, or N1 and M0; ¶Includes those with increasing PSA levels after radical prostatectomy or radiotherapy.*

TABLE 2 Mean S-ALP levels in patients with baseline metastatic disease, metastatic disease and Hb <13 g/dL and PSA ≥50 ng/mL at baseline and days 112, 224 and 364

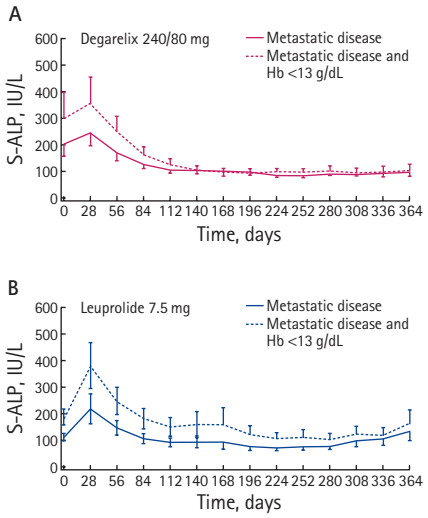
Group	S-ALP, IU/L (unadjusted mean) Metastatic disease	Metastatic disease, Hb <13	PSA ≥50 ng/mL
Degarelix 240/80 mg (207), *n*	37	16	48
Baseline	203	295	166
Day 112	104[a]	124[b]	95[c]
Day 224	84	97	73
Day 364	96*	101†	83‡
Degarelix 240/160 mg (202), *n*	40	21	61
Baseline	268	361	202
Day 112	154[d]	199[e]	130[f]
Day 224	115	134	112
Day 364	126¶	100§	81°
Leuprolide 7.5 mg (201)	47	26	55
Baseline	148	178	148
Day 112	125	148	114
Day 224	97	105	89
Day 364	179	163	163

*Between-treatment (degarelix-leuprolide) differences at day 364; *P = 0.013, †P = 0.070, ‡P = 0.007, ¶P = 0.257, §P = 0.399, °P = 0.052. Between-treatment (degarelix-leuprolide) differences from day 112–364, [a]P = 0.141, [b]P = 0.197, [c]P = 0.124, [d]P = 0.782, [e]P = 0.630 and [f]P = 0.874.*

patients (3%) in the degarelix group and eight (4%) in the leuprolide group received concomitant bisphosphonate treatment. Of these 14 patients, five of the six in the degarelix and five of the eight in the leuprolide group had metastatic disease at baseline. Overall, 14% vs 11% of patients with metastatic disease in the degarelix and leuprolide groups, respectively, received concomitant bisphosphonate treatment at any time during this study.

Baseline S-ALP levels were high in patients with metastatic disease, due to the presence of skeletal metastases, and were highest in patients with metastatic disease and haemoglobin (Hb) levels of <13 g/dL at baseline (Table 2). The effects of degarelix 240/160 mg on S-ALP levels are also included for completeness. Although the effects on S-ALP levels were similar during treatment with degarelix 240/80 mg and 240/160 mg, the magnitude of the effect differed, and so differences between degarelix and leuprolide were only statistically significant in the 240/80 mg group.

FIG. 1. The mean (SEM) S-ALP levels (normal range 44–147 IU/L) in patients with baseline metastatic disease or metastatic disease and Hb levels of <13 g/dL during (A) degarelix 240/80 mg and (B) leuprolide 7.5 mg treatment.

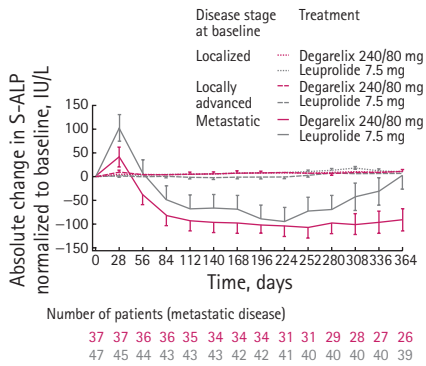


*Normal S-ALP range: 44–147 IU/L

Hb, haemoglobin; S-ALP, serum alkaline phosphatase

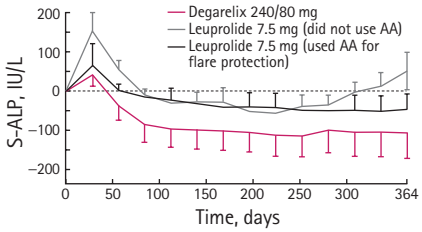
The mean absolute changes in S-ALP levels during degarelix 240/80 mg or leuprolide treatment in these patient subgroups are shown in Fig. 1. After initial peaks in both groups, by day 56, S-ALP was suppressed similarly below baseline levels with degarelix 240/80 mg in 37 patients with metastatic disease, or 16 with metastatic disease and Hb levels of <13 g/dL. S-ALP levels were also suppressed during leuprolide treatment, dropping below baseline levels by day 84, although the trough levels achieved in the 26 patients with Hb <13 g/dL did not match the levels in 47 metastatic patients overall receiving leuprolide. The rise in S-ALP levels with leuprolide late in the study was not observed with degarelix. Overall, the difference in S-ALP suppression in patients

FIG. 2. The mean (SEM) change in S-ALP levels (normalized to baseline) by baseline disease stage.



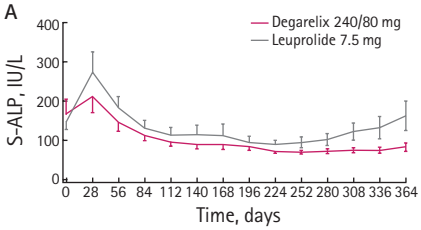
S-ALP, serum alkaline phosphatase

FIG. 3. The mean (SEM) change in S-ALP levels ((normal range 44–147 IU/L; normalized to baseline) in patients with baseline metastatic disease, showing the effect of concomitant AA flare protection. Only time points with more than five patients are shown.

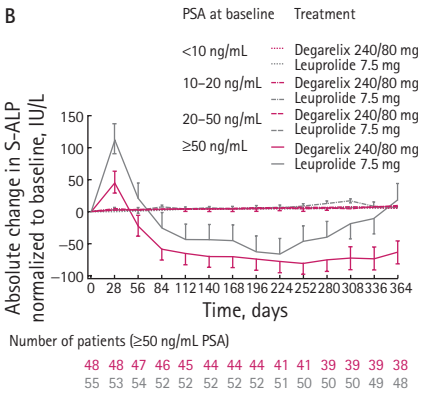


Only time points where $n \geq 5$ are displayed
*Normal S-ALP range: 44–147 IU/L
AA, antiandrogen; S-ALP, serum alkaline phosphatase

FIG. 4. The mean (SEM) S-ALP levels in patients with baseline PSA levels of (A) ≥50 ng/mL and (B) by baseline PSA level.



*Normal S-ALP range: 44–147 IU/L
S-ALP, serum alkaline phosphatase



PSA, prostate-specific antigen;
S-ALP, serum alkaline phosphatase

with metastatic prostate cancer was statistically significant between degarelix 240/80 mg and leuprolide 7.5 mg at day 364 (96 vs 179 IU/L; $P = 0.014$; Table 2). In general, S-ALP was maintained around baseline levels in patients with localized or locally advanced disease, irrespective of treatment received (Fig. 2).

Nine of the 47 patients with metastatic disease in the leuprolide group (19%) received concomitant antiandrogen treatment before day 7 for flare protection. Concomitant antiandrogen appeared to improve S-ALP control in patients with metastatic disease treated with leuprolide, reducing the initial S-ALP surge and preventing the late rise in S-ALP levels observed in patients on leuprolide not receiving antiandrogen treatment (Fig. 3). Nonetheless, the difference in S-ALP suppression at day 364 between the two leuprolide groups was not statistically significant ($P = 0.15$). At this time, the difference in S-ALP suppression in patients with metastatic disease was significantly greater with degarelix 240/80 mg than in patients on leuprolide who did not receive antiandrogen treatment ($P = 0.045$). Overall, S-ALP was suppressed earlier and to lower levels throughout the study in patients receiving degarelix compared with leuprolide, although the difference in suppression at day 364 was not statistically significant between patients receiving degarelix 240/80 mg and those receiving leuprolide plus concomitant antiandrogen ($P = 0.88$).

Overall, baseline S-ALP levels were three to four times higher in patients with PSA levels of ≥50 ng/mL at baseline than in those with levels of <50 mg/mL. After initial peaks in both groups, patients with baseline PSA levels of ≥50 ng/mL had greater absolute reductions in S-ALP and reductions from baseline with degarelix 240/80 mg than with leuprolide 7.5 mg (Fig. 4A,B). The late rise in S-ALP levels in patients on leuprolide with baseline PSA levels of ≥50 ng/mL beyond 10 months was not apparent during degarelix treatment. In patients on leuprolide with baseline PSA levels of ≥50 ng/mL, S-ALP returned to baseline levels before the end of the 1-year study, whereas S-ALP levels remained below baseline at the end of the study period in the degarelix group. The difference in suppression between degarelix 240/80 mg and leuprolide 7.5 mg in this patient subgroup was statistically significant at day 364 (83 vs 163 IU/L; $P = 0.007$; Table 2) and approached significance in the degarelix 240/160 mg group ($P = 0.052$). S-ALP was maintained around baseline levels in patients with PSA levels of <50 ng/mL, irrespective of treatment received (Fig. 4B).

DISCUSSION

The overall analysis of CS21 showed that, when compared with leuprolide, degarelix achieved a more rapid suppression of LH, testosterone and PSA levels, and was as effective as leuprolide in terms of the primary endpoint, i.e. inducing and sustaining testosterone suppression to castrate levels (≤0.5 ng/mL) throughout the 1-year treatment period [21]. The present analysis suggests that the faster onset of action noted previously with degarelix might give rise to a faster and more profound control of S-ALP levels than with leuprolide, particularly in those with metastatic disease and those with baseline PSA levels of ≥50 ng/mL. Degarelix 240/80 mg treatment also resulted in the earlier suppression of S-ALP levels than with leuprolide plus concomitant antiandrogen treatment. Furthermore, the late rise in S-ALP levels often seen during leuprolide treatment, which might suggest therapy failure, was not apparent with degarelix. These differences are unlikely to be due to any confounding effect of concomitant bisphosphonate treatment, as very few patients received this during the study, and similar proportions of patients received bisphosphonate treatment in the degarelix 240/80 mg and leuprolide 7.5 mg groups, irrespective of disease stage.

Initial levels of S-ALP were highest in the subgroup of patients with both metastatic disease and Hb <13 g/dL, indicating that these patients were likely to have microscopic skeletal metastases. S-ALP was reduced to the same extent for these patients and metastatic patients overall during degarelix, but not so with leuprolide treatment. Low Hb levels have previously been associated with poor outcome in patients receiving

ADT for advanced prostate cancer [22]. Non-metastatic patients had normal baseline S-ALP and little change in S-ALP levels during treatment, consistent with their nonmetastatic disease stage. The addition of concomitant antiandrogen as flare protection in some patients receiving leuprolide appeared to improve S-ALP control, although S-ALP levels remained higher throughout the study than those achieved in patients receiving degarelix 240/80 mg. This is similar to observations from the primary analysis, where the initial onset of PSA control was improved in patients on leuprolide receiving concomitant antiandrogen, compared with patients on leuprolide who did not [21]. These data suggest that the improved activity of degarelix in terms of S-ALP control might in part be due to its lack of stimulation of the hypothalamic-pituitary-gonadal axis, and therefore the lack of testosterone surge and microsurges, although the exact mechanism for this difference is currently unknown. Another potential explanation for this difference is that degarelix reduces plasma FSH levels significantly more than leuprolide [21]. FSH is thought to be important in regulating bone resorption and enhances formation of both osteoclasts and osteoblasts [23]. Overall, S-ALP effects were similar during degarelix 240/80 mg and 240/160 mg treatment; however, as the magnitude of effect differed, the differences between degarelix and leuprolide were not statistically significant in the 240/160 mg group. The reason for this apparent difference is currently unclear. It has been reported that the pharmacokinetic profiles of degarelix 240/80 mg and 240/160 mg regimens are not identical, probably due to differences in the dosing concentration (20 vs 40 mg/mL, respectively) [24] and it is possible that this could result in different bioavailability for these two regimens. Nonetheless, the effects of degarelix 240/80 mg or 240/160 mg treatment on testosterone and PSA levels were very similar in the overall analysis [21], although testosterone/PSA effects by baseline disease stage or PSA have not been analysed for these two dose regimens and so small differences within these subgroups cannot be excluded at present.

Assessment of ALP levels before and during prostate cancer treatment might provide useful prognostic information. For example, ALP levels after 6 months of ADT were previously shown to be predictive of survival outcome in patients with prostate cancer [13,14]. Consistent with this, normalization of bone markers during zoledronic acid treatment has also been shown to be associated with improved overall survival; there was also a benefit in patients whose levels reduced but did not normalize [25]. High levels of bone markers while on treatment have also been linked with an increased risk of skeletal-related events, disease progression and death in patients receiving placebo [26], or bisphosphonate treatment [27] in clinical trials in patients with solid tumours, including prostate cancer. These data suggest that reducing levels of bone turnover markers might delay the progression of bone metastases and potentially improve survival. S-ALP levels were prospectively measured in the CS21 trial as part of the laboratory tests included in the overall safety analysis, although the analysis of S-ALP as a disease marker was not pre-planned. However, this analysis would appear to hold little bias given that S-ALP is an objective laboratory measure. The differences between treatments need to be confirmed in a randomized, controlled clinical trial. Nonetheless, the results for the PSA ≥50 ng/mL and metastatic subgroups are consistent with a potential for improved activity (in terms of S-ALP control) with degarelix vs leuprolide in those with more advanced disease. Baseline disease stage and pretreatment PSA level have previously been linked to prostate cancer outcome in terms of PSA failure and clinical outcome [28,29].

The initial peaks in S-ALP levels observed in metastatic patients receiving ADT with either degarelix or leuprolide were reported previously in a study of the effects of estramustine phosphate or orchidectomy in a similar patient setting [8]. It has been speculated that these peaks might be due to increased osteoblastic activity associated with tumour cell death and the rebuilding of bone tissue around skeletal metastases. Initial ALP rises were also noted as a negative prognostic indicator for disease-free survival in patients with advanced prostate cancer [8]. In general the S-ALP peaks noted in the present study were smaller during degarelix treatment than with leuprolide, which might reflect the better prognosis in terms of progression-free survival in this setting. This is supported by the trends towards improved PSA progression-free survival and PSA failure rates with degarelix vs leuprolide in the CS21 study, which were particularly marked in those with advanced disease [30].

In summary, these exploratory analyses show that patients with metastatic disease or those with PSA levels of ≥50 ng/mL at baseline had greater reductions in S-ALP with degarelix 240/80 mg than with leuprolide. Patients in the degarelix 240/80 mg group maintained S-ALP suppression throughout the study and did not have the late increases in S-ALP level seen in patients receiving leuprolide. The difference in S-ALP suppression between degarelix 240/80 mg and leuprolide was statistically significant at day 364. These results indicate better S-ALP control with degarelix 240/80 mg than with leuprolide, and therefore generate the hypothesis that degarelix might further prolong the control of skeletal metastases compared with GnRH agonists over a 1-year treatment period. Reduced levels of bone turnover markers have previously been linked to delayed disease progression and potential survival benefits [26,27]; the consequences of improved S-ALP control with degarelix in certain patient subgroups need to be confirmed in a randomized controlled trial. These exploratory analyses support previous data indicating that degarelix provides effective ADT for patients with prostate cancer, with a fast onset of action and sustained disease control, and without the need for antiandrogen flare protection.

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CONFLICT OF INTEREST

Fritz H. Schröder and Kurt Miller are Paid Consultants to Sponsor, Bertrand Tombal and Neal D. Shore are Paid Consultants and Study Investigators Funded by Sponsor, E. David Crawford is a Speaker for Ferring, Judd Moul is an Advisor and Speaker for Ferring, Tine Kold Olesen and Bo-Eric Persson are Employees of Sponsor, and Laurent Boccon-Gibod is a Member of the Advisory Board.

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Abbreviations: **ADT**, androgen-deprivation therapy; **Hb**, haemoglobin; **(S)(B)-ALP**, (serum) (bone-specific) alkaline phosphatase.