Comparative efficacy of triptorelin pamoate and leuprolide acetate in men with advanced prostate cancer

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OBJECTIVE

To compare the efficacy of monthly administrations of the luteinizing hormone-releasing hormone agonists triptorelin pamoate and leuprolide acetate to induce and maintain castrate levels of serum testosterone in men with advanced prostate cancer.

PATIENTS AND METHODS

Men with advanced prostate cancer were randomly assigned to receive triptorelin 3.75 mg or leuprolide 7.5 mg. The agent was injected intramuscularly every 28 days for nine injections. Primary endpoints were the percentages of men whose serum testosterone concentrations declined to and were maintained at or below castrate levels (≤ 1.735 nmol/L or ≤500 ng/L) during 9 months (253 days) of treatment. Secondary endpoints were luteinizing hormone levels, bone pain, prostate specific antigen levels, quality of life, testosterone pharmacodynamics, survival, and safety variables.

RESULTS

In all, 284 men received either triptorelin (140) or leuprolide (144). The percentage of men with castrate levels of serum testosterone was lower at 29 days for triptorelin than for leuprolide (91.2% vs 99.3%; point estimate −8.0, 95% confidence interval −16.9% to −1.4%), but equivalent at 57 days (97.7% vs 97.1%). The mean (98.8% vs 97.3%) and cumulative (96.2% vs 91.2%) castration maintenance rates between 29 and 253 days were equivalent between the treatment groups. Secondary endpoints were equivalent between treatment groups except for the 9-month survival rate, which was significantly higher for triptorelin than for leuprolide (97.0% vs 90.5%; $P = 0.033$). Both treatments were well tolerated.

CONCLUSION

Triptorelin reduced testosterone concentrations less rapidly, but maintained castration as effectively as leuprolide. There was no evidence that the slower onset of castration caused deleterious effects.

KEYWORDS

prostate cancer, LHRH agonist, triptorelin pamoate, leuprolide acetate, testosterone

INTRODUCTION

Androgen deprivation is the treatment of choice for men with advanced prostate cancer and may provide control for long periods. Androgen deprivation can be achieved by bilateral orchidectomy, oestrogen therapy, antiandrogens, or administering a LHRH agonist. Many patients find surgical castration unacceptable, and oestrogen therapy is associated with increased cardiovascular risk [1,2]. Antiandrogens are associated with lower overall survival than other options [3]. In contrast, survival rates after treatment with a LHRH agonist are equivalent to those after surgical castration [3] and the treatment is well tolerated, making LHRH agonists the preferred option for suppressing androgens for many men. After initiating therapy with a LHRH agonist, castration levels of testosterone are generally reached within a month.

Triptorelin pamoate is a decapeptide agonist analogue of LHRH with a greater potency than endogenous LHRH. The amino-acid sequence for triptorelin is identical to that of endogenous LHRH except for the amino acid in the sixth position, where the L-glycine found in LHRH is replaced by D-tryptophan in triptorelin. This substitution increases biological potency by rendering the synthetic moiety less susceptible to cleavage by proteolytic enzymes [4–7].

We conducted a randomized phase III study to determine whether triptorelin pamoate is as effective as the LHRH agonist leuprolide acetate as first-line therapy in men with advanced prostate cancer. The assessment of efficacy was based on the ability to induce castration levels of serum testosterone and maintain them during 9 months of treatment. The secondary objectives were to assess the effects on LH levels, bone pain, PSA levels, quality of life (QoL), testosterone pharmacodynamics, survival and safety variables.

PATIENTS AND METHODS

This was a parallel-group, randomized, controlled, multicentre study designed to compare the efficacy, safety and testosterone pharmacodynamics of 1-month formulations of triptorelin and leuprolide. Eligible patients had histologically confirmed advanced prostate cancer (stage C or D) defined as T3–4NXMX, TXN1–3MX, or TXNXM1. Patients had to have had a bone scan within the previous 3 months and to have a serum testosterone concentration of >5 nmol/L (> 1440 ng/L); a Karnofsky performance index of >40; an expected survival of ≥12 months; and no other malignancy (except dermatological) for 5 years. Exclusion criteria were previous hormonal therapy for prostate cancer; hypophysectomy; adrenalectomy; another

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neoplastic lesion or brain metastases; known or suspected vertebral metastases with risk of spinal compression; renal (creatinine ≥ twice normal) or liver failure (aspartate and alanine aminotransferase ≥three times normal); use of an experimental drug within 3 months before the study or within five drug half-lives of the investigational drug, whichever was longer; hypersensitivity to test materials; use of recreational drug; alcohol dependence; current use (or use within 6 months) of medications that affect metabolism or secretion of androgenic hormones; use of corticosteroids except topical application, anticoagulants, heparin and coumarin derivatives; or inability to comply fully with the protocol. All patients gave written informed consent before entry into the study.

Patients were single-masked to treatment and, at enrolment, investigators and patients were unaware of the randomization. Eligible patients were randomly assigned to receive treatment with triptorelin pamoate microgranules 3.75 mg (Decapeptyl®, Debio RP, Martigny, Switzerland, also known as Trelstar®, Pharmacia Company, Kalamazoo, MI, USA) or leuprolide acetate microspheres 7.5 mg (Lupron®; manufactured by Takeda Chemical Industries Ltd, Osaka Japan for Tap Pharmaceuticals Inc., Lake Forest, IL, USA). Study medications were injected intramuscularly every 28 days for a total of nine injections. Medical and supportive treatment necessary for the patient's welfare was given at the discretion of the investigator and recorded. If analgesics were used, the patient was advised to use the same analgesic throughout the study. Treatments or procedures that affect androgenic hormones were not permitted.

Blood samples were obtained for the measurement of serum testosterone and LH concentrations before treatment, and thereafter every 28 days, beginning on day 1 and ending on day 253 (i.e. 28 days after the last dose). Additional blood samples were obtained for measuring serum testosterone concentrations at 2, 4, 8, 12 and 24 h after the fourth injection (85 days) in a subset of 15 patients from each treatment group (30 in all). Blood samples were also obtained before each injection and 28 days after the last injection (253 days) to measure nadir triptorelin concentrations in patients receiving triptorelin. PSA levels were measured on at 1, 85, 169 and 253 days. Bone pain was assessed by a visual analogue scale (VAS) [7] and QoL by a recognised instrument [8] at 1, 29, 57, 85, 169 and 253 days.

Safety assessments included a regular examination for potential adverse events using the WHO classification; survival at 9 months; haematology, coagulation and blood chemistry at baseline and at 1, 85, 169 and 253 days; vital signs and body weight; and local tolerance at the injection site at 1, 85 and 169 days. Patients were assessed before each injection unless otherwise stated. Investigators assessed the relationship between treatment and adverse events; 'related' was defined as including events of unlikely, possible, or probable relationship to treatment. Vital signs were also evaluated 2 and 4 h after injection at 1, 85 and 169 days.

STATISTICS

Data were analysed using commercial software, with the efficacy analysis using the intent-to-treat (ITT) population, which included all randomized patients regardless of protocol deviations, except for those who had missing testosterone values at 29 days. The safety analysis included all patients who received at least one dose of study medication, provided that they had safety data.

The study was powered to detect the superiority or equivalence of triptorelin over leuprolide for the proportion of patients with castration levels of testosterone at 29 days and maintenance of castration levels from 2 to 9 months. The target sample size was set at 140 patients in each treatment group, selected to yield a type I error rate of 5% (one-sided) and a type II error rate of 10% (90% statistical power). The following assumptions were made: 92% castration rate at 29 days and 92% castration maintenance rate for both treatments, a superiority margin within 10% of the leuprolide castration rate, and 10% loss-to-follow-up.

Categorical baseline characteristics and efficacy endpoints were summarized by treatment group using absolute and relative frequencies; treatment groups were compared using Fisher's exact test. Ordinal and continuous data were summarized by treatment group using descriptive statistics; treatment groups were compared using the Wilcoxon rank sum test.

The primary efficacy endpoints were the percentages of men with castration at 29 days and at 2–9 months of treatment; castration was defined as the suppression of testosterone concentration to ≤ 1.735 nmol/L. The castration rate at 29 days was evaluated using 95% CIs. The equivalence of the two treatments for the proportion of patients with castration levels of testosterone at 29 days was evaluated using exact two-sided 95% CIs for the difference in castration rates.

The probability of maintaining castration at 2–9 months was estimated using the Kaplan-Meier product-limit method. The approximate SEMs for the probability of maintaining castration were used to calculate two-sided 95% CIs for between-group differences. In the Kaplan-Meier analysis, missing testosterone data were handled as follows. The duration of maintenance of castration was censored if the reason for missing data (withdrawal) was not drug-related; if it was, failure to maintain castration was assumed. If data were missing between visits where castration levels were maintained, castration was assumed to be maintained during that interval and the patient could still maintain castration at a subsequent visit. No patient had more than one missing testosterone datum point between visits.

Secondary endpoints were generally evaluated in a manner analogous to that of the primary endpoint. The absence of gonadotrophin stimulation after injections at 85 and 169 days was defined as a ≤1.0 IU/L increase in serum LH from 0–2 h after injection. The proportion of patients with no gonadotrophin stimulation was calculated, with the 95% CIs, for the difference between groups. Change in bone pain as measured by the VAS was summarized using descriptive statistics; the group-specific change from baseline in VAS was compared using the Wilcoxon rank sum test. Descriptive statistics of the change from baseline in serum PSA and QoL subscales were presented for each visit. Treatment groups were compared by calculating nonparametric point estimates and 95% CIs for the difference in median change from baseline by visit. In the VAS, PSA, and QoL analyses, only patients with no missing baseline values were included; missing endpoints were replaced by the last observation carried forward.

Summary statistics were calculated for adverse-event incidence; the two groups were compared using the chi-squared test or when the expected cell frequencies were < 5, Fisher's exact test (two-sided). Nine-month survival was analysed using Kaplan-Meier survival curves; the treatment groups were compared using the log-rank test.

RESULTS

In all, 284 men received either triptorelin (140) or leuprolide (144) at 29 centres in South Africa, of whom seven were excluded from the ITT population because they had no primary efficacy data at 29 days. Thus 277 patients were in the ITT population (137 treated with triptorelin and 140 with leuprolide). Data from different centres were pooled because the treatment-by-centre interaction on castration rate was not significant. Patients were evenly distributed between treatment groups on the basis of demographic and disease characteristics at baseline (Table 1). Unless otherwise stated, differences between treatment groups were not significant.

EFFICACY

Testosterone concentrations fell below the predefined levels for medical castration in 91% of subjects at 29 days and in 98% at 57 days in the triptorelin group (Table 2), and in 99% and 97%, respectively, in the leuprolide group (Fig. 1). The mean difference between the treatment groups was significant at 29 but not at 57 days (Table 2).

The mean testosterone concentrations were maintained below castration levels in 99% of patients in the triptorelin group at 2–9 months; the cumulative maintenance rate was 96%. During this same period, the mean and cumulative maintenance rates were 97% and 91%, respectively, in the leuprolide group. The Kaplan-Meier survival analysis for the maintenance of castration levels of testosterone is shown in Fig. 2.

Mean LH concentrations, which were measured before injection, decreased from 7.43 IU/L at baseline to 0.81 IU/L at 29 days in the triptorelin and from 6.22 to 0.50 IU/L in the leuprolide groups. Mean LH concentrations remained at slightly lower or similar levels over subsequent visits in both groups. The mean LH concentrations measured immediately before and 2 h after injection to assess acute-on-chronic flare, increased at 1 day by 34.20 IU/L in the triptorelin and by 28.39 IU/L in the leuprolide group. The acute-on-chronic flare was absent at 85 and 169 days in both groups; the mean increases at 85 and 169 days were only 0.08 and 0.11 IU/L, respectively, in the triptorelin and 0.27 and 0.25 IU/L, respectively, in the

TABLE 1 Demographic and disease characteristics at baseline

Characteristic	Triptorelin (137)	Leuprolide (140)
Mean (range):		
age, years	70.5 (47–88)	71.6 (49–89)
weight, kg	76.2 (40–120)	75.5 (40–120)
duration of disease, months	7.8 (0–155)	4.7 (0–85)
Stage of disease, %		
C	62.0	60.7
D	38.0	39.3
Karnofsky performance status, n (%)		
50–70	16 (12)	18 (13)
80	16 (12)	20 (14)
90	61 (44)	64 (46)
100	44 (32)	38 (27)
Previous illness, n (%)	97 (71)	94 (67)
Renal or urogenital	54 (39)	60 (43)
Gastrointestinal	38 (28)	30 (21)
Musculoskeletal	27 (20)	34 (24)
Concomitant illness, n (%)	125 (91)	128 (91)
Cardiovascular	70 (51)	71 (51)
Musculoskeletal	59 (43)	63 (45)
Renal or urogenital	63 (46)	58 (41)
Other	29 (21)	42 (30)
Concomitant drugs, n (%)	131 (96)	136 (97)
Analgesics	83 (61)	86 (61)
Anti-inflammatory or anti-rheumatological	74 (54)	67 (48)
Systemic antibacterial	52 (38)	57 (41)
Antihypertensives	50 (37)	53 (38)
Diuretics	42 (31)	44 (31)
Mean testosterone, nmol/L	12.07	12.03

TABLE 2 The effect of treatment on castration levels and gonadotrophin stimulation

Endpoint	N/total (%) Triptorelin	N/total (%) Leuprolide	Point estimate (95% CI), %
Castration			
29 days	125/137 (91.2)	139/140 (99.3)	– 8.0 (– 16.9 to – 1.4)
57 days	128/131 (97.7)	135/139 (97.1)	5.9 (– 5.5 to 9.7)
2–9 months			
Maintenance			
Average	130/132 (98.8)	135/139 (97.3)	NA
Cumulative	(96.2)	(91.2)	5.1 (– 0.7 to 10.9)
Gonadotrophin stimulation*			
1 day	0/133 (0)	2/137 (1.5)	NA
85 days	124/126 (98.4)	122/130 (93.8)	4.6 (– 1.9 to 14.3)
169 days	114/122 (93.4)	121/123 (98.4)	5.0 (– 2.3 to 14.6)

**Defined as the number (%) of patients showing an increase from before to 2 h after dosing in serum LH of ≤ 1.0 IU/L. NA, not applicable*

FIG. 1. Mean (SD) testosterone serum levels in men treated with triptorelin pamoate 3.75 mg (green dashed line) or leuprolide acetate 7.5 mg (red solid line) for 253 days. The dotted line shows the castrate level of 1.735 nmol/L.

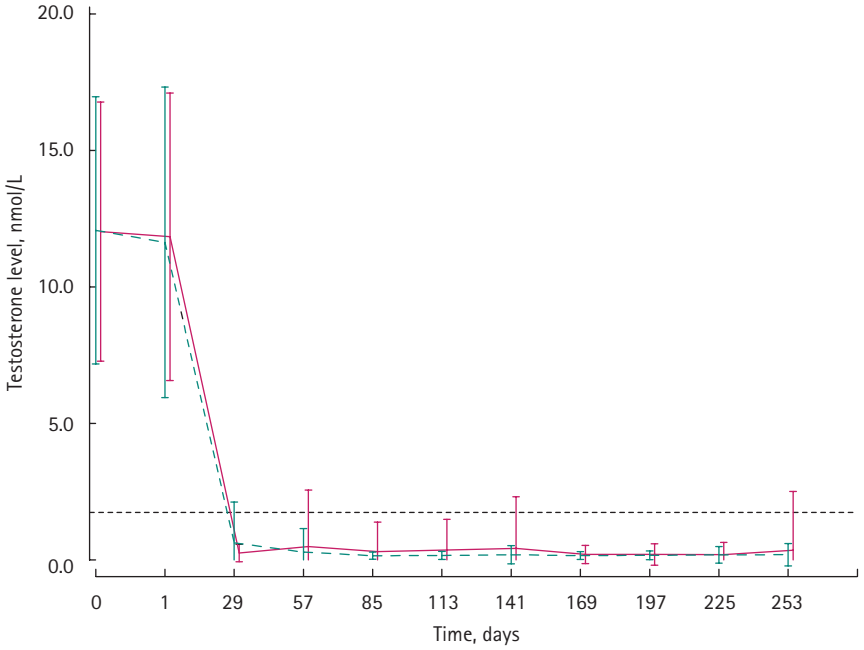
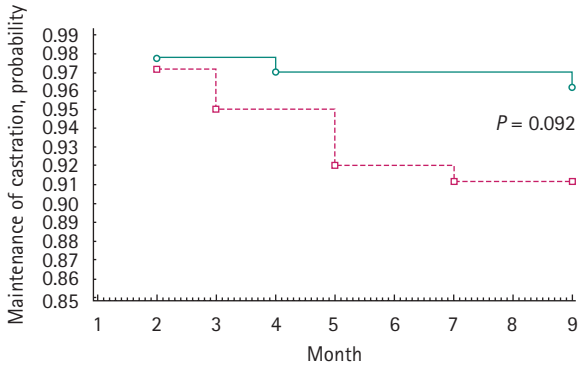


FIG. 2. The maintenance of castration in men treated with triptorelin pamoate 3.75 mg (green line, open circles) or leuprolide acetate 7.5 mg (red line, open squares) for 9 months (Kaplan-Meier survival analysis).



leuprolide group. The proportion of men showing a ≤1.0 IU/L increase in serum LH is summarized in Table 2.

Median (range) bone pain values were low on the VAS at baseline in both the triptorelin, at 4 (0–96) mm, and leuprolide, at 4 (0–97) mm, groups. Median bone pain values remained low throughout the study in both groups (both 4–7 mm).

Analgesics were used by 113 patients in the triptorelin (82%) and 115 in the leuprolide (82%) groups. The mean percentage of days on analgesics, recorded at each visit, was 49–58% and 57–62% in the triptorelin and leuprolide groups, respectively. There were no apparent trends in analgesic use, e.g. a decrease or increase in use, during the study.

The median PSA concentrations decreased from 46.8 at baseline to 1.3 μg/L at endpoint in the triptorelin, and from 36.7 to 1.1 μg/L in the leuprolide group. The difference in change from baseline to endpoint between treatment groups was not significant (– 2.7, 95% CI 15.6–6.1). There were no changes in any QoL variables, on either the functional or symptom scales, between baseline and endpoint in either treatment group.

TESTOSTERONE PHARMACODYNAMICS AND TRIPTORELIN PHARMACOKINETICS

The pharmacodynamic profile of testosterone was evaluated in 14 patients in the triptorelin and 15 in the leuprolide group. The geometric mean (range) testosterone concentration at 85 days was lower in the triptorelin than in the leuprolide acetate group, at 0.38 (0.1–13.8) and 0.16 (0.1–0.7) nmol/L, respectively (point estimate of the ratio of the geometric means, 41.9%, 95% CI 18.2–96.4). During the 24-h period at 85 days, none of the patients in the triptorelin but three in the leuprolide group had testosterone concentrations above castration levels. The mean (range) nadir triptorelin concentrations, measured after the first dose, were 0.41 (0.4–1.6) at 29 days and 0.41 (0.4–1.2) ng/mL at 253 days.

SURVIVAL AND SAFETY

The product-limit estimate of the probability of survival at 9 months was 97.0% in the triptorelin and 90.5% in the leuprolide group ($P = 0.033$). The safety analysis included 284 patients who received at least one dose of study medication. In the triptorelin group, 131 patients reported 670 adverse events (Table 3); in the leuprolide group, 137 reported 734 adverse events. The incidences of overall and system-specific adverse events were similar between treatment groups except for respiratory system disorders, which occurred in 20 (14.3%) in the triptorelin and 34 (23.6%) patients in the leuprolide group ($P = 0.045$). The most frequently mentioned adverse events were hot flushes, skeletal pain, headache and constipation (Table 3).

Most adverse events were of mild to moderate intensity; serious adverse events occurred in 29 patients in the triptorelin and in 43 in the leuprolide group. During or after the study six patients treated with triptorelin and 15 with leuprolide acetate died. None of the deaths were considered related to treatment.

Forty-three patients did not complete the study (20 in the triptorelin and 23 in the leuprolide group; Table 4). Only one patient was withdrawn from the study because of a serious adverse event; he developed asthenia 4 months after starting treatment with triptorelin.

There were no substantial changes in laboratory data, blood pressure, heart rate or body temperature from baseline to endpoint.

The mean body weight increased by 2.6 kg in the triptorelin and by 2.2 kg in the leuprolide group. The change in body weight between the first day and endpoint was not statistically significant between the groups ($P = 0.576$). Local tolerance at the injection site was good; no patients in either treatment group reported redness and induration, with swelling, bruising and pain reported only rarely (Table 3).

TABLE 3 Adverse events

Type of event	N (%) Triptorelin (140)	Leuprolide (144)
Any adverse event	131 (93.6)	137 (95.1)
Relationship		
Related*	104 (74.3)	100 (69.4)
Unrelated	113 (80.7)	124 (86.1)
Intensity		
Mild	117 (83.6)	122 (84.7)
Moderate	85 (60.7)	101 (70.1)
Severe	34 (24.3)	50 (34.7)
Serious adverse events†	29 (20.7)	43 (29.9)
Death during study	4 (2.9)	13 (9.0)
Death after study	2 (1.4)	2 (1.4)
Withdrawal because of serious adverse event	1 (0.7)	0 (0)
Serious adverse events not leading to withdrawal	22 (15.7)	28 (19.4)
Most frequently mentioned adverse events		
Hot flushes	82 (58.6)	78 (54.2)
Skeletal pain	30 (21.4)	24 (16.7)
Headache	19 (13.6)	27 (18.8)
Constipation	21 (15.0)	22 (15.3)
Injection site reactions‡		
Swelling, 1, 85 and 169 days	1 (0.7), 2 (1.6), 2 (1.6)	0 (0), 4 (3.0), 1 (0.8)
Bruising, 1 and 85 days	4 (2.9), 4 (3.1)	4 (2.8), 0 (0)
Pain, 1, 85 and 169 days	5 (3.6), 4 (3.1), 5 (4.1)	1 (0.7), 3 (2.2), 2 (1.6)

**Includes events with an unlikely, possible, or probable relationship to study drug. †Includes events that result in death, require inpatient hospitalization or prolongation of existing hospitalization, result in persistent or significant disability or incapacity, or that are life-threatening. ‡The number of patients decreased with time.*

TABLE 4 Reasons for withdrawal from the study

Reason	Triptorelin	Leuprolide
Drug-related adverse event	1	0
Patient lost to follow-up	11	5
Insufficient therapeutic effect	1	1
Death	4	13
Protocol violation	1	3
Consent withdrawn	1	1
Other	1	0
Total	20	23

DISCUSSION

LHRH agonists act by down-regulating the pituitary gland, thereby suppressing secretion of LH and FSH from the hypothalamus, which in turn suppresses the secretion of testosterone from the testes. In this study, the LHRH agonist triptorelin pamoate reduced testosterone concentrations to or below the predefined levels for medical castration in 91% of patients with advanced prostate cancer 28 days after the first injection and in 98% by 57 days. The 29-day value was significantly lower than the castration rate reached for leuprolide acetate at 29 days (99%), but at 57 days the values were similar. The 99% castration rate at 29 days for leuprolide in this study is higher than that reported by others [9]. A castration rate of 94% at 30 days after treatment with leuprolide 7.5 mg is reported in the product information (Lupron depot 7.5 mg, Tap Pharmaceuticals Inc, February 2001) and a mean rate of 93% by 29 and 97% by 57 days in the Lupron 4-month summary basis for approval, which also includes data for the 1-month formulation (Lupron 4-month Summary Basis for Approval; Tap Pharmaceuticals Inc, 1997). These rates for leuprolide acetate are comparable with rates reported for triptorelin pamoate in the current study. Furthermore, the mean testosterone profiles, as shown on Fig. 1, are almost superimposable after giving triptorelin pamoate or leuprolide acetate.

With 2–9 months of treatment the mean (99% and 97%) and cumulative castration maintenance rates (96% and 91%) were no different for triptorelin and leuprolide. Desensitization of the pituitary gonadotrophin receptors was complete after 84 days of treatment in both groups, as shown by the absence of any increase in LH concentrations.

The present results suggest that triptorelin may induce castration more slowly than does leuprolide, possibly attributable to differences in dose. The higher dose (7.5 mg) of leuprolide may induce castration more rapidly than the lower dose (3.75 mg) of triptorelin, but repeated exposure to the higher dose is more likely to cause an 'escape' as a result of weak desensitization of pituitary GnRH receptors. This hypothesis is supported by the insignificant trend toward more frequent LH stimulation with leuprolide than with triptorelin at 85 (98% vs 94%) and 169 days (98% vs 93%). It is also supported by data from individual patients showing that fewer treated with triptorelin (four) achieved castration by 29 days, but escaped at least once at 2–9 months, than those treated with leuprolide (11; data not shown). This also agrees with the pharmacodynamic data. When testosterone was assessed over 24 h in a subset of patients, three of 15 treated with

leuprolide escaped castration levels, compared with none of 14 treated with triptorelin.

It is not surprising that bone pain was not improved during treatment, because bone pain was minimal at baseline, as measured by the VAS. Consistent with this finding, there was no significant change in analgesic use, as measured by the percentage of days on analgesics. Similarly, it is not surprising that QoL did not improve because scores on the functioning and symptom scales were high at baseline. Importantly, there was no evidence of a deterioration in any of these secondary endpoints in either treatment group at any time during the study.

Tumour response rate was not evaluated in the current study because of the difficulty of assessing this endpoint in men with prostate cancer. Interestingly, the 9-month survival rate was significantly higher in the triptorelin than in the leuprolide group (97.0% vs 90.5%). Other safety endpoints showed no meaningful differences between the treatment groups. Monthly intramuscular injections of both triptorelin and leuprolide were well tolerated. The pharmacokinetic analysis of triptorelin confirmed that there was no evidence of drug accumulation over the 9-month study period.

In conclusion, the present results indicate that triptorelin pamoate may induce castration at a slightly slower rate than leuprolide acetate, but triptorelin maintains castration at least as effectively as leuprolide. Moreover, there is no evidence that the slower onset of castration caused deleterious effects. The higher 9-month survival rate in the triptorelin than in the leuprolide group is intriguing, but long-term data are required to determine the clinical significance of this observation. Meanwhile, the present findings suggest that triptorelin 3.75 mg offers a useful alternative to leuprolide 7.5 mg for treating men with advanced prostate cancer.

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Abbreviations: **QoL**, quality of life; **VAS**, visual analogue scale; **ITT**, intent-to-treat (population).