

Original Article

Efficacy and safety of leuprorelin acetate 6-month depot in prostate cancer patients: a Phase III, randomized, open-label, parallel-group, comparative study in Japan

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Abstract

Objective: Leuprorelin acetate (TAP-144-SR) is commonly used worldwide in prostate cancer patients. This study was conducted to assess the non-inferiority of a 6-month depot formulation of TAP-144-SR (TAP-144-SR [6M]) 22.5 mg to a 3-month depot formulation of TAP-144-SR (TAP-144-SR [3M]) 11.25 mg in prostate cancer patients in Japan.

Methods: This was a 48-week Phase III, open-label, parallel-group comparative study. TAP-144-SR (6M) 22.5 mg (6M group) and TAP-144-SR (3M) 11.25 mg (3M group) were administered to 81 and 79 subjects, respectively. The primary endpoint was the rate of serum testosterone suppression to the castrate level (≤ 100 ng/dl).

Results: Serum testosterone of all subjects excluding one subject in the 3M group was suppressed to the castrate level throughout 48 weeks. The estimated between-group difference (6M group – 3M group) in suppression rate was 1.3% (95% confidence interval: –3.4, 6.8), and its lower confidence interval was more than –10% of the pre-determined allowable limit value to judge the non-inferiority. The prostate-specific antigen concentrations were stable throughout the study in both groups. Progressive disease in the best overall response based on the Response Evaluation Criteria In Solid Tumors was 0.0% for the 6M group and 2.6% for the 3M group. Adverse events occurred in 92.6% in the 6M group and 89.9% in the 3M group. Adverse events leading to discontinuation were reported in 2.5% in the 6M group and 3.8% in the 3M group.

Conclusions: TAP-144-SR (6M) was not inferior to TAP-144-SR (3M) for the suppressive effect on serum testosterone level. TAP-144-SR (6M) was also as well tolerated as TAP-144-SR (3M).

Key words: leuprorelin, prostate cancer, luteinizing hormone-releasing hormone, testosterone, prostate-specific antigen

Introduction

Prostate cancer was the second most common cancer among new cases of cancer reported in males in 2011 in Japan, and the incidence rate has increased over the years while those of other male cancers have been showing a declining or stable trend (1–3). The incidence rate of prostate cancer is expected to keep increasing due to the prevalence of prostate-specific antigen (PSA) tests and aging, and the number of patients who develop prostate cancer predicted for 2020–24 in Japan is 105 800 per year, which is higher than for any other types of cancer (4).

It is well-known that cell growth in prostate cancer is stimulated by androgens (5). Hormone therapy and orchiectomy providing androgen deprivation have been established as the standard treatments for prostate cancer. The hormone therapy, monotherapy or combined androgen blockade therapy, includes luteinizing hormone-releasing hormone (LH-RH) agonists or an LH-RH antagonist that inhibits the production of testosterone following the suppression of gonadotropin release (6,7).

Leuporelin acetate is a LH-RH agonist that is commonly used worldwide. Leuporelin acetate was initially daily administered to patients, but the development of new formulation technology enabled 1-month (USA: 7.5 mg; EU and Japan: 3.75 mg), 3-month (USA: 22.5 mg; EU and Japan: 11.25 mg) and 6-month (USA: 45 mg; EU: 30 mg) depot formulations for prostate cancer, easing the burden on patients and physicians by reducing the number of injections and improving the quality of life of patients. A 6-month (24-week) depot formulation (TAP-144-SR [6M]) with the same formulation as that used in the USA has been developed in Japan (8), and a Phase II study was conducted in Japanese treatment-naïve prostate cancer patients. The results showed that the optimal clinical dosage of TAP-144-SR (6M) in Japan was 22.5 mg (9) since the serum testosterone level of all six subjects who received the dosage subcutaneously was suppressed below the castrate level and no new safety signals were observed compared with the safety profile of the approved 1-month and 3-month (TAP-144-SR [3M]) depot formulations of TAP-144-SR. A double-peak pharmacokinetic profile was found in the Phase II study.

A Phase III, open-label, parallel-group comparative study was therefore conducted to assess the non-inferiority of treatment with TAP-144-SR (6M) 22.5 mg compared with TAP-144-SR (3M) 11.25 mg for 48-week suppressive effect on serum testosterone in prostate cancer patients.

Patients and methods

Study design

A Phase III, open-label, parallel-group comparative study of TAP-144-SR (6M) to TAP-144-SR (3M) was conducted to evaluate the hormone dynamics, efficacy, pharmacokinetics and safety of the two formulations in prostate cancer patients who have remained stable on TAP-144-SR (3M) treatment. Subjects who were receiving the marketed product for 3 months (TAP-144-SR [3M]) were randomized to the TAP-144-SR (6M) 22.5 mg arm (6M group) or the TAP-144-SR (3M) 11.25 mg arm (3M group), and received two subcutaneous injections of TAP-144-SR (6M) or four subcutaneous injections of TAP-144-SR (3M) over a period of 48 weeks. The subjects were randomized to one of the two treatment groups, using dynamic allocation with the following factors of randomization: (i) TNM classification (\leq any T any N M0 or any T any N M1); (ii) with or without treatment with nonsteroidal antiandrogen; (iii) with or without radiotherapy or surgical therapy; and (iv) study sites. This study was conducted in accordance with the International Conference on Harmonisation of

Good Clinical Practice Guidelines, the principles of the Declaration of Helsinki, and all applicable laws and regulations. The protocol was reviewed and approved by the Institutional Review Boards of all participating study sites. All subjects provided written informed consent for participation before enrollment in the study. The clinical trial registration number is NCT01546623.

Subjects

Subjects who met the following criteria were enrolled: Japanese patients with histopathologically confirmed prostate cancer; prostate cancer of clinical stages \geq T1b and any NM assessed by TNM classification; Eastern Cooperative Oncology Group performance status \leq 2 at screening; PSA level that had not increased \geq 25% or \geq 2 ng/ml from the nadir at measurement points 4 weeks or longer apart within the screening period of 12 weeks; age \geq 20 years and \leq 85 years; use of the marketed TAP-144-SR (3M) at screening; previous use of the marketed leuporelin acetate for 24–96 weeks (excluding the period under neoadjuvant therapy); previous continuous use of the nonsteroidal antiandrogen for \geq 12 weeks if taking any; and a serum testosterone level at screening of $<$ 100 ng/dl.

Subjects were excluded from the study if they met any of the following criteria: active multiple primary cancers; previous use of chemotherapy for prostate cancer; use or previous use of the marketed leuporelin acetate as an adjuvant therapy; use or previous use of the marketed TAP-144-SR (3M) for intermittent androgen deprivation therapy; use of the following drugs within 24 weeks prior to the start of the study drug: steroidal antiandrogens or Type II 5 α -reductase inhibitors; use of any of the following within 16 weeks prior to the start of the study drug: radiotherapy, prostatectomy or experimental therapy; and a QTcF interval exceeded 460 msec on the 12-lead electrocardiogram (ECG) at screening.

Endpoints

The primary endpoint was the rate of serum testosterone suppression to the castrate level from the start of study drug administration through Week 48. The castrate level in this study was set as \leq 100 ng/dl, which has also been used as the castrate level in previous studies of leuporelin acetate 1-month depot and 3-month depot in Japan (10–12). The primary endpoint was also evaluated at a lower serum testosterone level of 50 ng/dl with reference to the recent castration level (8,13–15). The secondary endpoints included the following: serum testosterone concentrations, serum LH concentrations, serum follicle-stimulating hormone (FSH) concentrations and serum TAP-144 concentrations from the start of study drug administration through Week 48. The efficacy, PSA, soft tissues and bone lesions were evaluated based on the response evaluation criteria in ‘General Rule for Clinical and Pathological Studies on Prostate Cancer’ (4th edition) (16). The soft tissues were evaluated based on the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1 (17). Bone lesions were determined using bone scintigraphy. Safety assessments included adverse events (AEs), vital signs, clinical laboratory tests and 12-lead ECG.

Statistical analysis

The full analysis set (FAS) was defined as all subjects who were randomized and received at least one dose of the study drug, and the Hormone level Analysis Set (HAS) was defined as the population of subjects in whom serious protocol deviations were not reported, who satisfied the minimum requirements of the protocol, and in whom primary endpoints were evaluable. The suppression rate of

serum testosterone to the castrate level through 48 weeks in the FAS was analyzed by calculating the incidence rate by treatment group and the point estimates and two-sided 95% confidence intervals (CIs). The point of estimate and the two-sided 95% CIs of the difference between the treatment groups (i.e. 6M group minus 3M group) was calculated by Newcombe Score Confidence Limits (18). If the lower confidence bound for this percentage was greater than or equal to the allowable limit value (−10%), it was judged that the non-inferiority of TAP-144-SR (6M) to TAP-144-SR (3M) was confirmed. It should be noted that the sensitivity analysis was performed by applying the same analysis method used for the primary analysis in the HAS and in the case of a lower testosterone level (≤ 50 ng/dl). Summary statistics were obtained for the secondary efficacy endpoints in the FAS.

The required sample size was estimated to be 75 subjects in each treatment group, a total of 150 subjects, from which the condition was set to 10% allowable limit value, with a significance level of 5% on both sides, and ensuring 80% power.

For the safety analysis, AEs and their severity were analyzed by treatment group. AEs were coded by System Organ Class and Preferred Term using the Medical Dictionary for Regulatory Activities, version 16.1, and their severity was graded based on the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (19).

Results

Subject demographics

A total of 205 patients were screened, and 160 of the 162 randomized subjects received the study drugs with a breakdown of 81 subjects in the 6M group and 79 subjects in the 3M group (Fig. 1). Among the subjects who received the study drugs, 76 subjects in the 6M group and 74 subjects in the 3M group completed the study. Five subjects in each treatment group discontinued the study for the following reasons: AEs (two subjects in the 6M group and three subjects in the 3M

group); major protocol deviations (one subject each in both groups); elevated PSA levels (two subjects in the 6M group and one subject in the 3M group).

The subjects' baseline characteristics are summarized in Table 1. The administration period of marketed leuprorelin acetate before the start of the study drug was similar between the two treatment groups. No major differences were also observed in other subject demographics between the two treatment groups.

Hormone dynamics

Testosterone suppression rate

Serum testosterone of all subjects excluding one subject in the 3M group was suppressed to castrate level (≤ 100 ng/dl) throughout the 48 weeks in the FAS (Table 2). The estimated between-group difference in the suppression rate was 1.3% (two-sided 95% CI: −3.4, 6.8). The lower CI was more than −10% of the pre-determined allowable limit value. Therefore, non-inferiority of TAP-144-SR (6M) to TAP-144-SR (3M) was confirmed for the suppressive effect on serum testosterone level. One subject who did not maintain the castrate level in the 3M group did not meet the inclusion criterion. The serum testosterone level in this subject was 388 ng/dl before treatment with the study drug, 267 ng/dl after 1 week and 55 ng/dl after 2 weeks of treatment. For the sensitivity analysis, the same analysis that was applied to the primary analysis was utilized in the HAS as the secondary analysis. The results in both analysis sets were similar. In the case of the lower serum testosterone level (≤ 50 ng/dl), the suppression rate of serum testosterone throughout the 48 weeks (FAS) in the 6M group was 98.8% (80/81 subjects) and that in the 3M group was 98.7% (78/79 subjects). The estimated between-group difference in the suppression rate was 0.0% (two-sided 95% CI: −5.5, 5.7).

Changes in the hormone levels

The serum testosterone level before treatment was maintained throughout the study in both treatment groups. The median serum

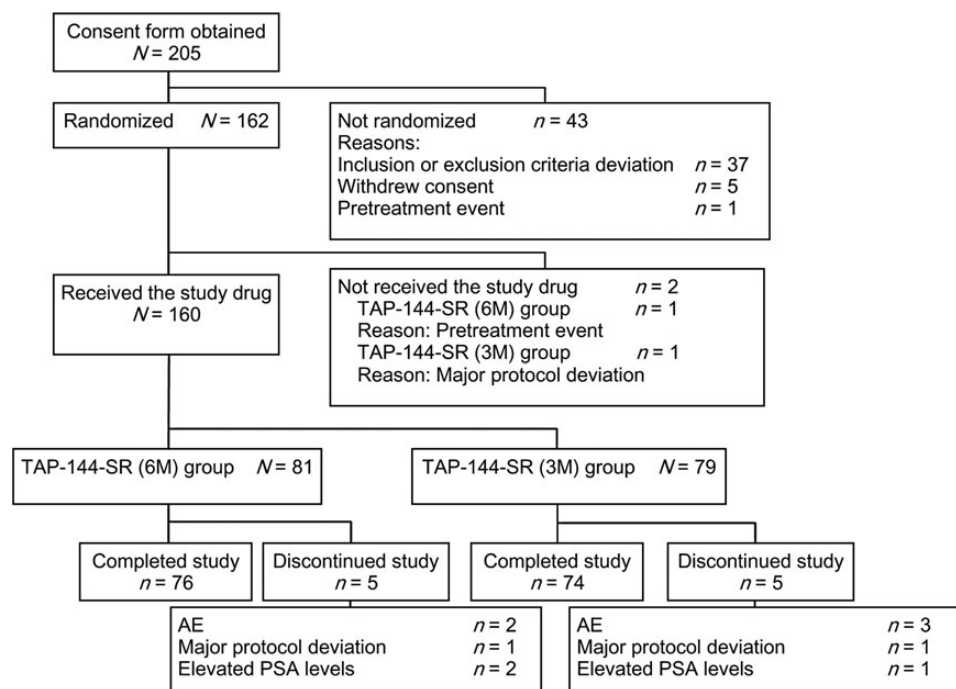


Figure 1. Subjects' disposition. AE, adverse event; PSA, prostate-specific antigen.

Table 1. Subjects' baseline characteristics

	TAP-144-SR (6M) (N = 82)	TAP-144-SR (3M) (N = 80)	Total (N = 162)
Age (years) (mean ± SD)	73.3 ± 6.3	72.6 ± 6.5	73.0 ± 6.4
BMI (kg/m ²) (mean ± SD)	23.6 ± 2.7	24.3 ± 2.8	24.0 ± 2.8
Gleason score, n (%)			
5	2 (2.4)	2 (2.5)	4 (2.5)
6	8 (9.8)	7 (8.8)	15 (9.3)
7	35 (42.7)	29 (36.3)	64 (39.5)
8	14 (17.1)	21 (26.3)	35 (21.6)
9	20 (24.4)	21 (26.3)	41 (25.3)
10	3 (3.7)	0	3 (1.9)
Stage of TNM classification, n (%)			
T			
T1	17 (20.7)	16 (20.3)	33 (20.5)
T2	32 (39.0)	24 (30.4)	56 (34.8)
T3	29 (35.4)	33 (41.8)	62 (38.5)
T4	4 (4.9)	6 (7.6)	10 (6.2)
N			
N0	69 (84.1)	62 (78.5)	131 (81.4)
N1	13 (15.9)	17 (21.5)	30 (18.6)
M			
M0	63 (76.8)	62 (78.5)	125 (77.6)
M1	19 (23.2)	17 (21.5)	36 (22.4)
Serum levels			
N			
Testosterone (ng/dl) (mean ± SD)	81 9.1 ± 8.5	79 13.3 ± 43.5	—
PSA (ng/ml) (mean ± SD)	0.9 ± 3.7	0.7 ± 3.0	—
Administration period of marketed leuprorelin acetate before the start of the study drug (weeks) (mean ± SD)	46.3 ± 20.1	46.6 ± 20.9	46.5 ± 20.4
ECOG PS, n (%)			
0	73 (90.1)	71 (89.9)	144 (90.0)
1	7 (8.6)	7 (8.9)	14 (8.8)
2	1 (1.2)	1 (1.3)	2 (1.3)

BMI, body mass index; PSA, prostate-specific antigen; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

Table 2. Rate of suppression of serum testosterone to castrate level (≤100 ng/dl)

	TAP-144-SR (6M) (N = 81)	TAP-144-SR (3M) (N = 79)
Rate of suppression of serum testosterone (%) (95% CI)	100.0 (95.5, 100.0)	98.7 (93.1, 100.0)
TAP-144-SR (6M) – TAP-144- SR (3M) (95% CI)	1.3 (–3.4, 6.8)	

testosterone concentration in the 6M group and the 3M group, respectively, was 8.0 and 7.0 ng/dl before treatment, 7.0 and 6.0 ng/dl after 24 weeks of treatment and 9.0 and 6.0 ng/dl after 48 weeks of treatment (Fig. 2A).

There were no noteworthy changes in the LH and FSH levels throughout the study, compared with those before treatment with

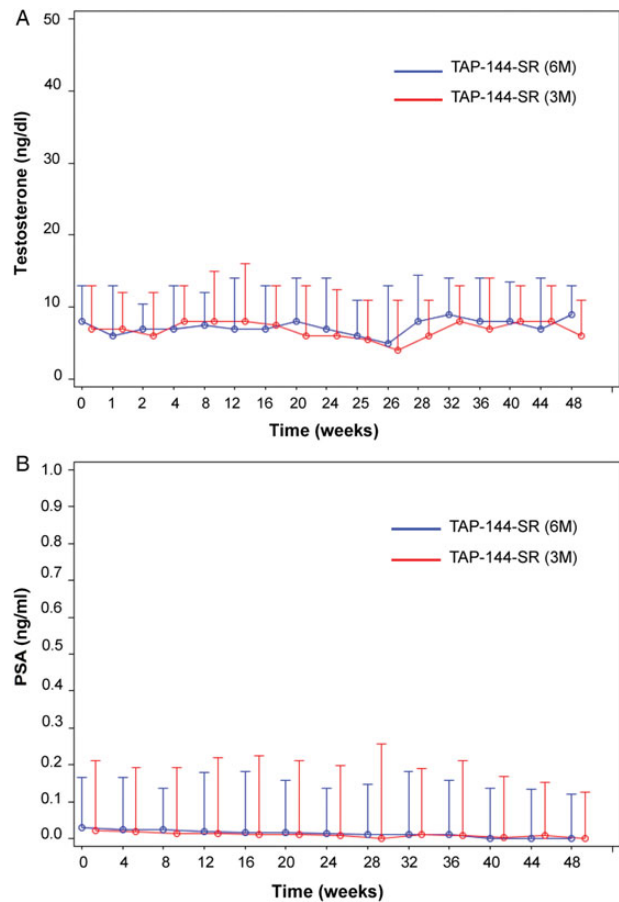


Figure 2. The median serum testosterone (A) and PSA (B) levels during the treatment period (48 weeks). Data are presented as the median and the 75th percentile.

the study drugs. No significant differences were found in the LH and FSH levels between the two treatment groups.

Efficacy analysis

PSA concentrations

The changes in the serum PSA before treatment with the study drug throughout the study in both treatment groups were similar. The PSA concentrations were stable throughout the study in both treatment groups. The median serum PSA concentration in the 6M group and the 3M group, respectively, was 0.0300 and 0.0220 ng/ml before treatment, 0.0130 and 0.0095 ng/ml after 24 weeks of treatment and 0.0000 and 0.0000 ng/ml after 48 weeks of treatment (Fig. 2B).

There were six subjects (7.5%) in the 6M group and five subjects (6.5%) in the 3M group who had disease progression.

Anti-tumor effects

The best overall response based on the RECIST showed that most subjects were evaluated as Not Evaluable, (68/79 [86.1%] in the 6M group, and 65/76 [85.5%] in the 3M group). The rate of subjects with Progressive Disease in the 6M group was 0.0% (0/79 subjects) and that in the 3M group was 2.6% (2/76 subjects). In the 6M group and the 3M group, 13.9% of subjects (11/79 subjects) and 11.8% of subjects (9/76 subjects), respectively, had Stable Disease.

No subjects were evaluated as Complete Response or Partial Response.

One subject in each treatment group had the newly observed bone lesions at two or more sites (6M group, 1.3% of subjects [1/78 subjects] and 3M group, 1.3% of subjects [1/75 subjects]) after 48 weeks of treatment with the study drugs.

Pharmacokinetics analysis

The profile of serum TAP-144 concentration after the initial administration of TAP-144-SR (6M) was similar to that after the second administration. The profile of serum TAP-144 concentration after the repeated administration of TAP-144-SR (3M) was also similar to that after the initial administration. No obvious accumulation was observed either with TAP-144-SR (6M) or TAP-144-SR (3M).

Safety analysis

AEs occurred in 75 subjects (92.6%) in the 6M group and 71 subjects (89.9%) in the 3M group. Although the most common AE was nasopharyngitis, most AEs were unrelated to the study drug (Table 3). Injection site reactions including induration, erythema and pain frequently occurred in both treatment groups. Most AEs were of Grade 1 or 2 in severity. AEs of \geq Grade 3 were reported in 11/81 subjects (13.6%) in the 6M group and 13/79 subjects (16.5%) in the 3M group. The serious AEs (SAEs) were reported in 10 subjects (12.3%) in the 6M group and 8 subjects (10.1%) in the 3M group. SAEs related to the study drug included one pulmonary infarction and one cerebral infarction in the 6M group and one peripheral arterial occlusive disease in the 3M group. There was one death of SAEs, which was unrelated to the study drug, in the 6M group. This death was due to metastatic gastric cancer with multiple liver metastases and it had been considered that the subject had gastric cancer when the subject participated in the study. AEs leading to discontinuation were

reported in two subjects (2.5%) in the 6M group and three subjects (3.8%) in the 3M group.

Vital signs, clinical laboratory tests and electrocardiogram

The change in the diastolic/systolic blood pressure (mean \pm SD) after 48 weeks of treatment with the study drug was $-2.1 \pm 10.4/-0.4 \pm 16.6$ mmHg in the 6M group and $-1.6 \pm 8.9/-3.9 \pm 14.9$ mmHg in the 3M group. The blood pressure levels in both groups were stable throughout the treatment period.

The changes in the glucose levels (mean \pm SD) after 48 weeks of treatment with the study drug in the 6M group and the 3M group were -3.1 ± 23.0 and 2.5 ± 22.5 mg/dl, respectively. The differences in the changes of all other clinical laboratory tests between treatment groups were also unremarkable.

The changes in the Fridericia's correction of QT (QTcF) interval from prior to the administration of the study drug through 48 weeks of the treatment period remained almost the same in both treatment groups. The QTcF interval (mean \pm SD) before treatment with TAP-144-SR (6M) was 429.0 ± 15.8 msec and the change in the QTcF interval after 48 weeks of treatment was -0.9 ± 12.2 msec. The QTcF interval (mean \pm SD) before treatment with TAP-144-SR (3M) was 436.2 ± 15.6 msec and the change in the QTcF interval after 48 weeks of treatment was -4.6 ± 11.6 msec.

Discussion

The primary endpoint of this study was to verify the non-inferiority of TAP-144-SR (6M) compared with TAP-144-SR (3M) for the suppressive effect on serum testosterone. Since the lower CI of the between-group difference in the suppression rate was more than -10% of the pre-determined allowable limit value, the non-inferiority of TAP-144-SR (6M) to TAP-144-SR (3M) was confirmed for the suppressive effect on the serum testosterone level. The results of disease progression, as assessed by the PSA concentrations and anti-tumor effects in both treatment groups, were similar. Therefore, there were no noteworthy differences between TAP-144-SR (6M) and TAP-144-SR (3M) in the overall efficacy.

There is general consensus that it is critical to suppress testosterone level to the castrate level for the treatment of prostate cancer (6). In this study in which the suppression of testosterone was investigated in patients receiving hormone therapy, it is shown that the testosterone levels were suppressed to the castrate level of ≤ 100 ng/dl throughout the 48 weeks in both treatment groups, excluding one subject in the 3M group whose testosterone level was not suppressed at the time of study initiation (inclusion criterion deviation). When testosterone suppression was assessed at the lower level of ≤ 50 ng/dl in reference to the recent castration level (8,13–15), 1 subject in the 6M group had a testosterone level exceeding 50 ng/dl in addition to the above-mentioned subject in the 3M group. This subject in the 6M group had a transient increase in testosterone (53 ng/dl) after 8 weeks of treatment with the study drug. In the previous Phase II study in hormone therapy naive patients, it has been shown that no subjects had a testosterone level exceeding 50 ng/dl after 4 weeks in the 22.5 mg subcutaneous injection group (9). Taking into account the present and previous results, the 22.5 mg of TAP-144-SR (6M) reliably suppresses serum testosterone in prostate cancer patients.

The PSA concentrations were stable throughout the study and there were no differences in disease progression assessed by the PSA values between the two groups. The results of best overall response assessed by RECIST indicated Stable Disease in all evaluable subjects,

Table 3. Incidence of adverse events (AEs) ($\geq 5\%$ in any groups)

Preferred Term	TAP-144-SR (6M) (N = 81)		TAP-144-SR (3M) (N = 79)	
Subjects with any AEs	75	(92.6)	71	(89.9)
Nasopharyngitis	18	(22.2)	25	(31.6)
Injection site induration	14	(17.3)	11	(13.9)
Injection site erythema	12	(14.8)	6	(7.6)
Blood creatine phosphokinase increased	5	(6.2)	7	(8.9)
Injection site pain	6	(7.4)	5	(6.3)
Arthralgia	5	(6.2)	5	(6.3)
Back pain	2	(2.5)	8	(10.1)
Hot flush	5	(6.2)	5	(6.3)
Fall	6	(7.4)	3	(3.8)
Constipation	3	(3.7)	5	(6.3)
DM	5	(6.2)	3	(3.8)
Hypertension	5	(6.2)	3	(3.8)
Insomnia	3	(3.7)	5	(6.3)
Contusion	6	(7.4)	1	(1.3)
Dental caries	6	(7.4)	1	(1.3)
Musculoskeletal stiffness	2	(2.5)	4	(5.1)
Weight increased	1	(1.2)	5	(6.3)
Inguinal hernia	1	(1.2)	4	(5.1)

Values represent *n* (%).

excluding two subjects in the 3M group who had Progressive Disease. Therefore, the effects of TAP-144-SR (6M) were comparable to those of TAP-144-SR (3M).

The incidence rate of AEs was 92.6% in the 6M group and 89.9% in the 3M group (Table 3). The AEs reported in the 6M group were similar to those observed in the 3M group, and injection site reactions were frequent in both treatment groups. Injection site reactions have been reported in studies of degarelix, LH-RH antagonists, as well as leuprolide acetate (8,13,20). In this study, a series of injection site reactions were reported in 30.9% of subjects in the 6M group and 22.8% of subjects in the 3M group, and the injection volume of both was 1 ml per injection. The injection site reaction in the 6M group was slightly greater than in the 3M group; however, none of the injection site reactions in the 6M group were severe. One event of injection site erythema was Grade 2 but the other events were all Grade 1 in the 6M group. One event of injection site ulcer in one subject was reported as Grade 3, one event of injection site induration and injection site erythema, respectively, in two different subjects were reported as Grade 2 and the others events were all Grade 1 in the 3M group. There were no injection site reactions that resulted in discontinuation of the study in the 6M group, but two subjects discontinued the study due to injection site reactions in the 3M group. In a study using degarelix, injection site reactions were reported in 46.3% (13), of which the initial injection volume was 3 ml per injection and the volume of the following maintenance injections was 4 ml per injection. Considering that both studies were conducted using subcutaneous injections, the frequency of injection site reactions might have been associated with the injection volume, because the study of degarelix, in which a higher volume than that of TAP-144-SR (6M) or TAP-144-SR (3M) in this study was used, showed a higher frequency of injection site reactions.

In the previous Phase II study, Grade 3 hypertension was reported in three out of six patients in the 22.5 mg intramuscular injection group (9). In this study with subcutaneous injections, hypertension was reported in five subjects (6.2%; Grade 3 in one subject and Grade 2 in four subjects) in the 6M group and in three subjects (3.8%; Grade 2 in all the subjects) in the 3M group, but no subjects discontinued the study due to hypertension. The results also showed that the changes in the mean systolic and diastolic blood pressure in the 6M group throughout the treatment period were slightly decreased, but no remarkable changes were observed. Since the same trend was observed in the 3M group, these results suggest that the effects of TAP-144-SR (6M) on the blood pressure are similar to those found with TAP-144-SR (3M).

It has been reported that androgen deprivation therapy increases insulin resistance and the risk of diabetes mellitus (DM) (8). DM was observed in six subjects (7.4%, Grade 2 in all subjects; five subjects coded DM and one subject coded Type 2 DM) in the 6M group and three subjects (3.8%, Grade 2 in all subjects) in the 3M group, but none of these subjects discontinued the study due to DM. The glucose levels in the 6M group and the 3M group hardly changed throughout the study. These results indicate that there are no significant differences between TAP-144-SR (6M) and TAP-144-SR (3M) concerning the risk of aggravation or the onset of DM and an increase in insulin resistance.

It has been shown that the QTcF interval was prolonged for longer than 10 msec after 24 weeks of treatment with TAP-144-SR (6M) in treatment-naïve prostate cancer patients in the previous Phase II study (9). Similar prolongation with leuprolide acetate was reported in another study, and the results showed that the change in the QTcF interval from baseline was 14.0 msec after 12 months in the leuprolide 7.5 mg group (14,21). However, in this study, the QTcF interval did

not fluctuate much throughout the 48 weeks of the treatment period in subjects receiving hormone therapy in both treatment groups. Therefore, reduced testosterone, rather than a direct pharmacological effect of leuprolide acetate, could have caused the prolongation of the QTcF interval because prolongation of the QTcF interval was not observed in subjects in whom the serum testosterone had already been suppressed to the castrate level. This hypothesis is supported by the fact that the QTcF prolongation with degarelix was also reported in hormonal therapy-naïve prostate cancer patients, and the change was 13.0 msec after 12 months (14,21), and some reports that indicate that the changes in the testosterone level would be related with prolongation of the QTcF interval (21–23).

TAP-144-SR (6M) can reduce the frequency of injections, and could thus reduce the burden on patients and medical staff. However, the intervals between visits might be much longer, and medical practitioners and staff need to keep reminding patients of the next appointment to visit the hospital.

The pharmacokinetic profile of TAP-144-SR (6M) in the Phase II study exhibited a double peak (9), which was different from that of TAP-144-SR (3M), indicating that TAP-144-SR (6M) was sustainably released for 24 weeks. In this study, there were no significant differences in efficacy and safety between TAP-144-SR (6M) and TAP-144-SR (3M) in prostate cancer patients, and no safety concerns were observed. TAP-144-SR (6M) was therefore confirmed to have excellent usability for the treatment of prostate cancer.

Conclusion

In conclusion, our results indicate that TAP-144-SR (6M) is not inferior to TAP-144-SR (3M) for the suppressive effect on serum testosterone level. The efficacy of TAP-144-SR (6M) was comparable to that of TAP-144-SR (3M), and TAP-144-SR (6M) was as well tolerated as TAP-144-SR (3M). Since TAP-144-SR (6M) can reduce the frequency of injections and the burden on patients and medical staff, and provide an option as a new administration method in the clinical setting, it is expected to become widely applied to patients depending on the patients' medical condition and life cycle.

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Conflict of interest statement

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