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ORIGINAL RESEARCH

# Assessment of Two Formulations of Triptorelin in Chinese Patients with Endometriosis: A Phase 3, Randomized Controlled Trial

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## ABSTRACT

***Introduction***: This phase 3, randomized, open-label, active-controlled, multicenter study investigated the efficacy of triptorelin pamoate prolonged-release (PR) 3-month in Chinese patients with endometriosis by demonstrating the noninferiority of the 3-month formulation to the standard of care, triptorelin acetate PR 1-month.

***Methods***: The trial was conducted in 24 clinical centers in China, and included 300 Chinese women (18–45 years) with endometriosis and regular menstrual cycles who required treatment with a gonadotropin-releasing hormone agonist for 6 months. One group of patients

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($n$ = 150) was treated with triptorelin pamoate PR 3-month (15 mg per injection, once every 12 weeks), and the other ($n$ = 150) with triptorelin acetate PR 1-month (3.75 mg per injection, once every 4 weeks). The primary outcome measure was the proportion of patients with estradiol (E2) concentrations suppressed to castration levels ($\leq$ 184 pmol/L, or 50 pg/mL) after 12 weeks of treatment.

***Results***: Triptorelin pamoate PR 3-month was noninferior to triptorelin acetate PR 1-month for the treatment of endometriosis: over 98% of patients in both groups were chemically castrated at week 12. Both formulations were also equally efficacious in reducing endometriosis-associated pelvic pain, and reducing serum concentrations of E2, luteinizing hormone, and follicle-stimulating hormone over time. No new safety concerns were identified.

***Conclusion***: Triptorelin pamoate PR 3-month is a valid alternative to triptorelin acetate PR 1-month for the treatment of Chinese women with endometriosis, with fewer injections and a potentially lower burden of care.

***Trial Registration***: NCT03232281.

**Keywords:** Chinese women; Endometriosis; Triptorelin pamoate

**Key Summary Points**

**Why carry out this study?**

The current standard of care for the treatment of endometriosis in China is the triptorelin acetate prolonged-release (PR) 1-month formulation.

The triptorelin pamoate PR 3-month formulation was designed to deliver equivalent exposure to the 1-month formulation but with a reduced frequency of injections.

This phase 3, randomized, open-label, active-control, multicenter study investigated the efficacy of triptorelin pamoate PR 3-month in Chinese patients with endometriosis by demonstrating noninferiority of the 3-month formulation to triptorelin acetate PR 1-month.

**What was learned from the study?**

Triptorelin pamoate PR 3-month was noninferior to triptorelin acetate PR 1-month for the treatment of endometriosis: over 98% of patients in both groups were chemically castrated at week 12.

This study demonstrates that triptorelin pamoate PR 3-month is a valid alternative to triptorelin acetate PR 1-month for the treatment of Chinese women with endometriosis.

## INTRODUCTION

Endometriosis is characterized by the presence of endometrial tissue fragments outside the uterine cavity [1]. Clinical manifestations vary from absence of symptoms to severe symptoms, consisting mainly of dysmenorrhea, cyclical abdominal pain, pelvic pain, and dyspareunia [1]. Worldwide, the prevalence of endometriosis

in fertile women is approximately 10% [2], and 30–50% of women with endometriosis are affected by infertility [3]. Endometriosis can also have an impact on pregnancy outcomes. Women with endometriosis who conceive naturally are reported to have an increased risk of preterm delivery and neonatal admission to the intensive care unit [4]. Evidence also suggests that endometriosis-related complications can lead to adverse pregnancy outcomes, including miscarriage and cesarean delivery [5]. While medical and surgical treatments for endometriosis demonstrate benefits in pain control and improvement in quality of life (QoL), it is well recognized that endometriosis impairs QoL in many women, including their social relationships, daily activity, productivity at work, and family planning [6]. In a large proportion of Asian women, endometriosis is associated with compromised QoL and substantial associated economic burden [7].

The aim of endometriosis treatment is to reduce the severity of symptoms and improve QoL [8, 9]. Two treatment options are currently recommended: surgery to remove the ectopic endometrial tissue, and hormonal treatment to reduce estradiol (E2) levels, resulting in suppression of endometrial tissue growth and symptom relief [10]. Additional treatment for pain relief may also be provided. Decisions about the best therapeutic approach should be based on the patient's medical history, disease stage, symptom severity, and personal choice. Medical treatment can control symptoms and stop the development of pathology. However, medical therapy does not offer a definitive treatment for symptomatic patients, side effects can arise from long-term treatment, and there is a risk of recurrence once treatment is suspended. Surgical treatment can achieve the complete removal of all lesions through a one-step surgical procedure, but should only be proposed when deemed necessary (failed hormone therapy, contraindications to hormone treatment, severity of symptoms, infertility) [11, 12].

Gonadotropin-releasing hormone (GnRH) agonists, such as triptorelin, are the principal hormonal E2 suppressants used for symptomatic relief of endometriosis [13, 14]. GnRH controls the synthesis and secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) by the pituitary gland [15, 16], thereby controlling hormonal and reproductive function of the gonads. GnRH agonists have proven to be effective and well-tolerated treatments that temporarily down-regulate the GnRH receptor, reducing secretion of LH and FSH, and subsequently E2 [13, 17–19]. The clinical effect in the treatment of endometriosis is associated with a reduction in E2 concentrations to postmenopausal levels, leading to suppression of menses, reduction of endometriotic deposits, and subsequent improvement of clinical symptoms [13].

The current standard of care for the treatment of endometriosis in China is the triptorelin acetate prolonged-release (PR) 1-month formulation (3.75 mg) [20]. The triptorelin pamoate PR 3-month formulation (15 mg) was designed to deliver equivalent exposure to the 1-month formulation but with a reduced frequency of injections [19]. The 1-month formulation was first marketed in France in 1996 and has since been approved (for indications in women and men) in more than 40 countries [21, 22]. In China, triptorelin pamoate PR 3-month has been approved for locally advanced or metastatic prostate cancer [23] since December 2008.

To support the potential use of the 3-month formulation of triptorelin for the treatment of Chinese patients with endometriosis, this phase 3 study was conducted. The primary study objective was to demonstrate noninferiority of the 3-month formulation compared with the 1-month formulation.

## METHODS

### Objectives

The primary objective was to assess the efficacy of triptorelin pamoate PR 3-month in Chinese women with endometriosis by demonstrating the noninferiority of this formulation (15 mg) injected once compared with triptorelin acetate PR 1-month (3.75 mg) injected three times consecutively. The primary outcome measure

was the proportion of patients who were chemically castrated (defined as E2 concentrations $\leq$ 184 pmol/L or 50 pg/mL) at week 12.

Efficacy was also assessed using the following secondary endpoints: percentage of patients chemically castrated at week 4 and week 8, and at weeks 4, 8, and 12 using an alternative definition of chemical castration (E2 $\leq$ 110 pmol/L or 30 pg/mL); change from baseline in endometriosis-associated pelvic pain (by 10 cm visual analog scale [VAS]) at weeks 4, 8, and 12; E2, LH, and FSH concentrations at weeks 4, 8, and 12; and time to menses recovery.

Exploratory endpoints included the percentage of patients chemically castrated according to the abovementioned definitions at week 24; change from baseline in endometriosis-associated pelvic pain at weeks 16, 20, and 24, and at end of study (EOS); and LH and FSH concentrations at week 24.

Pharmacokinetic (PK) parameters were also assessed for the triptorelin pamoate PR 3-month and triptorelin acetate PR 1-month formulations.

## Study Design

This was a phase 3, randomized, open-label, parallel group, active-controlled study conducted at 24 centers in China (NCT03232281; study funded by Ipsen). Patients were randomized 1:1 (allocation through an interactive web response system) to receive a total of two intramuscular injections with triptorelin pamoate PR 3-month (15 mg, once every 12 weeks) or a total of six intramuscular injections with triptorelin acetate PR 1-month (3.75 mg, once every 4 weeks) (Fig. 1).

The study comprised a screening period of up to 5 weeks, a 24-week treatment period, and a follow-up period up to week 40 or until the recovery of menses, whichever occurred first. The visit and dosing schedules are shown in Fig. S1. The first dose was given at baseline (day 1), which occurred in the patient's follicular phase (first to fifth day of menses). After week 12, add-back treatment (recommended as, but not limited to, tibolone 2.5 mg once daily) was administered if required, based on the investigator's judgement. After week 24, patients were followed-up once every 4 weeks via telephone until menses recovery or week 40, whichever occurred first. After this time point, all patients were requested to attend the study site for an EOS visit.

Sparse PK samples were collected in all patients; a full PK analysis was performed for 14 patients per group, with additional blood samples collected at weeks 1, 2, 3, and 32 for analysis of E2, LH, and FSH (further details on PK analyses are provided in the Supplementary Materials).

The study was conducted according to the Declaration of Helsinki of the World Medical Association and in compliance with applicable local regulations. The protocol, amendments, and informed consent forms were approved by the independent ethics committee and institutional review boards (details of ethics committees for each study site are provided in Table S1). The ethics committee at the leading site was the Clinical Trial Ethics Committee at Peking Union Medical College Hospital, Chinese Academy of Medical Sciences. All patients provided written informed consent before study entry.

## Patients

Eligible patients included women aged 18–-45 years with a diagnosis of endometriosis, confirmed by laparoscopy or laparotomy within 5 years, and a history of regular menstrual cycles (21–35 days), and who were considered by the investigator to require treatment with a GnRH agonist for a period of 6 months. Patients enrolled in this study were not categorized by their stage and score of endometriosis or recurrence rate of symptoms before starting treatment. Instead, all patients with a diagnosis of endometriosis were included, with all randomized patients having received surgery for endometriosis prior to study entry, and both treatment formulations were well balanced with respect to gynecological history.

Patients were not allowed to enter the study if they were menopausal, pregnant, or lactating, or if they had received treatment with a GnRH

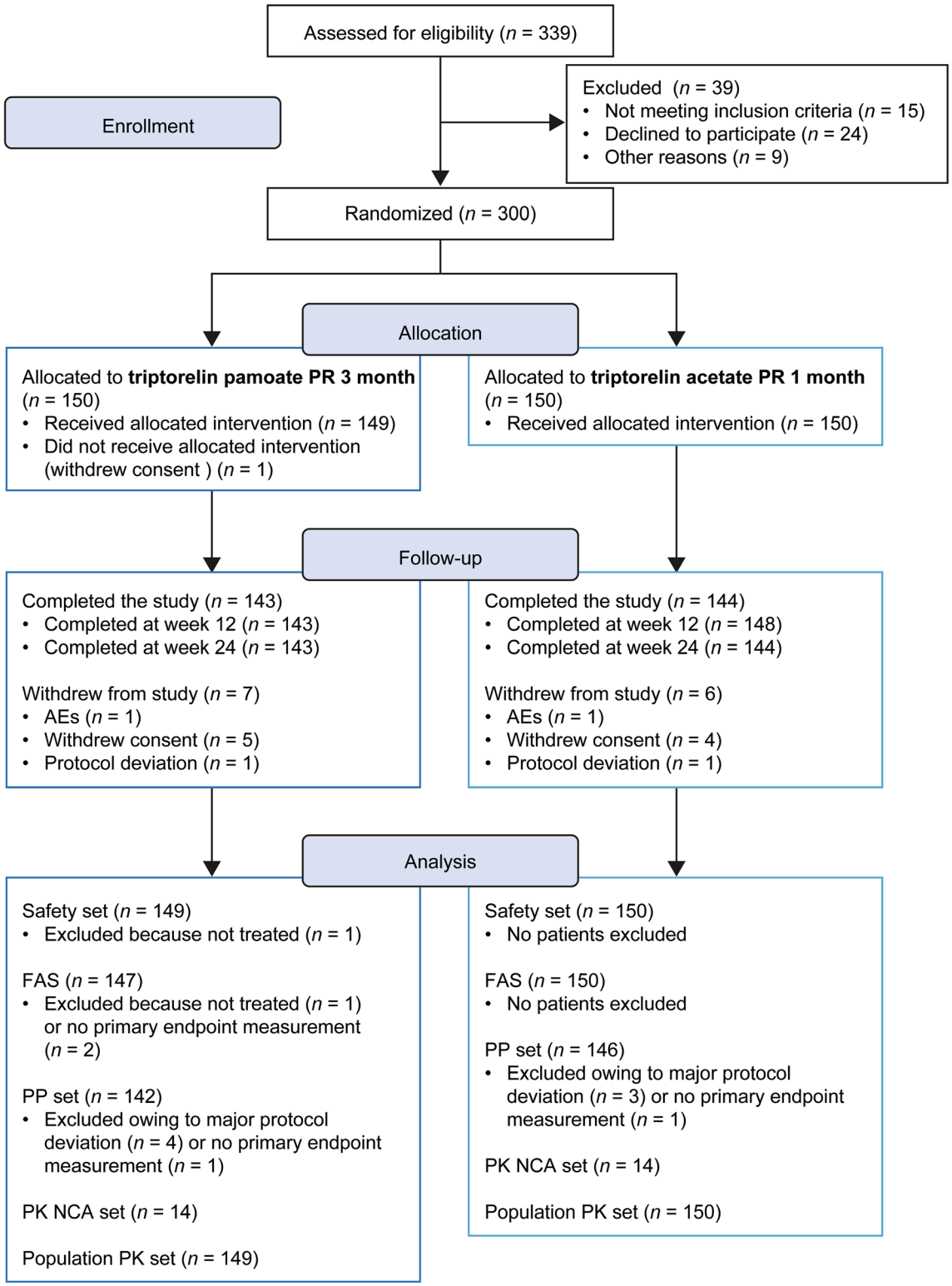


**Fig. 1** Patient disposition. *AE* adverse event, *FAS* full analysis set, *NCA* noncompartmental analysis, *PK* pharmacokinetic, *PP* per protocol, *PR* prolonged-release

agonist within the previous 6 months, other hormonal treatment within the previous 3 months, or a traditional Chinese medicine within the previous month.

### Safety

Safety and tolerability were assessed as a secondary study objective by means of incidence and severity of adverse events (AEs), laboratory tests (biochemistry, hematology, and urinalysis), and electrocardiogram findings.

### Pharmacokinetics and Pharmacodynamics

A PK comparison of the two formulations was also included as a secondary objective. Further analysis of the PK and pharmacodynamic (PD) properties of the 3-month formulation was performed in a subset of patients as an exploratory objective with E2, LH, and FSH as PD markers.

Using PK/PD subgroup data, a population PK model was built and used to derive individual PK parameters for both formulations for all patients (further details on the population PK and PD model analysis are provided in the Supplementary Materials).

### Statistical Analyses

A sample size of 300 (150 patients per group) was planned to ensure adequate precision and confidence in outcome estimates, based on previous study data [19]. Assuming that the proportion of patients chemically castrated at week 12 with triptorelin acetate PR 1-month would be no less than 92%, a sample size of 133 patients per treatment group was estimated to provide 85% power to demonstrate the noninferiority objective, with participant attrition estimated as 10%.

Analysis of efficacy objectives was conducted on the full analysis set (FAS), including all randomized patients receiving at least one treatment dose, and with at least one baseline and post-baseline primary endpoint assessment. The primary efficacy analysis was performed on the per-protocol (PP) set, including all patients in the FAS with a primary endpoint measurement at week 12 and without major protocol deviations. Safety endpoints were analyzed on the safety set, including all patients receiving at least one treatment dose.

The full PK profile analysis set included patients in the full PK/PD subgroup receiving at least one treatment dose, with no major protocol deviations, and with sufficient PK concentration measurements to estimate the main PK parameters: maximum concentration over a dosing interval ($C_{max}$), time to $C_{max}$ ($t_{max}$), and area under the curve over a dosing interval ($AUC_{tau}$), when applicable. The sparse PK sampling analysis set included all patients receiving at least one treatment dose, with no major protocol deviations and with at least one valid plasma concentration. The PD analysis set included all patients in the full PK/PD subgroup with sufficient PD measurements. The PK/PD relationship set included all patients receiving at least one treatment dose, with at least one valid plasma triptorelin concentration and at least one PD measurement.

The null hypothesis for the primary efficacy analysis was that triptorelin pamoate PR 3-month would be noninferior to triptorelin acetate PR 1-month when the prespecified noninferiority margin was −10%. The difference between groups in percentage of patients chemically castrated at week 12 and its two-sided 95% confidence interval (CI) were calculated using the Miettinen–Nurminen method, stratified by endometriotic surgical history and severity of endometriosis-associated pelvic pain at baseline with sample-size weighting. If the lower limit of the 95% CI was above −10%, triptorelin pamoate PR 3-month noninferiority to triptorelin acetate PR 1-month was confirmed. A sensitivity analysis was performed on the same analyses adding treatment center in the above Miettinen–Nurminen method. Supported analyses were performed using the Miettinen–Nurminen method without stratification factors.

Changes in endometriosis-associated pelvic pain and serum E2, LH, and FSH concentrations were presented using summary statistics; 95% CIs for the difference in mean values and

change from baseline were calculated using a linear model for repeated measurements, adjusting for treatment group and its interaction, with visit and randomization as stratification factors. Median time to menses recovery, 25th and 75th quartile times, and 95% CIs were estimated using the Kaplan–Meier method.

Patient demographics and baseline characteristics, and safety endpoints were analyzed using descriptive statistics.

Statistical evaluations were performed using Statistical Analysis System (SAS)® software (version 9.4). The noncompartmental analysis was performed using SAS software on the PK data collected for the PK/PD subgroup to assess the individual PK parameters for both formulations. Modeling was performed on PK data from all patients using the nonlinear mixed effects model (further details of PK analyses are provided in the Supplementary Materials).

## RESULTS

### Patients

Between July 28, 2017, and November 16, 2019, 300 patients from 24 centers in China were randomly allocated to receive triptorelin pamoate PR 3-month or triptorelin acetate PR 1-month ($n$ = 150 per group). Patient disposition and the number of patients in each analysis set are reported in Fig. 1. The mean (standard deviation) age of patients was 32.5 (6.1) years. Most patients had endometriosis confirmed by laparoscopy ($n$ = 254, 84.7%), with a mean (range) time since diagnosis of 5.87 (0.1–113.4) months. All patients received endometriosis surgery prior to study entry (Table S2). The distribution of significant medical and surgical history across treatment groups is shown in Table S3.

Add-back treatment, which was permitted after the primary endpoint evaluation at week 12, was required by 50 patients (16.7%; 18 patients [12.0%] in the triptorelin pamoate PR 3-month group and 32 patients [21.3%] in the triptorelin acetate PR 1-month group). The most common add-back treatment was tibolone (12 patients [8.0%] versus 24 patients [16.0%], respectively), mainly for hot flashes or reversal of menopausal symptoms, followed by estradiol valerate (four patients [2.7%] versus seven patients [4.7%], respectively). In the triptorelin pamoate PR 3-month group, 143 patients (96.0%) received the scheduled two injections of 2 mL, with a mean total volume administered until week 24 of 3.90 mL (range 1.8–4.4 mL). In the triptorelin acetate PR 1-month group, 144 patients (96%) received the scheduled six injections, corresponding to a mean actual total volume until week 24 of 11.99 mL (range 2.0–13.6 mL).

### Primary Efficacy Endpoint

Most patients in both study groups (> 98%) were chemically castrated (E2 concentrations ≤ 184 pmol/L or 50 pg/mL) at week 12, with a similar proportion in each group and a rate difference (triptorelin pamoate PR 3-month minus triptorelin acetate PR 1-month) of −0.7% (95% CI −4.41, 2.58) (Table 1). Findings were consistent with those observed for the FAS, as well as with findings from the sensitivity and supportive analyses.

### Secondary and Exploratory Efficacy Endpoints

Based on the two definitions of chemical castration, the vast majority (> 95%) of patients in both groups were chemically castrated at weeks 4, 8, 12, and 24 (FAS; Table 1).

Both triptorelin formulations were associated with a decrease from baseline in endometriosis-associated pelvic pain (by 10 cm VAS) at weeks 4, 8, and 12. The decrease was maintained up to weeks 16, 20, and 24 (FAS; Fig. 2). Absolute values were similar between the two treatment groups, with a rate difference (95% CI) of −0.1% (−4.0%, 3.9%), −0.8% (−4.4%, 2.9%), and 0.2% (−3.2%, 3.7%) at weeks 4, 8, and 12 respectively.

Evaluation of E2 concentrations indicated a marked decrease from baseline with both formulations. The decreased levels were maintained up to week 8 and week 12 (FAS; Table 2; Fig. S2b). Mean LH concentrations remained

**Table 1** Proportion of patients chemically castrated at weeks 4, 8, 12, and 24

| | | Triptorelin pamoate PR 3-month | Triptorelin acetate PR 1-month | Rate difference (95% CI) |
|---|---|---|---|---|
| E2 ≤ 184 pmol/L or 50 pg/mL, PP set (primary analysis) | | | | |
| Week 12 | Patients, *n* (%) | 140 (98.6) | 145 (99.3) | −0.7 (−4.41, 2.58) |
| | 95% asymptotic CI, % | 96.65, 100.00 | 97.98, 100.00 | |
| E2 ≤ 184 pmol/L or 50 pg/mL, FAS (secondary and exploratory analyses) | | | | |
| Week 4 | Patients, *n* (%) | 144 (98.0) | 149 (99.3) | −1.3 (−5.26, 1.93) |
| | 95% asymptotic CI, % | 95.67, 100.00 | 98.03, 100.00 | |
| Week 8 | Patients, *n* (%) | 143 (97.3) | 150 (100.0) | −2.7 (−6.80, −0.16) |
| | 95% asymptotic CI, % | 94.65, 99.91 | 100.00, 100.00 | |
| Week 12 | Patients, *n* (%) | 143 (97.3) | 149 (99.3) | −2.0 (−6.21, 1.29) |
| | 95% asymptotic CI, % | 94.65, 99.91 | 98.03, 100.00 | |
| Week 24[a] | Patients, *n* (%) | 147 (100.0) | 147 (98.0) | 2.0 (−0.58, 5.74) |
| | 95% asymptotic CI, % | 100.00, 100.00 | 95.76, 100.00 | |
| E2 ≤ 110 pmol/L or 30 pg/mL, FAS (secondary and exploratory analyses) | | | | |
| Week 4 | Patients, *n* (%) | 144 (98.0) | 149 (99.3) | −1.3 (−5.26, 1.93) |
| | 95% asymptotic CI, % | 95.67, 100.00 | 98.03, 100.00 | |
| Week 8 | Patients, *n* (%) | 140 (95.2) | 149 (99.3) | −4.1 (−8.93, −0.52) |
| | 95% asymptotic CI, % | 91.80, 98.68 | 98.03, 100.0 | |
| Week 12 | Patients, *n* (%) | 141 (95.9) | 148 (98.7) | −2.7 (−7.44, 1.17) |
| | 95% asymptotic CI, % | 92.72, 99.12 | 96.83, 100.0 | |
| Week 24[a] | Patients, *n* (%) | 143 (97.3) | 144 (96.0) | |
| | 95% asymptotic CI, % | 94.65, 99.91 | 92.86, 99.14 | 1.3 (−3.30, 6.12) |

95% asymptotic CI is calculated from binomial distribution

Rate difference and 95% CI were calculated using the Miettinen–Nurminen method

The number of patients in the PP (primary analysis) and FAS (secondary and exploratory analyses) populations was 142 and 147 for the triptorelin pamoate PR 3-month group and 146 and 150 for the triptorelin acetate PR 1-month group, respectively

*CI* confidence interval, *E2* estradiol, *FAS* full analysis set, *PP* per protocol, *PR* prolonged-release

[a]Week 24 is an exploratory endpoint

suppressed from baseline during the 12-week treatment period for both groups (Table S4; Fig. S2c). For FSH concentrations, a decrease from baseline by week 4 was also observed with both formulations, followed by a gradual but continual increase at week 8 and week 12 in both groups relative to week 4 (Table S4; Fig. S2d). For all the endpoints described above, findings were consistent when analyzed using the PP set (assessed at weeks 4–12).

For time to recovery of menses, most patients in both groups recovered menses after the last treatment dose (78.9% in the triptorelin pamoate PR 3-month group and 91.3% in the

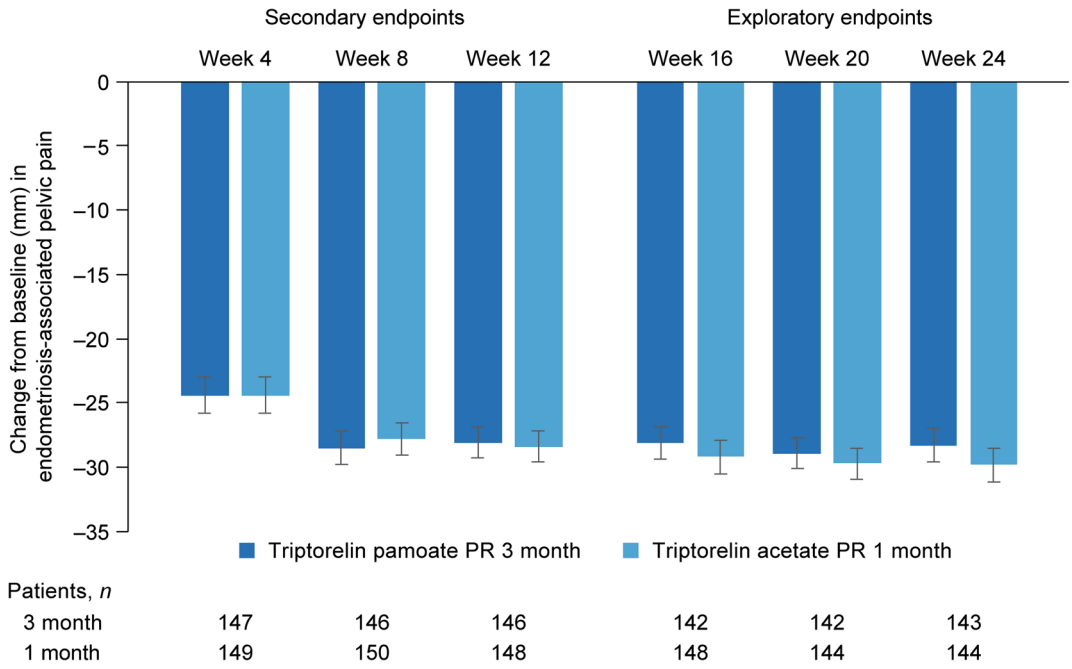


**Fig. 2** Change from baseline (in mm) in endometriosis-associated pelvic pain assessed by 10 cm VAS (FAS). LS means and CIs from a linear model for repeated measurements adjusting for treatment group and its interaction with visit, and randomized strata and its interaction with treatment group. Baseline was defined as the last available assessment prior to the first dose of IMP. Table indicates the number of patients included in the linear model. *CI* confidence interval, *FAS* full analysis set, *IMP* investigational medicinal product, *LS* least-squares, *PR* prolonged-release, *VAS* visual analog scale

triptorelin acetate PR 1-month group). In the FAS, the median [95% CI] time to menses recovery was longer for patients receiving triptorelin pamoate PR 3-month (179 [172, 182] days) than for patients receiving triptorelin acetate PR 1-month (85 [82, 87] days) (FAS; Fig. S3). Findings were consistent when analyzed using the PP set.

## Safety

Most patients experienced at least one treatment-emergent adverse event (TEAE) during the study (143 patients [96.0%] in the triptorelin pamoate PR 3-month group and 146 patients [97.3%] in the triptorelin acetate PR 1-month group). The majority of symptoms were mild to moderate in intensity (safety set; Table 2). Hot flashes were the most common TEAE, followed by vaginal hemorrhage, upper respiratory tract infection, nasopharyngitis, and night sweats (TEAEs reported in ≥ 5% of patients in either treatment group are reported in Table S5). In both groups, the most common treatment-related TEAE was hot flashes (86 patients [57.7%] in the triptorelin pamoate PR 3-month group and 89 patients [59.3%] in the triptorelin acetate PR 1-month group). Five patients reported severe TEAEs, which included abdominal pain (one patient receiving triptorelin acetate PR 1-month) and hypersensitivity, nasopharyngitis, upper respiratory tract infection, and hot flashes (each reported in one patient receiving triptorelin pamoate PR 3-month).

Three patients experienced at least one serious adverse event (SAE), including abdominal pain (one patient receiving triptorelin acetate PR 1-month), arrhythmia and sinus bradycardia (one patient receiving triptorelin pamoate PR 3-month), and acute pyelonephritis and sepsis (one patient receiving triptorelin pamoate PR 3-month).

TEAEs resulted in treatment withdrawal in two patients: one patient receiving triptorelin

**Table 2** Summary of treatment-emergent adverse events (safety set)

| | Triptorelin pamoate PR 3-month ($n$ = 149) | Triptorelin acetate PR 1-month ($n$ = 150) Patients, $n$ (%) [E] | Overall safety population ($N$ = 299) |
|---|---|---|---|
| Any TEAEs | 143 (96.0) [696] | 146 (97.3) [708] | 289 (96.7) [1404] |
| *Maximum intensity for any TEAEs* | | | |
| Severe | 4 (2.7) [4] | 1 (0.7) [2] | 5 (1.7) [6] |
| Moderate | 26 (17.4) [52] | 35 (23.3) [73] | 61 (20.4) [125] |
| Mild | 113 (75.8) [640] | 110 (73.3) [633] | 223 (74.6) [1273] |
| Serious TEAEs | 2 (1.3) [4] | 1 (0.7) [1] | 3 (1.0) [5] |
| Treatment-related TEAEs | 124 (83.2) [397] | 135 (90.0) [388] | 259 (86.6) [785] |
| Treatment-related serious TEAEs | 0 | 1 (0.7) [1] | 1 (0.3) [1] |
| TEAEs leading to withdrawal | 1 (0.7) [1] | 1 (0.7) [1] | 2 (0.7) [2] |
| TEAEs leading to treatment interruption | 0 | 0 | 0 |
| Serious TEAEs leading to treatment withdrawal | 0 | 0 | 0 |
| Serious TEAEs leading to treatment interruption | 0 | 0 | 0 |
| TEAEs leading to death | 0 | 0 | 0 |

*[E]* number of events, *MedDRA* Medical Dictionary for Regulatory Activities, *PR* prolonged-release, *TEAE* treatment-emergent adverse event

Note: if a patient experienced more than one event in a category, the patient was counted only once in that category. MedDRA version 22.1

A list of TEAEs reported in 5% or more of patients in either treatment arm is reported in Table S5

pamoate PR 3-month withdrew owing to alopecia, and one patient receiving triptorelin acetate PR 1-month withdrew owing to arthralgia. No deaths were reported during the study.

There were no major differences observed between the two formulations that were deemed clinically important for the clinical laboratory tests. No patients met the potentially clinically significant abnormality (PCSA) criteria at any visit for hematology parameters. PCSAs of high triglycerides and high cholesterol were reported as biochemical abnormalities at each assessed time point. The number of patients with abnormalities at baseline and post-baseline was numerically higher in the triptorelin acetate PR 1-month group than the triptorelin pamoate PR 3-month group; however, there were no substantial differences between treatment groups.

## Pharmacokinetic and Pharmacodynamic Analyses

The final PK data set comprised 299 patients, of whom 149 received triptorelin pamoate PR 3-month and 150 received triptorelin acetate PR

1-month. The population PK model was used to estimate individual PK parameters for all treated patients (Fig. S2, Table S6 and Table S7). The absolute bioavailability for triptorelin was estimated to be 0.439 for the 3-month formulation and 0.334 for the 1-month formulation. None of the tested covariates (age, body mass index, body surface area, body weight, or lean body weight) were found to statistically influence absorption PK parameters of either formulation. No significant drug accumulation was observed after repeat administration of either formulation.

In exploratory graphical analyses, no clinically relevant differences were observed between the triptorelin acetate PR 1-month and triptorelin pamoate PR 3-month data in terms of PD endpoints. The profiles of E2, LH, and FSH biomarkers over time were similar between formulations (Fig. S2). Additional exploratory PK/PD analyses with E2 were attempted; however, because most E2 values were below the limit of quantification (LOQ), no quantitative relationship between triptorelin plasma concentrations and castration could be confidently established.

The effect of triptorelin was reversible, since E2, LH, and FSH concentrations all returned to baseline levels over a period of several weeks following the end of the 24-week treatment period for both formulations. Further details on PK and PD findings are provided in the Supplementary Materials.

# DISCUSSION

### Main Findings

Triptorelin acetate PR 1-month is the current standard of care for patients with endometriosis in China [20], but the results of this study showed that triptorelin pamoate PR 3-month is a valid treatment alternative for Chinese patients with endometriosis. Noninferiority of triptorelin pamoate PR 3-month to triptorelin acetate PR 1-month was demonstrated based on the proportion of patients chemically castrated after 12 weeks of treatment. Consistent with the primary analysis, noninferiority of the 3-month formulation was also demonstrated at additional time points and when a more stringent definition of chemical castration was used.

Both formulations were associated with similar reductions in endometriosis-associated pelvic pain up to week 12, which were maintained up to the end of the treatment period (week 24). There was a marked decrease in E2, LH, and FSH serum concentrations from baseline in both treatment groups, with decreases maintained from week 4 until week 12. The effect of triptorelin pamoate PR 3-month was reversible, with E2, LH, and FSH gradually returning to baseline levels after the end of the treatment period; most patients recovered menses after the last treatment dose.

Safety findings were in line with the known safety profile of triptorelin in this indication [13] and no new safety signals were identified in this population of Chinese women with either formulation. The proportion of patients experiencing at least one treatment-related TEAE was similar between treatment groups, and most TEAEs were not serious and were mild or moderate in intensity.

For the first time, we report detailed PK and PD analyses of triptorelin acetate PR 1-month and triptorelin pamoate PR 3-month in Chinese women. For both formulations, maximum plasma concentrations were reached within a few hours of administration, followed by a decline to a pseudo-plateau; residual plasma levels were similar between formulations and remained detectable for the duration of the expected exposure (84 days for triptorelin pamoate PR 3-month and 28 days for triptorelin acetate PR 1-month). Median maximum plasma concentrations were reached at 4 h and 2 h with the respective formulations. There was no drug accumulation after repeat administration of either formulation. Overall, our PD analyses demonstrated pharmaco-equivalence between the two formulations in Chinese women with endometriosis. We had also hoped to measure the quantitative relationship between triptorelin plasma concentrations and E2 castration levels; however, given the efficiency of the response to triptorelin, E2 levels were below the LOQ for the majority of samples, preventing this analysis.

### Strengths and Limitations

The strengths of this study include its multicenter, randomized, and prospective design, the large sample size, and the inclusion of parallel treatment arms and of a rich PK sample subset. The open-label design is a limitation, but was selected to avoid patient exposure to unnecessary injections resulting from the different administration frequencies of the treatments. Because the primary efficacy endpoint was based on an objective laboratory measure, it was considered that any bias was sufficiently minimized to support an open-label design.

### Interpretation

Both formulations of triptorelin had a beneficial treatment effect, demonstrated by the proportion of patients chemically castrated after treatment and reduction in endometriosis-associated pelvic pain, which was similar between groups and consistent with numerous previous studies of triptorelin in the management of endometriosis [13, 24–26]. In addition, the present findings are consistent with a previous phase 2, prospective, randomized, open-label study comparing the 3-month formulation and 1-month formulation of triptorelin in 146 European women with endometriosis [19]. The two formulations were equivalent in terms of PD effects and the proportion of patients chemically castrated 84 days after treatment initiation (97% and 94%, respectively, based on E2 concentrations $\leq$ 50 pg/mL). The duration of chemical castration was significantly longer with the 3-month formulation. Improvements in clinical symptoms were also equivalent for the two formulations (based on dysmenorrhea, pelvic pain, pelvic tenderness, dyspareunia, and induration). There was no difference in the incidence of AEs between patients receiving the 3-month and 1-month formulations (69% versus 74%, respectively), and six out of 146 patients (4.1%) experienced SAEs (four patients receiving the 3-month formulation and two receiving the 1-month formulation) [19]. In the present study, a higher proportion of patients with AEs was reported; the incidence of SAEs was, however, substantially lower (three out of 299 patients). Consistent with previous studies, the most common AEs in patients treated with triptorelin were hot flashes and night sweats [14, 27]. The safety profiles of triptorelin pamoate PR 3-month and triptorelin acetate PR 1-month were also consistent with previous studies of triptorelin acetate PR 1-month, which reported that the formulation was generally well tolerated and did not result in serious AEs [24, 26].

Triptorelin pamoate PR 3-month is not currently licensed for use in patients with endometriosis in China. The findings of this study, however, confirm that the formulation is noninferior to the current standard of care, triptorelin acetate PR 1-month, in a Chinese patient population. Furthermore, the 3-month dosing schedule offers a more convenient treatment regimen, involving fewer injections, without loss of efficacy. Not only do fewer clinic visits offer the potential to reduce the disease burden associated with endometriosis for patients, the lower number of injections required with the PR 3-month formulation is expected to offer additional economic benefits. In the future, evaluation of quality of life and assessment of fertility by Anti-Müllerian Hormone levels and/or pregnancy rates in women undergoing the two different cycles of therapy would certainly be of interest.

## CONCLUSIONS

In conclusion, these data indicate that triptorelin pamoate PR 3-month represents a valid treatment option for Chinese women with endometriosis, demonstrating noninferiority to the current standard of care, triptorelin acetate PR 1-month, and an efficacy and safety profile that is consistent with data reported in patients from other geographical regions.

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***Compliance with Ethics Guidelines.*** The study was conducted according to the Declaration of Helsinki of the World Medical Association and in compliance with applicable local regulations. The protocol, amendments, and informed consent forms were approved by the independent ethics committee and institutional review boards (details of ethics committees for each study site are provided in Table S1). The ethics committee at the leading site was the Clinical Trial Ethics Committee at Peking Union Medical College Hospital, Chinese Academy of Medical Sciences. All patients provided written informed consent before study entry.

***Data Availability.*** The datasets generated during and/or analyzed during the current study may be available on reasonable request. Where patient data can be anonymized, Ipsen will share all individual participant data that underlie the results reported in this article with qualified researchers who provide a valid research question. Study documents, such as the study protocol and clinical study report, are not always available. Proposals should be submitted to DataSharing@Ipsen.com and will be assessed by a scientific review board. Data are available beginning 6 months and ending 5 years after publication; after this time, only raw data may be available.

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## REFERENCES

1. Bulun SE, Yilmaz BD, Sison C, Miyazaki K, Bernardi L, Liu S, et al. Endometriosis. Endocr Rev. 2019;40(4):1048–79.
2. Zondervan KT, Becker CM, Missmer SA. Endometriosis. N Engl J Med. 2020;382(13):1244–56.
3. Meuleman C, Vandenabeele B, Fieuws S, Spiessens C, Timmerman D, D'Hooghe T. High prevalence of endometriosis in infertile women with normal ovulation and normospermic partners. Fertil Steril. 2009;92(1):68–74.
4. Berlanda N, Alio W, Angioni S, Bergamini V, Bonin C, Boracchi P, et al. Impact of endometriosis on obstetric outcome after natural conception: a multicenter Italian study. Arch Gynecol Obstet. 2022;305(1):149–57.
5. Sorrentino F, M DEP, Falagario M, D'Alteri OM, A DISS, Pacheco LA, et al. Endometriosis and adverse pregnancy outcome. Minerva Obstet Gynecol. 2022;74(1):31–44.
6. D'Alterio MN, Saponara S, Agus M, Lagana AS, Noventa M, Loi ES, et al. Medical and surgical interventions to improve the quality of life for endometriosis patients: a systematic review. Gynecol Surg. 2021;18.
7. Dai Y, Li X, Shi J, Leng J. A review of the risk factors, genetics and treatment of endometriosis in Chinese women: a comparative update. Reprod Health. 2018;15(1):82.
8. Bedaiwy MA, Allaire C, Yong P, Alfaraj S. Medical management of endometriosis in patients with chronic pelvic pain. Semin Reprod Med. 2017;35(1):38–53.
9. Vercellini P, Viganò P, Somigliana E, Fedele L. Endometriosis: pathogenesis and treatment. Nat Rev Endocrinol. 2014;10(5):261–75.
10. Barbieri RL. Hormone treatment of endometriosis: the estrogen threshold hypothesis. Am J Obstet Gynecol. 1992;166(2):740–5.
11. D'Alterio MN, Saponara S, D'Ancona G, Russo M, Lagana AS, Sorrentino F, et al. Role of surgical treatment in endometriosis. Minerva Obstet Gynecol. 2021;73(3):317–32.

12. D'Alterio MN, D'Ancona G, Raslan M, Tinelli R, Daniilidis A, Angioni S. Management Challenges of Deep Infiltrating Endometriosis. Int J Fertil Steril. 2021;15(2):88–94.

13. Leone Roberti Maggiore U, Scala C, Remorgida V, Venturini PL, Del Deo F, Torella M, et al. Triptorelin for the treatment of endometriosis. Expert Opin Pharmacother. 2014;15(8):1153–79.

14. Bergqvist A, Bergh T, Hogström L, Mattsson S, Nordenskjöld F, Rasmussen C. Effects of triptorelin versus placebo on the symptoms of endometriosis. Fertil Steril. 1998;69(4):702–8.

15. Conn PM. The molecular basis of gonadotropin-releasing hormone action. Endocr Rev. 1986;7(1): 3–10.

16. Kiesel L. Molecular mechanisms of gonadotrophin releasing hormone-stimulated gonadotrophin secretion. Hum Reprod. 1993;8(Suppl 2):23–8.

17. Olive DL. Gonadotropin-releasing hormone agonists for endometriosis. N Engl J Med. 2008;359(11):1136–42.

18. Hornstein MD, Yuzpe AA, Burry KA, Heinrichs LR, Buttram VL Jr, Orwoll ES. Prospective randomized double-blind trial of 3 versus 6 months of nafarelin therapy for endometriosis associated pelvic pain. Fertil Steril. 1995;63(5):955–62.

19. Donnez J, Dewart PJ, Hedon B, Perino A, Schindler AE, Blumberg J, et al. Equivalence of the 3-month and 28-day formulations of triptorelin with regard to achievement and maintenance of medical castration in women with endometriosis. Fertil Steril. 2004;81(2):297–304.

20. Cooperative Group of Endometriosis, Chinese Society of Obstetrics and Gynecology, Chinese Medical Association; Cooperative Group of Endometriosis Chinese Society of Obstetrics and Gynecology Chinese Medical Association. Guideline for the diagnosis and treatment of endometriosis. Zhonghua Fu Chan Ke Za Zhi. Chin J Obstet Gynecol 2015;50:161–9.

21. Ipsen Limited. Summary of product characteristics, Decapeptyl SR 11.25mg (triptorelin pamoate). European Medicines Agency, 2017. Available from: https://www.medicines.org.uk/emc/product/780/smpc#gref. Accessed December 2021.

22. Allergan USA, Inc. Prescribing information, TREL-STAR® (triptorelin pamoate for injectable suspension). US Food and Drug Administration, 2018. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/020715s040,021288s035,022427s015lbl.pdf. Accessed December 2021

23. Ipsen Limited. Patient informatin leaflet; Diphereline® Triptorelin Pamoate for Injection Leaflet. 2018.

24. Zhu L, Guan Z, Huang Y, Hua K, Ma L, Zhang J, et al. The efficacy and safety of triptorelin-therapy following conservative surgery for deep infiltrating endometriosis: A multicenter, prospective, non-interventional study in China. Medicine (Baltimore). 2022;101(5):e28766.

25. Sun W, Hua K, Hong L, Zhang J, Hao M, Wang J, et al. Symptom control after different duration of triptorelin treatment following conservative surgery for deep infiltrating endometriosis: Post-hoc analysis of a multicentre, prospective, real-world study. Medicine (Baltimore). 2021;100(30): e26753.

26. Xue H, Liu M, Hao W, Li Y. Clinical evaluation of laparoscopic surgery combined with triptorelin acetate in patients with endometriosis and infertility. Pak J Med Sci. 2018;34(5):1064–9.

27. Choktanasiri W, Boonkasemsanti W, Sittisomwong T, Kunathikom S, Suksompong S, Udomsubpayakul U, et al. Long-acting triptorelin for the treatment of endometriosis. Int J Gynaecol Obstet. 1996;54(3): 237–43.