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ORIGINAL RESEARCH ARTICLE

Safety, Pharmacokinetics, and Pharmacodynamics of SHR7280, a Non-peptide GnRH Antagonist in Premenopausal Women with Endometriosis: A Randomized, Double-Blind, Placebo-Controlled Phase 1 Study

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Abstract

Background Oral gonadotropin-releasing hormone (GnRH) antagonists are promising agents in the treatment of endometriosis-related pain. Here we assessed the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of SHR7280, an oral non-peptide GnRH antagonist in premenopausal women with endometriosis.

Methods In the Phase 1 part of the randomized, double-blinded, placebo-controlled, dose-ascending, Phase 1/2 trial, premenopausal women with endometriosis were randomized (4:1) to receive SHR7280 or placebo treatment for 21 consecutive days. The treatment dose started from 200 mg QD, and then increased to 300 mg QD and 200 mg BID. Safety, PK, and PD parameters were assessed.

Results In total, 30 patients received assigned treatment, 24 with SHR7280 and 6 with placebo. SHR7280 was well tolerated. Adverse events (AEs) were reported in 19 (79.2%, 19/24) patients in the SHR7280 group and 5 (83.3%, 5/6) patients in the placebo group. Most AEs were mild and no severe AEs occurred. SHR7280 showed a rapid absorption, with a time to maximum plasma concentration (T_{max}) of 1.0 h, 1.0 h, and 0.8 h for the 200 mg QD, 300 mg QD, and 200 mg BID regimens, respectively. Plasma concentration of SHR7280 was dose dependent. The mean half-life ($t_{1/2}$) at steady state was 6.9 h, 7.4 h, and 2.8 h, respectively, and little or no accumulation was observed. Pharmacodynamic analysis showed that SHR7280 could effectively suppress estradiol and luteinizing hormone concentrations and prevent progesterone increase in a dose-dependent manner. SHR7280 at doses of 300 mg QD and 200 mg BID could suppress estradiol levels within the desired therapeutic window of 20–50 pg/mL throughout the treatment period.

Conclusions SHR7280 showed favorable safety, PK, and PD profiles in the doses of 200 mg QD, 300 mg QD, and 200 mg BID. The results of this study provide evidence to support the further development of SHR7280 as a GnRH antagonist for the treatment of endometriosis-related pain in the subsequent Phase 2 trial.

Trial Registry Trial registration number: Clinicaltrials.gov, identifier: NCT04417972. Trial registration date: 5 June 2020.

1 Introduction

Endometriosis is a chronic gynecological condition characterized by the presence, growth, infiltration, and recurring bleeding of endometrial-like tissue outside the uterine cavity [1–4]. The clinical symptoms of endometriosis vary among individuals, with the most common symptoms including dysmenorrhea, non-menstrual pelvic pain,

Key Points

SHR7280 had tolerable toxicities, and most adverse events were mild in severity in premenopausal patients with endometriosis.

SHR7280 was absorbed rapidly and the plasma exposure was dose proportional from 200 mg QD to 300 mg QD.

SHR7280 effectively suppressed the concentrations of sex hormones.

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dyspareunia, dyschezia, dysuria, infertility, somatosensory amplification, and fatigue [5, 6]. Endometriosis affects approximately 10% of women of childbearing age [1, 3]. Endometriosis-related pain can significantly impair the quality of life and work productivity and can impose a substantial economic burden on patients and society [7–10].

Endometriosis can be triggered by multiple factors, such as retrograde menstruation, transformation of peritoneal cells, embryonic cell transformation, surgical scar implantation, endometrial cell transport, and immune system disorder [1, 3]. Estrogen robustly stimulates the proliferation and inflammation of endometrial tissues [11], thus, suppressing estrogen levels to reduce pelvic pain and other symptoms associated with this disease has become a potential treatment strategy for endometriosis-related pain [12].

Traditionally, non-surgical therapies for endometriosis have included nonsteroidal anti-inflammatory drugs, progestogens, oral contraceptives, levonorgestrel intrauterine system, and gonadotropin-releasing hormone (GnRH) agonists. However, the clinical utility of these agents is often limited by undesirable side effects [13–15]. Continuous use of oral contraceptives can cause breakthrough bleeding, while treatment with progestogens is often accompanied by irregular vaginal bleeding. Continuous progestogen treatment can cause irritability, breast hyperplasia, and a low pregnancy rate. GnRH agonists are commonly associated with a temporary worsening of the condition (flare-up effect), a slow onset of action, and accompanying hypoestrogenic side effects such as hot flushes and changes in bone mineral density, which limit the treatment duration to less than 6 months. Surgical removal of endometriosis lesions can effectively relieve pain; however, recurrence is common, and symptoms tend to increase over time [16–18]. Therefore, there is an unmet medical need for safe, effective, and long-term therapies in the treatment of endometriosis symptoms.

In recent years, oral non-peptide GnRH antagonists have been shown to be effective in suppressing estradiol (E_2) level in patients with endometriosis [19, 20]. Elagolix, as well as the relugolix combination therapy (a combination of relugolix, estradiol, and norethindrone acetate), had been approved by the US Food and Drug Administration (FDA) for treatment of endometriosis-associated pain [21–23]. However, in some countries or regions, including China, elagolix and the relugolix combination therapy have not yet been approved for use in women with endometriosis-associated disorders. Therefore, it is essential to develop alternative therapies for patients with endometriosis.

SHR7280 is a novel, oral, non-peptide GnRH antagonist currently under clinical development for the treatment of endometriosis, leiomyomas, assisted reproduction, and prostate cancer. SHR7280 shares certain structural similarities with relugolix, but their design principles differ, and they possess distinct core structures. The core structure of SHR7280 cannot currently be disclosed due to intellectual property considerations. A Phase 1 study demonstrated that SHR7280 exhibited a fast onset of action and efficient inhibition of sex hormones in premenopausal healthy women [24]. In this context, we conducted a Phase 1/2 study to assess the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of SHR7280 in premenopausal patients with endometriosis. Here, we present the results from the Phase 1 part of this Phase 1/2 study.

2 Methods

2.1 Study Design and Participants

This study is a randomized, double-blind, placebo-controlled, dose-ascending, Phase 1/2 trial of SHR7280 involving women with endometriosis (clinicaltrials.gov, NCT04417972). The Phase 1 part of this Phase 1/2 study was conducted in nine centers in China (Table S1).

Patients were eligible if they were premenopausal women aged between 18 and 45 years; had a body mass index (BMI) of 18–30 kg/m^2; had regular menstrual cycles with an interval of 24–32 days and bleeding of 3–7 days per month for at least 3 months before screening; were neither pregnant nor breastfeeding, nor planning a pregnancy within the next 12 months, nor less than 6 months post-partum or post-abortion; were diagnosed surgically (laparoscopy or laparotomy) or using imaging findings (transvaginal ultrasonography) with endometriosis within 10 years; and had an endometriosis-associated pain score by visual analog scale (VAS) of 60 mm or less at screening.

Patients were excluded from this study if they had an FSH level of 25 U/L or higher; had a mean value of Fridericia-corrected QT interval (QTcF) $\geq$ 450 ms during three baseline visits or screening; had chronic pelvic pain not caused by endometriosis that required chronic analgesic or other chronic therapy; and had used GnRH agonists and GnRH antagonists 6 months before screening, medroxyprogesterone acetate 3 months before screening, oral contraceptives or hormone drugs for endometriosis 2 months before screening.

The study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice Guideline. The study protocol and all amendments were approved by the independent ethics committee of each participating site. All patients provided written informed consent before enrollment.

2.2 Procedures

Eligible patients were randomized in a 4:1 ratio to receive SHR7280 tablets or placebo in each dose group orally on an empty stomach for 21 consecutive days. Each participant began receiving the assigned drug on the second to fourth day after the onset of menstruation, which was recorded as Day 1. The dose escalation started at 200 mg and gradually increased to 200 mg QD, 300 mg QD, 200 mg BID, and 300 mg BID (optional). Ten patients were enrolled in each dose group; eight received SHR7280 treatment and two received placebo. Dose escalation was performed according to the evaluation of safety data by the Safety Review Committee (SRC) after all patients in the previous lower dose group had completed treatment on Day 23 or 2 days after the last administration. Dose escalation was terminated if one of the following criteria was met: a serious adverse event (AE) related to SHR7280 occurred, a severe AE related to SHR7280 of the same organ system occurred in two or more patients in the same dose group, or $\geq 50\%$ of patients in the same dose group had a moderate or severe AE related to SHR7280.

During the treatment period, if analgesics were needed due to the physical condition of the patients, ibuprofen could be used for no more than 2 days with the permission of the investigator.

2.3 Safety Assessment

Safety was evaluated from the initiation of study drug treatment to Day 49 ± 2 or 28 ± 2 days after the last dose. AEs were classified according to the Medical Dictionary for Regulatory Activities (MedDRA, v23.0) and graded according to the National Cancer Institute's Common Terminology Criteria for AEs (NCI-CTCAE, v5.0). Grade 1 AE was defined as a mild event, grade 2 AE was defined as a moderate event, and grade 3 or higher AE was defined as a severe event.

2.4 PK and PD Analysis

Blood samples for PK assessments were collected at pre-dose, 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 16 h on Day 1, pre-dose on Day 2, Day 3, Day 5, Day 7, Day 15, Day 17, and Day 19, and pre-dose, 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 16, 24, 36, 48 h on Day 21. About 3 mL of venous blood was collected using a vacuum blood collection tube at each time point for PK analysis. The blood samples were mixed thoroughly, centrifuged within an hour, and the obtained plasma was stored in an ultra-low temperature freezer. SHR7280 concentrations in plasma were measured using liquid chromatography with tandem mass spectrometry (LC-MS-MS) SCIEX API 4000 (Applied Biosystems-SCIEX, Concord, Ontario, Canada) in positive ion mode, with 0.1% formic acid, methanol, and acetonitrile as the mobile phase by Frontage Laboratories Co., Ltd. (Shanghai, China). The lowest limit of quantitation (LLOQ) was set as 2 ng/mL.

Blood samples for PD assessments were obtained at pre-dose, 2, 4, 6, 8, 10, 12, 16 h on Day 1, pre-dose on Day 2, Day 3, Day 5, Day 7, Day 9, Day 11, Day 13, Day 15, Day 17, and Day 19, and pre-dose, 2, 4, 6, 8, 10, 12, 16, 24, 36, 48 h on Day 21. About 3.5 mL of venous blood was collected at each time point, and the serum was separated for the assessments of serum hormone. Serum hormone concentrations were measured using the Architect iSR2000 Immunoassay analyzer and Alinity analyzer (Abbott Laboratories, Abbott Park, IL, USA) by KingMed Diagnostics Group Co., Ltd (Guangzhou, China). The LLOQ values for serum E_2, progesterone, FSH, and luteinizing hormone (LH) with Architect iSR2000 Immunoassay analyzer was 13 pg/mL, 0.35 nmol/L, 0.75 mIU/mL, and 0.11 mIU/mL, respectively; and with Alinity analyzer was 10 pg/mL, 0.32 nmol/L, 0.05 mIU/mL, and 0.09 mIU/mL, respectively.

2.5 Outcomes

The primary endpoints included safety parameters, and the duration from cessation of SHR7280 treatment to the onset of the next menstruation. Secondary endpoints were PK and PD. PK parameters included area under the plasma concentration-time profile (AUC), time to maximum plasma concentration (T_{max}), and maximum plasma concentration (C_{max}), half-life ($t_{1/2}$), apparent volume of distribution (V_z/F), and apparent total clearance (CL/F) on Day 1, and $t_{1/2,ss}$, mean residence time (MRT_{ss}), AUC_{ss}, $V_{z,ss}/F$, apparent total clearance (CL_{ss}/F), $C_{max,ss}$, $T_{max,ss}$, trough plasma concentration (C_{trough}), and accumulation ratio (R_{acc}) on Day 21. The PD parameters included changes in E_2, LH, FSH, and progesterone concentrations.

2.6 Statistical Analysis

The sample size of this Phase 1 part of this Phase 1/2 study was determined according to the policy of the China National Medical Products Administration on the clinical pharmacokinetics of chemical drugs and the recommendation of a previous study [25], and the statistical assumptions of the sample size were not involved.

Patients who received at least one dose of SHR7280 or placebo were included in the safety assessment. Patients who received at least one dose of SHR7280 and had at least one

qualified blood sample for the evaluation of plasma drug concentration and PK parameters were involved in the evaluation of plasma concentration and PK parameters. Patients who received at least one dose of SHR7280 or placebo and had at least one qualified sample for the evaluation of PD were included in the PD analysis.

A non-compartment model was conducted to estimate the plasma PK of SHR7280. The ANOVA model was performed to analyze the association of the dose and standardized PK parameters after log transformation, estimate the geometric ratio of the least squares mean and the corresponding 90% confidence interval (CI). Area under the plasma concentration-time curve (AUC_{0-21d}) of E_2, progesterone, LH, and FSH versus dose (as well as C_{trough}) were presented in scatter plots on a log-log scale, and relationship between them were evaluated by fitting a linear regression model. The safety data and concentrations of E_2, LH, FSH, and progesterone were summarized using descriptive statistics. PK and PD parameters were analyzed using Phoenix WinNonlin, v8.1 or higher (Certara, Princeton, NJ, USA) and statistical analyses were conducted using SAS v9.2 or higher (SAS Institute, Inc., Cary, NC, USA).

3 Results

3.1 Patients

In total, 30 eligible women with endometriosis were enrolled in this study and were randomized to the SHR7280 ($n = 24$, 8 patients for each dose) or placebo group ($n = 6$; Fig. 1). One patient in the 200 mg BID dose group discontinued treatment due to AEs, while the remaining 29 patients completed the assigned treatment. Nine (30%) patients used concomitant drugs during this study and all were in the SHR7280 group. The most commonly used concomitant drugs were anti-infection drugs (3 patients, 10%) and analgesic drugs (2 patients, 6.7%). Patients in different dose groups of SHR7280 and in the placebo group had similar baseline characteristics (Table 1).

3.2 Safety

Safety was assessed in all the 30 patients. AEs were reported in 24 (80.0%) patients, including 19 (79.2%) in the SHR7280 group and 5 (83.3%) in the placebo group (Table 2). The most frequently reported AEs in the SHR7280 group included white blood cells urine positive (25.0%), decreased white blood cell count (12.5%), and dizziness (12.5%). Most AEs were mild (66.7% [16/24] with SHR7280 vs 66.7% [4/6] with placebo), with four patients had moderate AEs (12.5% [3/24] with SHR7280 vs 16.7% [1/6] with placebo), and none severe. The four moderate AEs were decreased white blood cell count, decreased neutrophil count, and bacterial vaginosis in three patients receiving SHR7280, and abdominal pain in one patient receiving a placebo. Treatment-related AEs were reported in 15 (62.5%) in the SHR7280 group and 3 (50.0%) in the placebo group, and the most common with SHR7280 were white blood cells urine positive (20.8%, 5/24) and dizziness (12.5%, 3/24; Table 2).

One patient (3.3%) in the 200 mg BID group discontinued treatment due to moderate AEs (decreased white blood cell count and decreased neutrophil count), which AEs regressed spontaneously. No serious AEs or deaths were reported. By the last follow-up visit, 91.5% of AEs in SHR7280 group and all AEs in placebo group had regressed.

The mean (± SD) duration from drug cessation to the onset of the next menstruation in the 200 mg QD, 200 mg

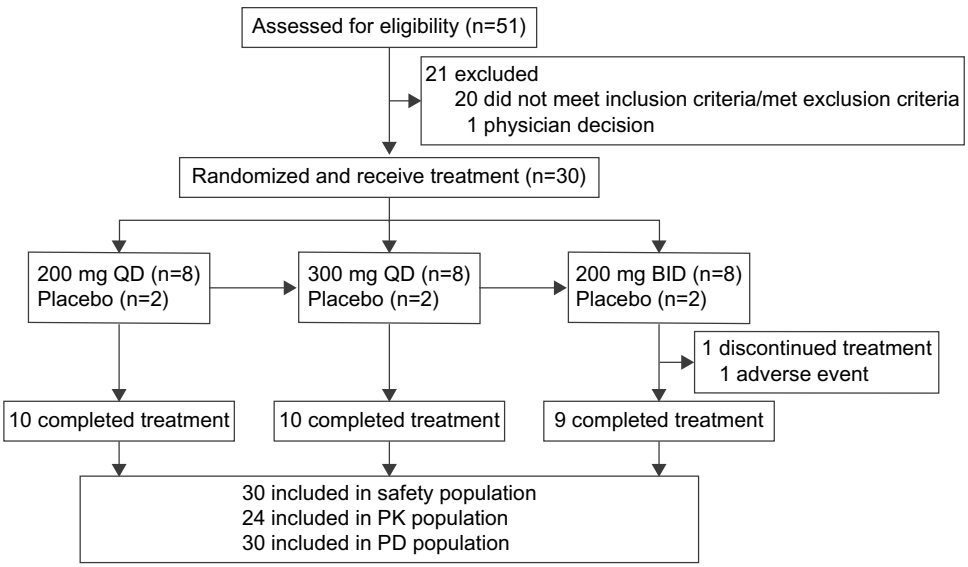

Fig. 1 Patient disposition. *BID* twice daily, *PD* pharmacodynamic, *PK* pharmacokinetic, *QD* once daily

Table 1 Baseline characteristics

	Placebo ($n = 6$)	200 mg QD ($n = 8$)	300 mg QD ($n = 8$)	200 mg BID ($n = 8$)	SHR7280 total ($n = 24$)
Age, years, median (range)	38 (29–42)	32 (24–39)	35 (31–41)	32 (26–39)	34 (24–41)
BMI, kg/m^2, mean ± SD	23.3±3.4	23.1±2.7	21.8±1.9	22.7±3.4	22.5±2.7
Endometriosis-associated pain score by VAS, mm, mean ± SD	16.0±17.4	30.0±20.5	13.8±8.9	28.5±21.3	24.1±18.6
Time since diagnosis, years, mean ± SD	1.6±1.4	2.3±2.8	2.5±3.2	2.3±1.8	2.4±2.5
History of pregnancy and delivery, *n* (%)	4 (66.7)	4 (50.0)	8 (100.0)	5 (62.5)	17 (70.8)
History of ibuprofen, *n* (%)	0	1 (12.5)	0	0	1 (4.2)

BID twice daily, *BMI* body mass index, *QD* once daily, *SD* standard deviation, *VAS* visual analogue scale

Table 2 Safety results by dose group

	Placebo ($n = 6$)	200 mg QD ($n = 8$)	300 mg QD ($n = 8$)	200 mg BID ($n = 8$)	SHR7280 total ($n = 24$)
AE	5 (83.3)	6 (75.0)	6 (75.0)	7 (87.5)	19 (79.2)
White blood cells urine positive	0	2 (25.0)	3 (37.5)	1 (12.5)	6 (25.0)
White blood cell count decreased	0	0	1 (12.5)	2 (25.0)	3 (12.5)
Dizziness	0	0	1 (12.5)	2 (25.0)	3 (12.5)
Blood thyroid stimulating hormone decreased	0	0	0	2 (25.0)	2 (8.3)
Neutrophil count decreased	1 (16.7)	0	1 (12.5)	1 (12.5)	2 (8.3)
Upper respiratory tract infection	0	1 (12.5)	1 (12.5)	0	2 (8.3)
Vaginal hemorrhage	0	0	0	2 (25.0)	2 (8.3)
Vaginal discharge	0	0	1 (12.5)	1 (12.5)	2 (8.3)
Anemia	0	1 (12.5)	1 (12.5)	0	2 (8.3)
Treatment-related AE	3 (50.0)	3 (37.5)	5 (62.5)	7 (87.5)	15 (62.5)
White blood cells urine positive	0	1 (12.5)	3 (37.5)	1 (12.5)	5 (20.8)
Dizziness	0	0	1 (12.5)	2 (25.0)	3 (12.5)
White blood cell count decreased	0	0	1 (12.5)	1 (12.5)	2 (8.3)
Neutrophil count decreased	0	0	1 (12.5)	1 (12.5)	2 (8.3)
Vaginal hemorrhage	0	0	0	2 (25.0)	2 (8.3)

Data are *n* (%). AE or treatment-related occurring in 5% or more of patients in SHR7280 group are listed. Events are shown in descending order of frequency in the SHR7280 group

AE adverse event, *BID* twice daily, *QD* once daily, *SD* standard deviation

BID, 300 mg QD, and placebo groups was 18.8 (± 7.8), 21.6 (± 5.8), 22.1 (± 4.6), and 10.5 (± 10.7) days, respectively. The mean (± SD) duration of bleeding after the onset of menstruation was 6.1 (± 1.1), 6.9 (± 1.9), 6.5 (± 0.5), and 5.7 (± 1.0) days, respectively.

3.3 PK

The 24 patients who received SHR7280 treatment were included in the PK analysis. After a single administration on Day 1, SHR7280 was rapidly absorbed at a dosage of 200 mg QD, 300 mg QD and 200 mg BID, with peak plasma concentration reached within 1.0 h, 1.0 h, and 0.8 h, respectively (Table 3). The exposure of SHR7280 increased with an increasing dose from 200 mg QD to 300 mg QD. On Day 1, the mean maximum concentration of SHR7280 of the three doses was 2020, 2440, and 1940 ng/mL, and the AUC $_{0-t}$ was 6230, 7950, and 4880 h·ng/mL, respectively (Fig. 2).

At the steady state of the concentration of SHR7280, the half-life of drug elimination ($t_{1/2}$) in the 200 mg QD, 300 mg QD, and 200 mg BID groups was 6.9, 7.4, and 2.8 h, respectively on Day 21. The shorter $t_{1/2}$ in the 200 mg BID group could be due to the terminal elimination phase point collected by QD administration being later than that of BID. Drug exposure on Day 21 after multiple dosing was consistent with that on Day 1 with a single dosing. Twice-daily

Table 3 PK parameters of SHR7280

		200 mg QD (n = 8)	300 mg QD (n = 8)	200 mg BID (n = 8)
Day 1				
T_{max}, h	Median (range)	1.0 (0.5–1.5)	1.0 (0.5–1.5)	0.8 (0.5–1.5)
C_{max}, ng/mL	Mean ± SD (%CV)	2020 ± 819 (40.6)	2440 ± 1020 (42.0)	1940 ± 814 (42.0)
	GeoMean (%GeoCV)	1880 (41.7)	2260 (42.5)	1810 (40.8)
$AUC_{0-\infty}$, h·ng/mL	Mean ± SD (%CV)	6300 ± 3430 (54.4)	8010 ± 3140 (39.3)	–
	GeoMean (%GeoCV)	5770 (42.7)	7430 (44.4)	–
AUC_{0-t}, h·ng/mL	Mean ± SD (%CV)	6230 ± 3340 (53.5)	7950 ± 3120 (39.3)	4880 ± 1340 (27.5)
	GeoMean (%GeoCV)	5720 (42.1)	7380 (44.5)	4700 (31.2)
$t_{1/2}$, h	Mean ± SD (%CV)	3.6 ± 0.6 (17.3)	3.8 ± 0.6 (16.5)	2.7 ± 0.4 (15.8)
V_z/F, L	Mean ± SD (%CV)	186 ± 49.4 (26.6)	238 ± 116 (49.0)	160 ± 44.8 (28.1)
	GeoMean (%GeoCV)	179 (33.3)	216 (47.6)	154 (27.9)
CL/F, L/h	Mean ± SD (%CV)	36.8 ± 11.3 (30.8)	43.7 ± 18.7 (42.9)	42.2 ± 14.1 (33.5)
	GeoMean (%GeoCV)	34.7 (42.6)	40.3 (44.5)	40.4 (31.7)
Day 21				
T_{max}, h	Median (range)	1.0 (0.5-1.6)	1.0 (0.5-1.5)	1.0 (0.5-1.5)
C_{max}, ng/mL	Mean ± SD (%CV)	1740 ± 760 (43.7)	2130 ± 712 (33.4)	1890 ± 796 (42.1)
	GeoMean (%GeoCV)	1450 (95.2)	2040 (32.3)	1780 (38.3)
$AUC_{ss0-12h}$, h·ng/mL	Mean ± SD (%CV)	5640 ± 3010 (53.3)	6940 ± 2750 (39.6)	5680 ± 1630 (28.7)
	GeoMean (%GeoCV)	4550 (103.7)	6420 (46.6)	5460 (31.6)
AUC_{ss0-t}, h·ng/mL	Mean ± SD (%CV)	6030 ± 3280 (54.3)	7480 ± 2950 (39.4)	5680 ± 1630 (28.7)
	GeoMean (%GeoCV)	4860 (102.1)	6910 (46.6)	5460 (31.6)
$t_{1/2}$, h	Mean ± SD (%CV)	6.9 ± 8.5 (122.5)	7.4 ± 6.7 (90.3)	2.8 ± 0.4 (15.0)
V_z/F, L	Mean ± SD (%CV)	1560 ± 3900 (249.8)	603 ± 763 (126.5)	154 ± 55.4 (35.9)
	GeoMean (%GeoCV)	294 (291.4)	377 (120.4)	146 (38.3)
CL/F, L/h	Mean ± SD (%CV)	63.8 ± 87.5 (137.3)	47.3 ± 21.9 (46.2)	38.2 ± 12.5 (32.6)
	GeoMean (%GeoCV)	41.1 (102.1)	43.4 (46.5)	36.6 (31.7)
MRT_{ss}, h	Mean ± SD (%CV)	5.2 ± 2.5 (47.8)	4.9 ± 0.4 (9.1)	4.0 ± 0.9 (21.8)
	GeoMean (%GeoCV)	4.8 (38.3)	4.9 (9.1)	4.0 (20.3)
C_{trough}, ng/mL	Mean ± SD (%CV)	10.0 ± 7.74 (77.7)	14.8 ± 6.58 (44.5)	75.8 ± 37.1 (48.9)
	GeoMean (%GeoCV)	7.77 (86.3)	13.5 (48.1)	67.9 (55.7)
R_{acc},%	Mean ± SD (%CV)	104 ± 56.7 (54.4)	109 ± 51.8 (47.7)	122 ± 26.1 (21.4)
	GeoMean (%GeoCV)	85.0 (95.1)	98.4 (52.0)	119 (22.0)

$R_{acc} = AUC_{ss0-t}/AUC_{0-t}$. PK parameters of 200 mg QD and 300 mg QD group on Day 1 were calculated based on the plasma concentration 0–24 hours after the first administration; parameters of 200 mg BID group on Day 1 were calculated based on the plasma concentration 0–12 h after the first administration. PK parameters of 200 mg QD and 300 mg QD group on Day 21 were calculated based on the plasma concentration 0–48 h after administration on Day 21, and parameters of 200 mg BID group on Day 21 were calculated based on the plasma concentration of 0–12 h after administration on Day 21. Therefore, the AUC_{0-t} in the 200 mg BID group represents AUC_{tau} (the area under the concentration-time curve of the dosing interval) and the $AUC_{ss,\ 0-t}$ in the 200 mg BID group represents $AUC_{ss,\ tau}$

AUC area under the plasma concentration-time, *BID* twice daily, *CL/F* apparent total clearance, C_{max} maximum plasma concentration, C_{trough} trough plasma concentration, *MRT* mean residence time, *PK* pharmacokinetic, *QD* once daily, R_{acc} accumulation ratio, $t_{1/2}$ half-life, V_z/F apparent volume of distribution

administration resulted in a higher trough concentration than administered by QD, and the mean C_{trough} of 200 mg QD, 300 mg QD, and 200 mg BID was 10.0, 14.8, and 75.8 ng/mL, respectively. Little-to-no accumulation was observed over the 21 days of QD or BID treatment, and the mean R_{acc} values based on AUC accumulation were 104, 109, and 122%, respectively.

From steady-state PK data on Day 21, the ANOVA model revealed that the dose-normalized C_{max}, AUC_{0-t}, and C_{trough} of SHR7280 showed no differences between groups (Table S2). Box-whisker plots also showed similar PK parameters after dose normalization, indicating proportional PK exposure to SHR7280 dosage (Fig. S1).

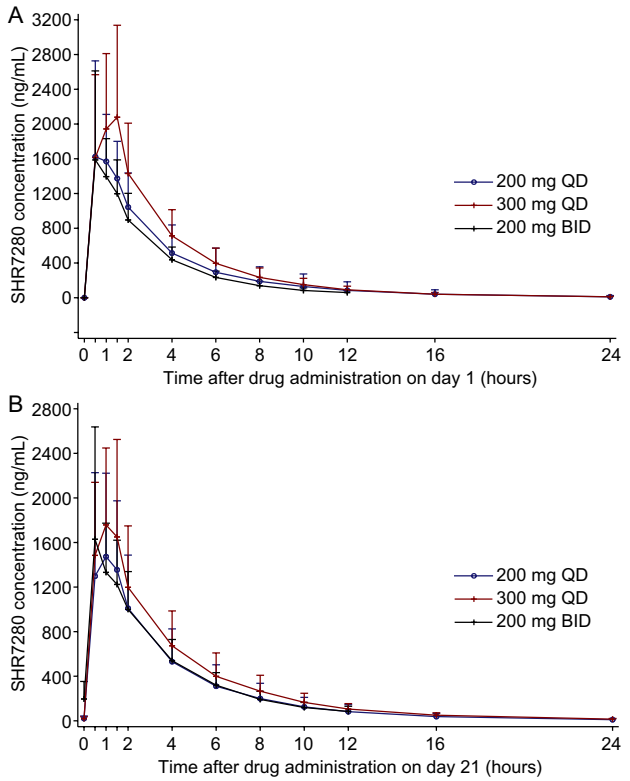

Fig. 2 Plasma concentration-time profiles of SHR7280 on Day 1 (**A**) and Day 21 (**B**). Data are mean ± SD. *BID* twice daily, *QD* once daily

3.4 PD

The 30 patients who received SHR7280 or placebo treatment were included for PD assessment.

The E_2 levels in SHR7280 groups showed a downward trend with an increase in dose, compared to placebo (Fig. 3A). Partial E_2 inhibition was observed in patients with 200 mg QD, 300 mg QD, and 200 mg BID of SHR7280. In the 300 mg QD group, E_2 concentration fluctuated around 45 pg/mL from Day 1 to Day 17 and began to rebound on Day 19. The 200 mg BID group achieved E_2 suppression within the 20–50 pg/mL range throughout treatment, rebounding 48 h after treatment discontinuation.

SHR7280 inhibited the increase of progesterone in a dose-dependent manner (Fig. 3B). In the 200 mg QD group, the progesterone level was maintained below 5 nmol/L until Day 13, then rebounded. In the 300 mg QD and 200 mg BID groups, progesterone remained below 5 nmol/L throughout treatment, achieving the concentrations of progesterone for the inhibition of ovulation.

SHR7280 delayed the peak in LH levels compared to placebo, and the LH peak in placebo, 200 mg QD, 300 mg QD, and 200 mg BID group occurred on Days 11, 17, 22, and 15, respectively (Fig. 3C). The suppression of FSH

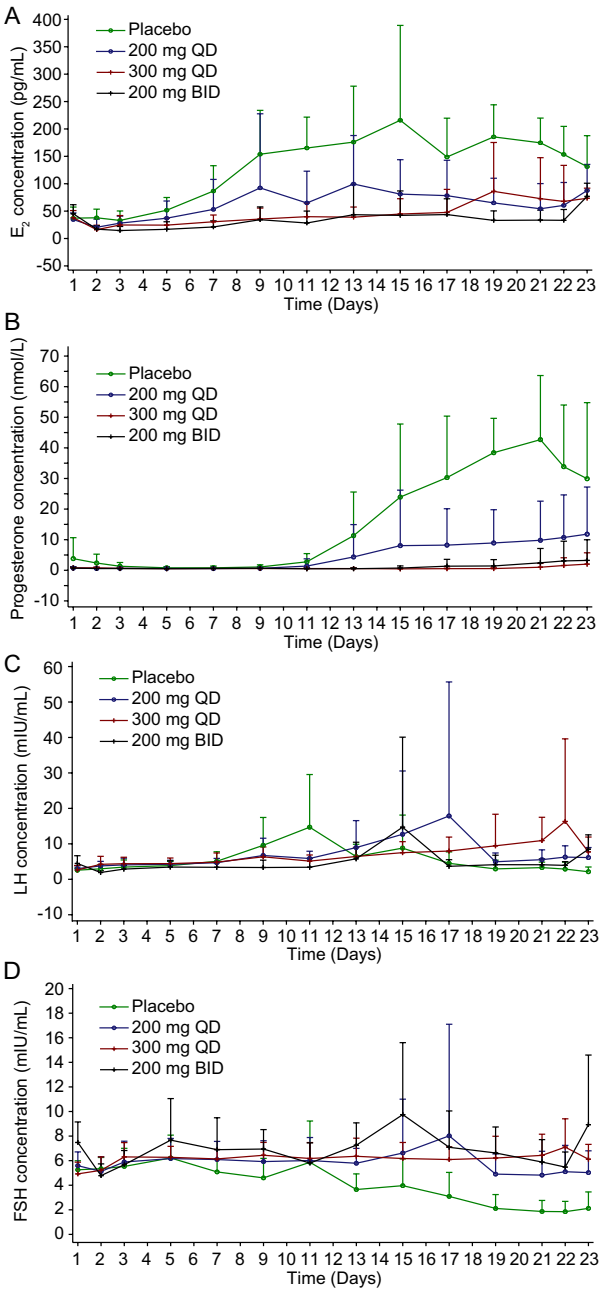

Fig. 3 Inhibition effects of SHR7280 on sex-hormones over 21 days of treatment. (**A**) Estradiol [E_2] (**B**) progesterone (**C**) luteinizing hormone [LH] (**D**) follicle-stimulating hormone [FSH]. Data are mean ± SD

concentration by SHR7280 was relatively weak, compared to the placebo group. However, the maximum FSH in the three dose groups was also disrupted by SHR7280 treatment (Fig. 3D). These results indicated that SHR7280 treatment had the ability to affect the regular fluctuation of LH and FSH levels during a menstrual cycle.

3.5 Trends of PD Parameters in Relation to the PK

The trends of PD parameters in relation to the doses of SHR7280 showed that with an increasing dose, $AUC_{0–21d}$ of E_2, LH, and progesterone decreased, while the $AUC_{0–21d}$ of FSH increased (Fig. S2). The $AUC_{0–21d}$ of E_2, and progesterone also showed trends with C_{trough}, but LH and FSH did not (Fig. S3).

4 Discussion

This study revealed that SHR7280 was rapidly absorbed, with plasma exposure being dose-proportional from 200 mg QD to 300 mg QD. Little-to-no accumulation was observed after multiple dosing of SHR7280. Administration of 200 mg BID SHR7280 achieved suppression of E_2 within the 20–50 pg/mL range, which was considered the best available compromise between efficacy, tolerance, and safety [12]. Both 300 mg QD and 200 mg BID maintained progesterone levels at an anovulatory status throughout the treatment period. SHR7280 was well tolerated across all tested doses.

The majority of AEs were mild and regressed by the last visit of the safety follow-up. The incidence of AEs for SHR7280 was similar to that with elagolix and relugolix, but without the common hot flush, mood swings, and hepatic transaminase elevation observed with elagolix and relugolix [21, 26, 27]. However, larger studies with longer follow-up are needed to confirm these findings.

The half-life of SHR7280 was slightly shorter than that of elagolix, and the exposure of SHR7280 at the dose range of 200 to 300 mg was about three times that of elagolix [28–30]. The PK parameters of the 200 mg BID group in this study were consistent with those of the 200 mg BID of SHR7280 in healthy female subjects [24], indicating that the PK profile of 300 mg BID in patients with endometriosis could be similar to that of healthy women. Therefore, if we refer to the PK parameters of the 200 mg BID and 300 BID groups in healthy subjects [24], the combined data of the two studies indicate that the exposure of SHR7280 increased proportionally to the dose within the range of 200 mg QD, 300 mg QD, 200 mg BID, and 300 mg BID.

The PD results showed certain trends between the suppression of sex hormone concentrations and the increase of SHR7280 dose, similar to the inhibition pattern of elagolix [28–30]. Compared with elagolix, SHR7280 demonstrated similar suppression effects on E_2 and LH, similar prevention effect on progesterone increase, but slightly weaker inhibition on FSH concentration. The PD parameters of the 200 mg BID group in endometriosis patients were in line with those of healthy women [24], suggesting similar PD profiles of SHR7280 at multiple doses in both populations. SHR7280 at 300 mg QD in patients with endometriosis and 200 mg BID in patients with endometriosis and healthy women could partially inhibit E_2 concentration; full inhibition of E_2 was observed in healthy women with 300 mg BID of SHR7280 [24]. These results demonstrated that SHR7280 inhibited E_2 in a dose-dependent manner.

The major limitation of this study was the small sample size, short treatment duration, and short follow-up period, which may have introduced bias in interpreting data. The results of this study need to be validated in the on-going Phase 2 study. Additionally, given that SHR7280 at doses ranging from 200 mg BID to 500 mg BID in healthy women was well tolerated and that the PK parameters of 200 mg BID in both healthy women and patients with endometriosis were comparable [24], we hypothesized that the PK parameters for 300 mg BID in healthy women could also be representative of those for 300 mg BID in endometriosis. As a result, the final optional dose of 300 mg BID was not evaluated in this study.

In conclusion, oral administration of SHR7280 had a rapid absorption and plasma drug exposure was dose dependent. It effectively repressed the concentration or prevented the increase of sex hormones in premenopausal women with endometriosis. The safety was well tolerated and most AEs were mild events. Based on the results of the Phase 1 part of this Phase 1/2 study, the Phase 2 part has been initiated to further develop SHR7280 as a GnRH antagonist for the treatment of endometriosis-related pain.

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Declarations

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Conflict of interest Sheng Feng, Yiming Liu, and Zhenyi Zhu are employees of Jiangsu Hengrui Pharmaceuticals Co., Ltd. Other co-authors declare no competing interests.

Ethics approval and consent to participate The study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice Guideline. Study protocol and all amendments were approved by the independent ethics committee of each participating sites.

Consent to participate All patients provided written informed consent before enrollment.

Consent for publication Not applicable.

Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author contributions HG, QY, and ZZ were responsible for the conception and design of the study. YL, YZ, BX, LC, ZZ, QY, and HG contributed to the data collection. SF and YL was responsible for the statistical analysis. All authors were responsible for data interpretation and manuscript writing, reviewing, and approving for submission.

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