Informed Consent Form

Project Title:

The Effects of the 3-month Formulation of Triptorelin (TP) Compared to the 1-month Formulation on the Efficacy, Glucose and Lipid Metabolism, and Bone Mineral Density(BMD) in Idiopathic Central Precocious Puberty(ICPP)

Sponsor:

Sun Yat-sen Memorial Hospital of Sun Yat-sen University

Principal Investigator:

Zhe Meng

Version Number:

V1.0

Version Date:

June 23, 2024

Dear Participant,

We invite you to voluntarily participate in a real-world study comparing the efficacy and safety of triprorelin 3-month formulation with 1-month formulation in the treatment of patients with central precocious puberty (CPP). This study is initiated by Sun Yat-sen Memorial Hospital of Sun Yat-sen University, with Principal Investigator Zhe Meng. The study has been approved by the Ethics Committee of Sun Yat-sen Memorial Hospital of Sun Yat-sen University.

Please carefully read the following information before deciding whether to participate. If you understand the study in detail and decide to participate, you need to sign this informed consent form.

Study Background

Central precocious puberty (CPP) is an important treatable disease causing pubertal growth disorders. Gonadotropin-releasing hormone analogues (GnRHa) are the first-choice drugs for treating CPP. Currently, the 1-month formulation (3.75 mg) is most commonly used in China. The development of long-acting formulations will reduce the number of injections and treatment costs, and decrease the clinical visit burden. The triprorelin 3-month formulation (15 mg) was approved in March 2023 for the treatment of CPP. Currently, there is only one small-sample, single-arm clinical study publicly reported in China, and no large-sample, concurrent control studies on the efficacy and safety of triprorelin 3-month formulation and 1-month formulation in the treatment of CPP. The domestic and foreign safety events reported rarely mention the effects of triprorelin 3-month formulation on patient body composition and bone density. Our previous small-sample retrospective study in girls with idiopathic central precocious puberty (ICPP) observed that the 3-month GnRHa (11.25 mg leuprolide) effectively inhibited the hypothalamic-pituitary-gonadal axis and bone age progression after one year of treatment, improved predicted adult height, and had no serious safety events. Therefore, based on previous work, we plan to conduct a real-world large-sample concurrent control study to evaluate the suppression of the hypothalamic-pituitary-gonadal axis and the predicted adult height benefits of triprorelin 3-month formulation compared to 1-month formulation in patients with CPP, and to assess the short-term impact of triprorelin 3-month formulation on body composition and bone density in ICPP patients. The study results are expected to provide clinical evidence for the use of triprorelin 3-month formulation in the treatment of CPP in China.

Study Objectives

Primary Objective: To compare the efficacy and safety of triprorelin 3-month formulation and 1-month formulation in the treatment of patients with idiopathic central precocious puberty in a large real-world sample.

Secondary Objective: To evaluate the short-term impact of triprorelin 3-month formulation on glucose and lipid metabolism, body composition, and bone density in

ICPP patients.
Clinical Study Design
Study Subjects: A total of 134 subjects will be included in this study. The inclusion and exclusion criteria are as follows:

Inclusion Criteria:

Patients meeting the diagnostic criteria for central precocious puberty according to the "Expert Consensus on the Diagnosis and Treatment of Central Precocious Puberty (2022)"
Patients who have not previously received GnRHa treatment
Patients weighing at least 20 kg
Exclusion Criteria:

Patients with secondary central precocious puberty, including CNS abnormalities (tumors, acquired lesions, congenital anomalies, etc.) and other diseases (congenital adrenal hyperplasia, familial male-limited precocious puberty, McCune-Albright syndrome, etc.)
Patients with slow-progressing central precocious puberty
Patients with known hypersensitivity to any study substance or related compounds
Patients with chronic diseases or treatments deemed by the investigator to interfere with growth or other study endpoints
Girls with bone age over 12.5 years or menarche for $\geqslant$ 1 year; boys with bone age over 14 years
Patients with congenital long QT syndrome or abnormal ECG
Patients with BMI $\geqslant$ 95th percentile for age and sex
Study Design: This is a single-center, prospective, non-randomized controlled cohort study. The study is planned to be conducted from May 2024 to December 2026 in the Pediatric Endocrinology Clinic and Ward of our hospital. The study will compare the efficacy and safety of triprorelin 3-month formulation and 1-month formulation in the treatment of patients with idiopathic central precocious puberty and evaluate the short-term impact of triprorelin 3-month formulation on glucose and lipid metabolism, body composition, and bone density in ICPP patients.

Study Duration: June 2024 - December 2026

Clinical Study Process
Signing the Informed Consent Form:
Screening for Study Enrollment: (description of the clinical and diagnostic data and tests required during the screening period)
Medical and medication history, vital signs, physical examination, routine blood tests, urinalysis, liver and kidney function, glucose and lipid metabolism, sex hormones, GnRHa stimulation test, imaging tests (bone age, ovarian and uterine ultrasound, cranial and pituitary MRI, body composition and bone density), 12-lead ECG

Study Grouping and Treatment:

If you meet the inclusion criteria, you will be assigned to the trial group or control group based on your preference and receive the corresponding treatment according to the study protocol.
Trial Group: Triprorelin pamoate (15 mg), intramuscular injection in the buttocks, fixed dose of 15 mg every 3 months, for a total of 4 injections.
Control Group: Triprorelin acetate (3.75 mg), intramuscular injection in the buttocks, fixed dose of 3.75 mg every 28 days, for a total of 12 injections.
Follow-Up Visits: During the study, you are required to attend follow-up visits at 3, 6, 9, and 12 months after the start of treatment, and undergo the required examinations until the end of the study. During each follow-up visit, your doctor will arrange the following examinations:

Medical history, physical examination
Routine blood tests, urinalysis, liver and kidney function, blood biochemistry and lipids, sex hormones, GnRHa stimulation test
Imaging tests: ECG, bone age, reproductive system ultrasound, body composition, bone density
Other Matters Requiring Your Cooperation:

You are required to report any physical and mental changes during the study, regardless of whether they are related to the study. Inform your doctor of any medications you are currently taking or will take during the study. Do not take any other medications that affect growth and development without consulting your doctor.
Alternative Treatments
Participation in this study is completely voluntary. If you do not participate or choose to withdraw at any stage, you will receive alternative treatments. Alternative treatments include other GnRHa medications such as leuprolide. You can discuss specific alternative treatments with your doctor before deciding whether to participate in this study.

Costs Associated with This Study
The medications used in this study, triprorelin (3-month formulation and 1-month formulation), are recommended treatment medications according to clinical guidelines. Routine tests such as routine blood tests, urinalysis, fecal routine, liver and kidney function, blood biochemistry and lipids, sex hormones, GnRHa stimulation test, ECG, bone age, reproductive system ultrasound, and bone density are standard examination items. Therefore, you will need to bear the costs of these items yourself. Participating in this study will not incur additional financial burdens on you.

Possible Benefits
Participation in this clinical study may likely control your child's sex hormone levels, inhibit the progression of sexual development, improve predicted adult height, and

address psychological and behavioral issues related to precocious puberty. The 3-month formulation of triprorelin, compared to the 1-month formulation, reduces the number of injections, enhances treatment convenience and medication adherence, and improves the quality of life. During the study, your child will receive priority consultations and medical advice.

Possible Risks

Any disease diagnosis and treatment may bring discomfort and unpredictable risks. According to the "Expert Consensus on the Diagnosis and Treatment of Central Precocious Puberty (2022)" and the drug instructions, possible side effects of GnRHa treatment include weight gain, headache, rash, gastrointestinal reactions, and acne, but these are usually temporary and mild and do not affect treatment. Local and allergic reactions may occur in 10%-15% of patients, and a few may experience emotional changes, nipple pain, neck pain, nosebleeds, etc. Other rare adverse reactions include visual disturbances, emotional disorders, intracranial hypertension, elevated prolactin levels, and increased blood pressure. Some patients may experience slight vaginal bleeding 3-7 days after the first use of GnRHa due to the "flare effect," which temporarily increases estrogen levels and leads to follicle growth and cyst formation. Long-term treatment has good safety.

Handling and Compensation for Study-Related Injuries

If adverse events occur due to the study drug or required diagnostic tests and treatments, and cause you harm, your doctor will provide active treatment. If medical incidents occur, they will be handled according to medical incident procedures, and our center will bear the treatment costs and legal compensation costs for study-related injuries.

Confidentiality Measures

The results of this clinical study are for scientific research purposes only. Therefore, your participation in the study and your personal data during the study are confidential and protected by law. Your name will not appear in any study reports and public publications. Government regulatory agencies, hospital ethics committees, and researchers have the right to access all your study data, including clinical observation forms and test data, as required by their work and according to regulations.

Study Termination

You can withdraw from the study at any time without any reason, and your decision will not affect your continued medical treatment. Your doctor may also stop your participation for the following reasons:

You do not follow the doctor's instructions and requirements for medication.
Disease progression or intolerable adverse reactions occur, and the doctor believes that continued participation will harm you.
You receive treatments not allowed in this study.
The study doctor, ethics committee, or government regulatory agencies request the

termination of the study.

When you withdraw or the study is terminated, the study doctor will discuss follow-up treatment measures with you.

Rights

This clinical study has been reviewed and approved by the Ethics Committee of Sun Yat-sen Memorial Hospital of Sun Yat-sen University. The study design meets ethical requirements, ensuring that your rights will not be violated during the study.

Your participation in this clinical study is entirely voluntary. You can refuse to participate or withdraw at any time without discrimination or retaliation, and your medical treatment and rights will not be affected. If you withdraw from the study, for safety reasons, you should complete some corresponding medical examinations when you withdraw. If the study doctor deems you unsuitable to continue participating, the doctor has the right to terminate your participation to protect your interests. You can access information related to the study at any time during the study. If we obtain any new information about the study, we will inform you promptly, allowing you to decide whether to continue participating.

If any discomfort or worsening of your condition occurs during the study, please immediately notify your study doctor, and we will take appropriate medical measures in time. If you comply with the study protocol and experience any adverse events related to the study, the researchers will provide active treatment.

Detailed Contact Information

If you have any concerns or questions about participating in this study, or if you experience any abnormal reactions or emergencies during the study, you should contact:

Doctor: Siqi Huang Contact Number: 15692418384

If you have any complaints, concerns, or questions about the way the study is conducted by the study physician, or as a research participant, you can contact the ethics committee of our center:

Email: sysyxllwyh@163.com Contact Number: 020-81332587

Informed Consent Form • Agreement Signature Page

Participant Statement:

I have carefully read this informed consent form. The researcher has provided me with detailed explanations and answered my related questions. I fully understand the following:

As a participant, I will comply with the requirements for participants, voluntarily participate in this study, and fully cooperate with the researchers, providing truthful and objective information about my health status and related conditions before participating in the study.

I agree that Sun Yat-sen Memorial Hospital of Sun Yat-sen University can access my medical records and study results for scientific research purposes. I understand that the results of this clinical study are for scientific research purposes only. Except for government regulatory agencies, ethics committees, and researchers, my participation and personal data during the study are confidential and protected by law.

My participation in this study is entirely voluntary. I can refuse to participate or withdraw at any time without discrimination or retaliation, and my medical treatment and rights will not be affected.

I also declare that:

I am willing to comply with the study procedures. I have received this informed consent form.

Participant Signature:

Contact Information:

Date: Year Month Day

Guardian Signature:

Relationship to Participant:

Contact Information:

Date: Year Month Day

Witness Signature (if necessary):

Contact Information:

Date: Year Month Day

Researcher Statement:

I have provided the participant with a full explanation of the purpose, methods, procedures, and potential risks and benefits of participating in this study, and satisfactorily answered all the participant's questions.

Researcher (person informing the participant) Signature:

Contact Information:

Date: Year Month Day