The Efficacy and Safety of Silodosin Singly or Combined with Ningmitai Capsules in the Treatment of Benign Prostatic Hyperplasia (BPH) Complicated with Lower Urinary Tract Symptoms (LUTS) —A Multicenter, Prospective, Randomized, Double-blind, Positive Controlled Study

Date: September 8, 2022

Research Proposal Summary

Scheme number	NM-22-A-001-YJ-001
Scheme name	The Efficacy and Safety of Silodosin Capsules Singly or Combined with Ningmitai Capsules in the Treatment of Benign Prostatic Hyperplasia
Version number/date	Version 1.0, December2, 2021
sponsor	Shanghai Haitian Pharmaceutical Technology Development Co., Ltd.
Clinical trial staging	Post-marketing clinical re-evaluation
test drug	Ningmitai Capsules (Ningmitai®, Z20025442), each 0.38g, was produced by Guiyang Xintian Pharmaceutical Co., Ltd. Silodosin Capsules (Qianweitai®, H20213612), each 4mg, was produced by Shanghai Huilun Pharmaceutical Co., Ltd. Tamsulosin Hydrochloride Sustained Release Capsules(H20000681), each0.2mg, was produced by Astellas Pharma Inc. Placebo, Ningmitai capsule simulator, each0.38g, was produced by Guiyang Xintian Pharmaceutical Co., Ltd.
Indications	Benign Prostatic Hyperplasia with Lower Urinary Tract Symptom
Test purposes	1.To evaluate the efficacy and safety of Silodosin Capsules alone versus Tamsulosin Hydrochloride Sustained Release Capsules in the treatment of BPH with lower urinary tract symptoms. 2.To evaluate the efficacy and safety of Ningmitai Capsules combination with Silodosin Capsules versus Silodosin Capsules alone in the treatment of BPH with lower urinary tract symptoms.
Research design	A multicenter, prospective, randomized, controlled clinical trial design
total number of cases	It is planned to complete 312 cases (considering the 20% dropout rate)
number of research	8

centers	
Study period	6 months
research object	**Diagnostic criteria:** 1. Male Subjects aged 60 ~ 80 years, clinically diagnosed as benign prostatic hyperplasia. 2. Has an IPSS score ≥ 8 points at Screening and Baseline. 3. Has a $4 \leq Q_{max} \leq 15$ ml/s when urination volume > 150 ml. 4. Has a prostate volume (PV) ≥ 30 ml by ultrasound examination. 5. Subjects who can read, understand, and complete the research questionnaire. 6. Subjects willing to participate voluntarily in this clinical trial, give informed consent and sign informed consent. **Exclusion criteria:** 1. Subjects with prostate cancer or other malignant tumors. 2. Subjects have serum tPSA > 10ng/ml, or 4 ≤ tPSA ≤ 10ng/ml while fPSA/tPSA < 0.16 times. 3. Subjects suffered from other diseases causing dysuria, such as bladder neck spasm, urethral stricture, neurogenic bladder dysfunction, etc. 4. Subjects have suffered from acute urinary retention, or complicated with gross hematuria, urinary tract infection, bladder stones, secondary upper urinary tract hydronephrosis, urinary incontinence, renal insufficiency and other subjects that researchers believe meet the surgical indications. 5. Subjects have undergone prostate surgery, microwave therapy, urethral dilatation or acute urinary retention catheterization or other invasive procedures. 6. Subjects have residual urine volume (PVR) > 100ml, or those who may have urinary retention and need catheterization. 7. Subjects who took α receptor blockers, traditional Chinese Medicine or botanical drugs for treating BPH within two weeks before participating this clinical trial. 8. Subjects who take 5α reductase inhibitor or other antiandrogen therapy drugs within half a year before participating this clinical trial. 9. Subjects who need to take drugs prohibited in this study or adopt prohibited treatment methods during treatment. 10. Subjects who Complicated with severe cardiovascular and cerebrovascular diseases, respiratory diseases, blood diseases, liver, and kidney diseases. 11. There are significant abnormalities in clinical or laboratory examination indexes of patients,

	such as ALT and AST ≥ 2.5 times of the upper limit of reference value, creatinine (Scr) > 1.5 times of the upper limit of reference value, or poor blood glucose control (fasting blood glucose FPG ≥ 10 mmol/L). 12. Subjects who are allergic to the drugs or ingredients used in the test definitely. 13. Any other Subjects in the opinion of researchers is not suitable for inclusion.
Trial grouping and medication	According to the random sequence generated by computer, eligible patients were randomly assigned to three groups according to 1: 1: 1. **Group A: Tamsulosin combined with Ningmitai Capsules placebo.** Oral Tamsulosin Hydrochloride Capsules (each 0.2mg), 1 capsule per time, 1 time a day. Oral Ningmitai Capsules placebo (each 0.38g), 4 capsules per time, 3 times a day. Continuous medication for 12 weeks. **Group B: Silodosin Capsules combined with Ningmitai Capsules placebo.** Oral Silodosin Capsules (each 4mg), 1 capsule per time, 2 times a day. Oral Ningmitai Capsules placebo (each 0.38g), 4 capsules per time, 3 times a day. Continuous medication for 12 weeks. **Group C: Silodosin Capsules combined with Ningmitai Capsules.** Oral Silodosin Capsules (each 4mg), 1 capsule per time, 2 times a day. Oral Ningmitai Capsules (each 0.38g), 4 capsules per time, 3 times a day. Continuous medication for 12 weeks.
Combined medication	**Combination drugs banned during the study:** (1) CYP3A4 inhibitors (eg. Ketoconazole, Clarithromycin, Itraconazole, Ritobuvir) (2) Other α-receptor blockers besides this study and other drugs with therapeutic effects on BPH include 5-α reductase inhibitors, phosphodiesterase type 5 (PDE-5) inhibitors, M receptor blockers, β3 receptor agonists, botanical drugs or traditional Chinese medicines, etc. **Combination drugs used with caution during the study:** (1) Strong inhibitors of CYP2D6 (such as Paroxetine) may lead to a significant increase in exposure to Tamsulosin. (2) Potential P-glycoprotein (P-gp) inhibitors (such as Cyclosporin), in vitro studies have shown that Silodosin is a P-gp substrate, and the inhibition of P-gp may lead to an increase in the blood concentration of Silodosin. (3) Antihypertensive drugs, there is a decline in blood pressure regulation ability when standing up and pay close attention to blood pressure changes when combined with α-receptor blockers. (4) Drugs that may induce or aggravate urinary retention, such as Anticholinergic Atropine, Antiallergic Chlorpheniramine, Antidepressant Imipramine, and ready-for-use traditional Chinese

	medicine or decoction containing ephedra. **Concomitant drugs allowed during the study period:** If the subjects have basic diseases and need to take drugs for a long time, and they are not prohibited drugs in this study, they can continue to use them during the study period. If the subject has adverse reactions, it is up to the researcher to decide whether to use symptomatic treatment drugs. All drugs used at the same time should be recorded and explained in detail on CRF table.
Treatment and follow-up	Course of treatment: 12 weeks Visit points: screening period, days -28 to 0), after 1 week of treatment (day 7±2), after 2 weeks of treatment (day 14±3), after 4 weeks of treatment (day 28±5), after 8 weeks of treatment (day 56±7), after 12 weeks of treatment (day 84±10).
Research steps	This trial is divided into two stages: screening period, treatment period and follow-up period. Screening period (days -28 to 0): After signing the informed consent form, the subjects entered the screening period, and made a 24-hour urination diary and screening examination. Treatment and Follow-up period: eligible patients were randomly assigned to three groups according to 1: 1: 1 and received Tamsulosin + placebo, Silodosin + placebo or Silodosin + Ningmitai for 12 weeks. During the treatment period, the subjects' diaries were recorded according to the requirements of the scheme, and they were followed up at 1 week (7±2 days), 2 weeks (14±3), 4 weeks (28±5 days), 8 weeks (56±7 days) and 12 weeks (84±10 days). During the visit, relevant scale scores and laboratory examinations were performed, and the occurrence of adverse events during the follow-up was recorded to evaluate the safety.
study endpoint	**Primary endpoint:** International Prostate Symptom Score (IPSS), Changes of scores at the 12th week of treatment compared to the baseline scores. **Secondary endpoints:** 1.IPSS Score ①changes of IPSS total score: Changes of IPSS scores at 1, 2, 4 and 8 weeks after treatment compared with baseline scores ②Proportion of patients with IPSS total score severity decreased by at least one grade at 12 weeks ③IPSS sub-score: IPSS Stimulation Score at 1, 2, 4, 8, 12 weeks (Sum of Question 2, 4, 7) and

Changes of IPSS obstruction score (sum of question 1, 3, 5, 6) compared with baseline.

2.Quality of life (QoL) score: Changes in scores at 4, 8 and 12 weeks of treatment compared with baseline

3. Maximum urinary flow rate (Q_{max})

The change of Q_{max} at 12 weeks of treatment compared with baseline.

4. Patient response rate

Patient response rate is defined as the proportion of patients whose IPSS total score decreased by ≥ 25% and Q_{max}.

increased by ≥ 30% compared with baseline value after treatment.

5. Residual urine volume (PVR)

Changes of PVR at 12 weeks of treatment compared with baseline.

6. Prostate specific antigen (PSA)

Changes of PSA at 12 weeks of treatment compared with baseline.

7. Prostate volume (PV)

Changes of PV at 12 weeks of treatment compared with baseline.

8. Proportion of patients with BPH clinical progression

Clinical progress is defined as the first occurrence of one of the following two conditions during the trial:

① Acute urinary retention (AUR).

② Clinical diagnosis requires surgical treatment of BPH.

Subgroup analysis:

Patients were grouped according to the following conditions of subjects at baseline, and the therapeutic effect of curative effect indicators was evaluated among different subgroups to determine whether the therapeutic effect was consistent among subgroups:

①The scores of IPSS were moderate (8-19) and severe (20-35);

②Routine examination of EPS (EPS leukocytes > 4HP or < 4HP. If EPS is not collected after prostate massage, it is not advisable to repeat massage for many times, and it is recommended to take urine after prostate massage for analysis.).

③Symptoms of chronic prostatitis (NIH-CPSI pain score ⩾ 4 and < 4)

security indicators	**The incidence of adverse drug events/reactions was calculated according to the following indicators:** 1.Vital signs: Blood pressure, heart rate 2.Laboratory examination index: Blood routine, Urine routine, liver function (ALT, AST, ALP) and renal function (BUN, Scr). 3.Possible adverse drug events/reactions.