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

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Statistical analysis Plan

1.Statistical analysis of population:

(1) **FAS:** According to the basic principle of intentionality analysis (ITT), all the randomized subjects with more than one medication record and effectiveness evaluation were included in the full analysis set. The total analysis set is the main validity evaluation population of this study.

(2) **PPS:** Include all subjects who have completed the treatment stipulated in the scheme or have not seriously violated the trial scheme. The exact definition of the serious violation scheme will be finalized during the data review. PPS is the secondary analysis population of validity, but if its results are inconsistent with the full analysis set, it is necessary to analyze the inconsistent results in detail.

(3) **SS:** Defined as all subjects who were randomized and received at least one trial drug treatment. The safety analysis set is the safety evaluation population of this study.

2.Statistical analysis method:

(1) **General principle:** All statistical analysis shall be processed by SPSS 23.0 and above statistical software, and shall be carried out according to the pre-established statistical analysis plan. Measurement data are described by mean, standard deviation, median, quartile, maximum and minimum. The counting data are described by frequency and percentage. After 12 weeks of treatment, the changes of IPSS scores between Tamsulosin + placebo group and Silodosin + placebo group were compared by non-inferior test, while the changes of IPSS scores between Ningmitai + Silodosin group and Silodosin + placebo group were compared by superior test, and the test levels were $\alpha = 0.025$ (unilateral). Other hypotheses were tested by two-side test with a test level of $\alpha=0.05$, and the secondary index was adjusted by Bonferroni method with a test level of $\alpha=0.0167$.

(2) **Balance analysis of baseline value:** Comparability analysis of demographic characteristics, general situation and baseline situation (before treatment) of the two groups of data. Among them, t test or Wilcoxon rank sum test was used for measurement data and grade data, and X^2 test or Fisher exact probability method was used for classification data.

(3) **Effectiveness analysis:** Conducted in FAS and PPS at the same time.

①**Main endpoint indicators:** After 12 weeks of treatment, the difference of IPSS score decline and 97.5% CI of the three groups were calculated. If the lower limit of unilateral 97.5% confidence interval of the difference of IPSS score decline between Silodosin + placebo group and Tamsulosin + placebo group is greater than the non-inferiority threshold of 1 (-1 point), then "Silodosin + placebo" is not inferior to "Tamsulosin + placebo" group. If the lower limit of unilateral 97.5% confidence interval of the difference between the IPSS scores of Silodosin + Ningmitai group and Silodosin + placebo group is greater than the superior effect threshold of 2 (0 points), then "Silodosin + Ningmitai" is superior to "Silodosin +

placebo". Subgroup analysis was considered according to whether the NIH-CPSI pain score was ≥ 4 before treatment and the severity of IPSS total score.

②**Secondary endpoint index:** The changes of IPSS scores, IPSS sub-scores and QoL scores were compared between groups at 1, 2, 4, 8 and 12 weeks after treatment. The changes of Q_{max}, PVR, serum PSA and prostate volume were compared between groups by single factor analysis of variance or Wilcoxon rank sum test. Bonferroni method was used to adjust the test $\alpha = 0.0167$. The clinical progression curve of BPH was drawn by Kaplan-Meier; COX regression model was used to compare the factors affecting the clinical progression of BPH. The proportion of patients with IPSS total score decreased in severity was compared between groups by X^2 test or Fisher exact probability method.

(4) Security analysis: To evaluate the safety of SS population. The data of safety evaluation include the adverse events observed during the trial and the changes of laboratory examination data before and after treatment. Descriptive statistics were used for adverse events, and the total incidence of adverse events and the incidence of various adverse events were compared among each group. In addition to comparing the average data before and after treatment, the laboratory examination data mainly analyzed and listed the specific situation of normal cases before treatment and abnormal cases after treatment or abnormal cases before treatment and abnormal cases after treatment.

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 day s). 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.