Explanatory document

"Add-on or switch to vibegron in patients with overactive bladder insufficiently responding to initial 4-Week antimuscarinics: A randomized, parallel-group, multicenter trial"

1. Introduction

Research conducted on human subjects for the purpose of preventing diseases, elucidating their causes, improving diagnostic and therapeutic methods, or verifying their effectiveness is called "clinical research. Among these, clinical research to confirm the efficacy and safety of drugs and medical devices can be divided into two major categories: clinical trials, which are conducted in accordance with legal regulations and are intended to obtain approval as a drug or medical device from the Ministry of Health, Labor and Welfare, and other types of research. The clinical research in which we are requesting your participation is non-clinical trial, and will be conducted in accordance with the "Clinical Research Act" after obtaining approval from the "Institute of Science Tokyo Clinical Research Review Committee," a review committee authorized by the Ministry of Health, Labor and Welfare, and obtaining permission from the director of the hospital where the research will be conducted. The implementation plan is also submitted to the Minister of Health, Labor and Welfare.

Clinical research differs from routine medical treatment in that it involves the evaluation of drugs or medical devices according to a research objective or plan. Depending on the research plan, the frequency of visits to the hospital may be

determined, certain medications may not be used, and other restrictions not found in routine medical care may be determined. You are free to decide whether or not to participate in the study. If you do not participate, you will not be disadvantaged in any way in your future treatment. You may withdraw from participation at any time, even during the course of your participation.

Over active bladder (OAB) is a condition in which a person has an urgency to urinate, which leads to an increase in the frequency and leakage of urine. The diagnostic criteria for OAB are urgency at least once a week and a total score of 3 or higher on the over active bladder symptom score (OABSS). In a large-scale epidemiological survey of people aged 40 years or older in Japan, 14.1% were reported to have overactive bladder symptoms, and the actual number was estimated to be as high as 10.4 million based on the population composition in 2012.

Various factors can cause OAB, including age-related changes in bladder function, weakening of the muscles supporting the bladder and urethra, benign prostatic hyperplasia, and the aftereffects of cerebral hemorrhage or stroke. Antimuscarinics that inhibit bladder contractions have been the main pharmacological therapy for OAB, but recently, β3 receptor agonists have emerged as medications that relax bladder muscle tone. Although antimuscarinics have established efficacy and safety, they have side effects such as dry mouth and constipation. When patients are unable to continue treatment or antimuscarinics is insufficiently effective, dose increase, switching to another antimuscarinics, changing to β3 receptor agonists, or introducing combination therapy should be considered. There is limited evidence that patients who do not respond to first-line antimuscarinics will respond to higher doses or different antimuscarinics. Only two types of β3-receptor agonists can be used for OAB in Japan:

mirabegron (Betanis®), which was launched in 2011, and vibegron (Beova®), which will be used in this study. β3-receptor agonists are reported to have fewer side effects such as dry mouth and constipation that are characteristic of antimuscarinics. we will assess vibegron's efficacy and safety in two scenarios: as an adjunct to antimuscarinics and as their replacement.

2. Purpose of this study

Vibegron, a β3-receptor agonist, is considered an effective drug in the treatment of overactive bladder. The purpose of this study is to evaluate whether (A) adding vibegron to anticholinergic drugs or (B) switching to vibegron improves symptoms of overactive bladder or reduces side effects in patients whose overactive bladder treatment with conventional anticholinergic drugs seems to be inadequately effective. The purpose of this study is to compared to (B), (A) may result in better efficacy, but may lead to an increase in side effects. Therefore, by comparing treatments (A) and (B), we will consider which treatment will benefit the patient more overall in terms of efficacy and side effects.

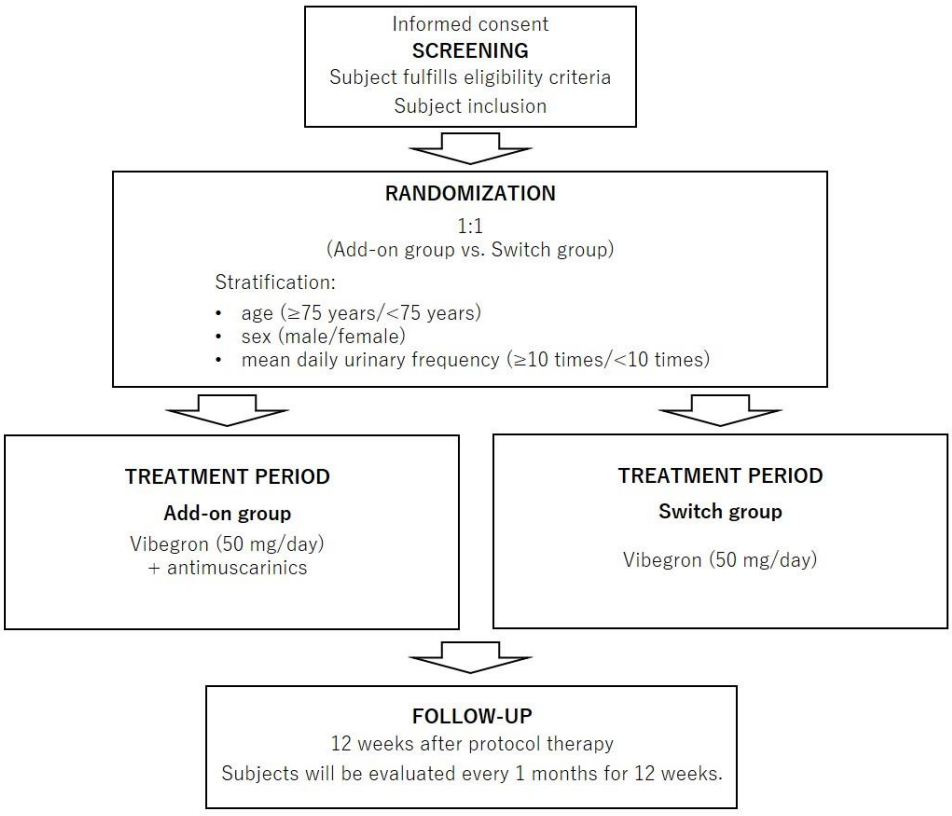
3. Methods of this study

To correctly judge the efficacy of the vibegron for OAB, the patients participating in the study will be divided into two groups—one group will receive vibegron only and the other group will receive vibegron plus antimuscarinic agent. The group assignment will not be based on your physician’s judgment or your wishes, but it will be done mechanically for objective evaluation. The probability of being in each group is 50%.

The effect of treatment will be evaluated every 4 weeks based on findings of 3-day urinary diary and some questionnaires. Your test results obtained in this study will be used to evaluate your condition. We will also use the test information obtained prior to your consent to participate in this study. Your name, test information, and other personal information will be kept strictly confidential and anonymized so that your information will not be identifiable throughout the study. The information will be stored in a password-protected electronic file for 10 years after the completion of the study (university regulations) by Soichiro Yoshida, who will be responsible for storing the information; at the time of disposal, the information will be disposed of in such a way that your personal information cannot be identified.

If you are currently undergoing treatment another hospital, please let us know the name of the hospital, the name of the disease, and the medication you are taking. This is important for ensuring the safety of the study. If you are a patient at another hospital, please understand that we may inform the hospital of your participation in this study.

Flowchart of the tests



The flow chart of this study is shown above.

Schedule

	Screening period	Protocol therapy 4th week	Protocol therapy 8th week	Protocol therapy 12th week	Protocol therapy at discontinuation
Informed consent	×				
Hospital visit	×	×	×	×	×
Check patient background	×				
Voiding diary check	×	×	×	×	×
OABSS questionnaire	×	×	×	×	×
IPSS/QOL questionnaire	×	×	×	×	×
ICIQ-SF questionnaire	×				
Residual urine volume	×	×	×	×	×
Adverse event check*	×	×	×	×	×

*according to the Common Toxicity Criteria for Adverse Events (CTCAE v 5.0)

- Residual urine volume and adverse events check are performed to confirm safety. 3-day voiding diary, OABSS questionnaire and IPSS/QOL questionnaire are performed to confirm the effectiveness of the treatment.
- Adverse events are all events that are undesirable to health, such as side effects, regardless of whether they are causally by the medication.

4. Eligibility for this study

Patients are eligible for this study if they meet all the following criteria:

- Patients aged 18 years or older at the time of enrollment.
- Patients diagnosed with OAB based on the OABSS and treated with one of the following antimuscarinics for at least 4 weeks:
  - ✓ Propiverine hydrochloride 20 mg (orally once daily)
  - ✓ Imidafenacin 0.2 mg (orally once daily / orally twice daily)
  - ✓ Solifenacin succinate 5 mg (orally once daily)
  - ✓ Fesoterodine fumarate 4 mg (orally once daily)
  - ✓ Oxybutynin hydrochloride transdermal 73.5 mg (once daily, applied to the lower leg, lumbar region, or thigh)
- Patients willing and able to accurately complete the voiding diary/questionnaire, including measuring urine output over a 3-day period.
- Patients willing and able to follow and comply with the study protocol, including study visits

and tests.

- Patients who fully understand the study content and have given their written consent.

Patients are not eligible for this study if they meet all the following criteria:

- Patients with clinically significant bladder outlet obstruction.
- Patients with high residual urine volume (>150 ml).
- Patients with significant stress incontinence or mixed incontinence where stress incontinence is the predominant factor.
- Patients using a continuously placed urinary catheter or clean intermittent catheterization.
- Patients receiving non-pharmacological treatment for urinary incontinence, including sacral nerve stimulation. However, bladder training programs or pelvic floor muscle exercises initiated more than 30 days prior to enrollment are acceptable.
- Patients determined by the principal investigator or co-investigator to have a history of disease or surgery that affects the assessment of OAB-related voiding (e.g., patients treated with intravesicval botulinum toxin injection).
- Patients with chronic inflammatory disease or malignant disease in the pelvic region.
- Patients who have undergone intravesical treatment for bladder malignancy within 12 months or have a history of bladder, prostate, or uterine cancer within 5 years prior to enrollment. However, patients with a history of these cancers may be enrolled if they have been treated, are cancer-free, and have not had a recurrence in 5 years.
- Patients with uncontrolled narrow-angle glaucoma, urinary retention, pyloric stenosis, severe ulcerative colitis, toxic megacolon, myasthenia gravis, or any other contraindication to antimuscarinics as determined by the principal investigator or co-investigator.
- Patients with a history of hypersensitivity to the components of vibegron.
- Pregnant, potentially pregnant, or lactating patients.
- Patients deemed ineligible by the principal investigator or co-investigator for medical, psychological, or other reasons.

5. Expected duration of participation in this study

If you participate in this study, your expected participation period will be until August 31, 2026. The expected duration of participation in this study is 4 weeks for the pre-observation period, 12 weeks for the study drug administration period.

6. Number of patients expected to participate in this study

This study will be conducted at eleven hospitals in Japan, and 110 patients are expected to participate.

7. Anticipated benefits and possible side effects of this study drug

Participation in this study will not directly benefit you, but the results of the study may contribute to future medical advances.

Vibegron, the drug used in this study, is approved for the treatment of overactive bladder. Side effects reported with vibegron include constipation (1.6%), dry mouth (1.4%), and urinary retention (frequency unknown). In the group that adds vibegron to antimuscarinics (A), the concomitant use of two drugs may increase side effects. However, when mirabegron, a drug with a similar mechanism of action to vibegron, was combined with an antimuscarinic drug (solifenacin), side effects were all mild and no serious side effects were reported. In the group switching (B) from anticholinergics to vibegron, participation in this study is not expected to result in an increased risk of adverse effects compared to routine practice.

If you have any of the following symptoms, please consult your doctor:

Symptoms of constipation

lower abdominal discomfort, infrequent bowel movement or straining to have a bowel movement

Symptoms of dry mouth

Dryness or a feeling of stickiness in your mouth

Symptoms of urinary retention

No ability to start urination, pain as your bladder stretches or swelling in your lower belly

8. Other treatment options if you do not participate in this study

Even if you do not participate in this study, there are conventional ways to treat your disease, and your doctor will choose the appropriate treatment for you, taking your wishes into consideration.

9. In case of any damage to your health during this study

This study has been scientifically planned and will be carefully conducted based on previous reports. If you experience any side effects or other health problems during or after the clinical study, your doctor will provide you with appropriate medical attention and treatment. Since this study will be conducted using medications that are already available in the market within their indications, any health problems caused by these medications will be treated in the same way as normal medical treatment. In addition, if a certain amount of health damage occurs due to side effects, the patient may be eligible for benefits under the Adverse Drug Reaction Relief System.

This study is covered by clinical research insurance, and compensation may be provided in the event of side effects not included in the list of possible side effects caused by vibegron administration.

10. Participation in this study is voluntary

Participation in this study is voluntary. You may withdraw your consent at any time, even after you have participated. Even if you do not participate or revoke your consent

to participate, we will provide the most appropriate treatment for you, and you will not be treated adversely or suffer any disadvantage in treatment.

11. Information regarding the use of vibegron will be communicated to you as needed

If we obtain any information that may affect your family's opinion, we will inform you as soon as possible and ask for your consent to continue the study. If you do not give your consent, you will still be able to receive other treatments. If you want to know more about the study and its methods, please let the principal investigator know. To the extent that it does not interfere with our research, you will be given access to materials related to the protocol and methods.

12. We may discontinue the use of vibegron in some cases

In case of side effects caused by vibegron administration, the dose will be reduced or withdrawn according to the following criteria. The degree of side effects will be evaluated in accordance with the Common Terminology Criteria for Adverse Events, version 3.0.

Side effects	Treatment
Grade ≥3 constipation, dry mouth, or urinary tract infection	Administration should be postponed until recovery to Grade ≤2 and then resumed after confirmation of recovery. If the grade does not recover to ≤2 within 2 weeks from the last dose, administration should be discontinued.

13. If you participate in this study, your medical records and other information may be examined during or after the study

To confirm that this study is being conducted properly while protecting the human rights of patients, your medical records may be reviewed by persons involved in this research (such as hospital staff; review committees; Ministry of Health, Labour and Welfare personnel; monitoring personnel; and auditors). In such cases, personal information will be handled appropriately. By signing the consent form, you are giving permission for access.

14. Even if the results of this study are made public, your identity will not be revealed

The results obtained in this study will be registered in the Japan Registry of Clinical Trials (jRCT: https://jrct.niph.go.jp/) of the Ministry of Health, Labour and Welfare and may also be published in medical journals, websites of universities, academic societies, or other platforms. However, your name and other personal information will not be revealed. For example, we will use a different code number that cannot be inferred from your name or initials; therefore, your privacy will be protected. The samples and information obtained in this study will be strictly controlled and stored, but they may be used in the future or provided to other research institutions. For example, we may want to reanalyze your samples due to new discoveries or we may want to aggregate the information with data from a larger number of patients. In such cases, when a new research plan is formulated, the Institute of Science Tokyo Clinical Research Review Committee will be consulted for approval, and you will be notified of the details of the research.

15. If you agree to participate in this research, please observe the following points

When visiting other departments or hospitals or when purchasing medicines at pharmacies, please be sure to inform the doctor or pharmacist concerned that you are participating in the research and consult with the doctor in charge of the research in advance whenever possible. When this study is completed, a normal insurance-covered treatment will be provided if necessary. If you wish to continue to receive outpatient consultations after the completion of this study, please inform the principal investigator.

16. About your cost burden

Drug administration in this study will be performed within the scope of normal insurance coverage as the use of over-the-counter drugs is within the scope of this study.

This study is funded by Kissei Pharmaceutical Corporation and KYORIN Pharmaceutical Company, which manufactures and sells vibegron, but there is no conflict of interest.

17. These doctors will take care of you

- Tokyo Metropolitan Tama-Nambu Chiiki Hospital

(Principal investigator) Takanobu Yamamoto, Department of Urology

At night (5:00–9:00 p.m.) and on holidays, please call the emergency room (042-338-5111) and ask for the urologist on duty.

- Institute of Science Tokyo

(Principal investigator) Soichiro Yoshida, Department of Urology (ext. 5295).

(Subinvestigator) Yasuhisa Fujii, Department of Urology (ext. 5295)

(Subinvestigator) Hajime Tanaka, Department of Urology (ext. 5295)

(Subinvestigator) Kenji Fukushima, Department of Urology (ext. 5295)

At night (5:00–9:00 p.m.) and on holidays, please call the emergency room (03-3813-6111) and ask for the urologist on duty.

- Japanese Red Cross Oomori Hospital

(Principal investigator) Yukihiro Ootsuka, Department of Urology

At night (5:00–9:00 p.m.) and on holidays, please call the emergency room (03-3775-3111) and ask for the urologist on duty.

- Showa General Hospital

(Principal investigator) Tetsurou Tsukamoto, Department of Urology

(Subinvestigator) Sho Uehara, Department of Urology

At night (5:00–9:00 p.m.) and on holidays, please call the emergency room (042-461-0052) and ask for the urologist on duty.

- Kohnodai Hospital, National Center for Global Health and Medicine

(Principal investigator) Katsushi Nagahama, Department of Urology

(Subinvestigator) Saori Araki, Department of Urology

At night (5:00–9:00 p.m.) and on holidays, please call the emergency room (47-372-3501) and ask for the urologist on duty.

- Saitama Red Cross Hospital

(Principal investigator) Shuichiro Kobayashi, Department of Urology

(Subinvestigator) Takashi Tamiya, Department of Urology

At night (5:00–9:00 p.m.) and on holidays, please call the emergency room (048-852-1111) and ask for the urologist on duty.

- Soka Municipal Hospital

(Principal investigator) Atsushi Yoshinaga, Department of Urology

At night (5:00–9:00 p.m.) and on holidays, please call the emergency room (048-946-2200) and ask for the urologist on duty.

- Tsuchiura Kyodo General Hospital

(Principal investigator) Yasuyuki Sakai, Department of Urology

(Subinvestigator) Yuuya Maezawa, Department of Urology (ext. 8033)

At night (5:00–9:00 p.m.) and on holidays, please call the emergency room (029-830-3711) and ask for the urologist on duty.

- Tokyo Metropolitan Ohtsuka Hospital

(Principal investigator) Ryoji Takazawa, Department of Urology

At night (5:00–9:00 p.m.) and on holidays, please call the emergency room (03-3941-3211) and ask for the urologist on duty.

- Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital

(Principal investigator) Masaya Ito, Department of Urology (ext. 4021)

(Subinvestigator) Masahiro Toide, Department of Urology (ext. 4021)

At night (5:00–9:00 p.m.) and on holidays, please call the emergency room (03-3823-2101) and ask for the doctor on duty in the Department of Nephrology and Urology.

- JA Toride Medical Center

(Principal investigator) Naoko Kawamura, Department of Urology

At night (5:00–9:00 p.m.) and on holidays, please call the emergency room (0297-74-5551) and ask for the urologist on duty.

18. Please contact the consultation service any time

If you have any questions or concerns about this study, please do not hesitate to contact your physician or the physician responsible for this study. In addition, there are other contact points at the following locations:

Department of Urology, Institute of Science Tokyo Hospital

Tel: 03-5803-6111 (ext. 5295) (weekdays 8:30–17:00 except Saturdays, Sundays, and holidays)

Complaint consultation

Clinical Trial Management Center, Institute of Science Tokyo Hospital

Tel: 03-5803-4575 (weekdays 8:30–17:00 except Saturdays, Sundays, and holidays)

19. Others

The Accreditation Committee for Clinical Research is responsible for reviewing and confirming initial applications, applications for changes, applications for minor changes, periodic reports, reports of diseases, reports of major nonconformities, reports of discontinuation, reports of termination, and providing a written opinion to the principal investigator.

Name of accreditation committee: Institute of Science Tokyo Clinical Research Review Committee

Contact for inquiries and complaints about the accreditation committee: Clinical Trial Management Center

Tel: 03-5803-4575 (weekdays 8:30–17:00 except Saturdays, Sundays, and holidays)