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

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Complete List of Authors:	Yamamoto, Takanobu; Tokyo Metropolitan Tama-Nambu Chiiki Hospital, Urology Yoshida, Soichiro; Institute of Science Tokyo, urology Maezawa, Yuya; Tsuchiura Kyodo General Hospital, urology Tamiya, Takashi; Japanese Red Cross Saitama Hospital, urology Toide, Masahiro; Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, urology Fukushima, Hiroshi; Institute of Science Tokyo, urology Uehara, Sho; Showa General Hospital, urology Araki, Saori; Kohnodai Hospital, National Center for Global Health and Medicine, urology Ito, Masaya; Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, urology Kobayashi, Shuichiro; Japanese Red Cross Saitama Hospital, urology Yoshinaga, Atsushi ; Soka Municipal Hospital, urology Kawamura, Naoko; JA Toride Medical Center, urology Takazawa, Ryoji; Tokyo Metropolitan Ohtsuka Hospital, urology Sakai, Yasuyuki; Tsuchiura Kyodo General Hospital, urology Ootsuka, Yukihiro; Japanese Red Cross Oomori Hospital, urology Tsukamoto, Tetsuro; Showa General Hospital, urology Nagahama, Katsushi; Kohnodai Hospital, National Center for Global Health and Medicine, urology Tanaka, Hajime; Institute of Science Tokyo, urology Kitabayashi, Ryo; Institute of Science Tokyo, Clinical Biostatistics Hanazawa, Ryoichi; Institute of Science Tokyo, Clinical Biostatistics Ishiguro, Megumi; Institute of Science Tokyo, Health Science Research & Development Center Sato, Hiroyuki; Institute of Science Tokyo, Department of Clinical Biostatistics Koike, Ryuji; Institute of Science Tokyo, Health Science Research & Development Center Fujii, Yasuhisa; Institute of Science Tokyo, urology
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Title

Add-on or switch to vibegron in patients with overactive bladder insufficiently responding to initial 4-week antimuscarinics: A randomized, parallel-group, multicenter trial (**ADVISR**)

Takanobu Yamamoto[1], Soichiro Yoshida[2], Yuya Maezawa[3], Takashi Tamiya[4], Masahiro Toide[5], Hiroshi Fukushima[2], Sho Uehara[6], Saori Araki[7], Masaya Ito[5], Shuichiro Kobayashi[4], Atsushi Yoshinaga[8], Naoko Kawamura[9], Ryoji Takazawa[10], Yasuyuki Sakai[3], Yukihiro Ootsuka[11], Tetsuro Tsukamoto[6], Katsushi Nagahama[7], Hajime Tanaka[2], Ryo Kitabayashi[12], Ryoichi Hanazawa[12], Megumi Ishiguro[13], Hiroyuki Sato[12], Ryuji Koike[13], Yasuhisa Fujii[2]

[1] Department of Urology, Tokyo Metropolitan Tama-Nambu Chiiki Hospital, Tokyo, Japan.

[2] Department of Urology, Institute of Science Tokyo, Tokyo, Japan.

[3] Department of Urology, Tsuchiura Kyodo General Hospital, Ibaraki, Japan.

[4] Department of Urology, Japanese Red Cross Saitama Hospital, Saitama, Japan.

[5] Department of Urology, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan.

[6] Department of Urology, Showa General Hospital, Tokyo, Japan.

[7] Department of Urology, Kohnodai Hospital, National Center for Global Health and Medicine, Chiba, Japan.

[8] Department of Urology, Soka Municipal Hospital, Saitama, Japan.

[9] Department of Urology, JA Toride Medical Center, Ibaraki, Japan.

[10] Department of Urology, Tokyo Metropolitan Ohtsuka Hospital, Tokyo, Japan.

[11] Department of Urology, Japanese Red Cross Oomori Hospital, Tokyo, Japan.

[12] Department of Clinical Biostatistics, Institute of Science Tokyo, Tokyo, Japan.

[13] Health Science Research & Development Center, Institute of Science Tokyo, Tokyo, Japan.

Correspondence: Soichiro Yoshida, MD, PhD

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Department of Urology, Institute of Science Tokyo

1-5-45 Yushima, Bunkyo-Ku, Tokyo 113–8510, Japan.

Tel: +81 3-3813-6111; Fax: +81 3-3813-6111

Email: s-yoshida.uro@tmd.ac.jp

Keywords

Vibegron, β3 receptor agonists, antimuscarinics, OAB

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Abstract

Introduction

Overactive bladder (OAB) is a condition characterized by urinary urgency, often accompanied by frequency and nocturia. Antimuscarinics and β3 receptor agonists are first-line therapies that improve urinary symptoms and the quality of life. For insufficient antimuscarinic response, options include dose increase, switching medications, or combination therapy. However, evidence for these strategies, especially combinations with vibegron, is limited and needs further study.

Methods and Analysis

The study is designed as a randomized, open-label, parallel-group, multicenter trial conducted in Japan□. A total 110 patients with OAB who did not respond adequately to the initial 4-week antimuscarinics treatment will be randomized in a 1:1 ratio into two groups: an add-on group in which vibegron 50 mg/day is added to the current antimuscarinic drug and a switch group in which the current antimuscarinics is discontinued and replaced with vibegron 50 mg/day□. The primary endpoint is the inter-group comparison of changes in daily urinary frequency between the add-on group and the switch group at 12 weeks after the initiation of protocol treatment□. The primary analysis aims to confirm the non-inferiority of the switch group compared to the add-on group using a Bayesian mixed model for repeated measures. Non-inferiority will be confirmed if the posterior probability that the difference in the change urinary frequency at 12 weeks between the two groups falls within the non-inferiority margin of one-time is 80% or greater.

Ethics and Dissemination

The trial has been reviewed and approved by the Institute of Science Tokyo Certified Clinical Research Review Board (approval number: NR2024-001)□. Participants will provide informed consent to participate before taking part in the study. Results will be reported in a separate publication.

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Trial Registration number

Japan Registry of Clinical Trials (jRCT) (jRCTs031240134).

Strengths and limitations of this study

⇒ This is the first randomized trial assessing the non-inferiority of switching to vibegron following antimuscarinic therapy in patients with OAB.

⇒ The adoption of Bayesian statistics, an innovative approach in the ADVISR trial, is expected to provide deeper insights into OAB treatment and more precise treatment effect evaluation.

⇒ This open-label randomized controlled trial with unblinded participants and therapists study has an inherent risk of selection bias.

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Introduction

Overactive bladder (OAB) is a condition characterized by urinary urgency, often accompanied by frequency and nocturia, with or without urgency urinary incontinence (UUI). 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. OAB is diagnosed when urinary urgency occurs at least once a week and the total Overactive Bladder Symptom Score (OABSS) is 3 or higher. A comprehensive Japanese epidemiological study of patients aged 40 and above revealed that, in 2012, the prevalence of OAB symptoms and urinary urgency was 14.1% for both [1]. This study defined OAB symptoms as urinating eight or more times daily and experiencing urgency at least once weekly. Based on this research using Japan's 2012 population data, an estimated 10.4 million individuals were affected by OAB symptoms [1].

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. The 2024 guidelines from the American Urological Association (AUA) and the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU) recommend that clinicians offer antimuscarinics or β3 receptor agonists as evidence-level grade A to improve urinary urgency, frequency, and/or urgency incontinence in patients with OAB [2]. Clinical studies have also demonstrated that OAB agents significantly improve other outcomes of interest, including overall and disease-specific quality of life (QOL), treatment satisfaction, and work productivity [2].

When 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 [3]. In Japanese guidelines, switching from antimuscarinics to β3 receptor agonists is expected to reduce antimuscarinic-specific adverse effects such as dry mouth and constipation, and is recommended as grade B [4]. However, the efficacy of this switch in improving symptoms in patients who do not respond adequately to antimuscarinics is not yet well established and remains a grade C1 recommendation [4]. For patients who do not

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respond adequately to antimuscarinics, a combination therapy with β3 receptor agonists is also an option. The 2024 AUA/SUFU guidelines recommend the combination of antimuscarinics and β3 receptor agonists as a grade B recommendation for patients with OAB who do not achieve sufficient improvement with monotherapy [2]. In Japan, only the combination of antimuscarinics solifenacin succinate and β3 receptor agonists mirabegron is recommended for this combination therapy [4]. Several clinical trials have shown that this combination therapy significantly reduces daily urination frequency and urinary incontinence episodes in patients who did not respond adequately to the antimuscarinic drug solifenacin succinate alone [5-10]. However, evidence for the combination of other antimuscarinics and mirabegron is currently limited.

A Phase IIb clinical trial demonstrated that combining β3 receptor agonists vibegron 100 mg/day with antimuscarinic drug tolterodine 4 mg/day significantly reduced both the mean daily urination frequency and urinary urgency episodes compared with tolterodine alone [11]. However, the efficacy of combining antimuscarinics with the standard Japanese vibegron dose (50 mg/day) remains inadequately evaluated. In a Phase III long-term clinical trial conducted in Japan to evaluate the safety and efficacy of vibegron 50 mg/day for 52 weeks, antimuscarinics were concomitantly administered in some cases, but the efficacy and safety of these drugs have not been fully evaluated [12]. In other research, Tachikawa et al. reported real-world data on the efficacy and safety of vibegron, but cases of concomitant use with antimuscarinics were excluded from the analysis [13]. While numerous studies have reported on the efficacy and safety of mirabegron in combination with antimuscarinics for secondary OAB treatment, research on vibegron remains scarce, resulting in a significant evidence gap [5-10].

In this Phase II randomized trial—**AD**d-on or switch to **V**ibegron in patients with overactive bladder **I**n**S**ufficiently **R**esponding to initial 4-week antimuscarinics (**ADVISR** trial)—we will assess vibegron's efficacy and safety in two scenarios: as an adjunct to antimuscarinics and as their replacement.

Methods and analysis

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Trial design

This study is a randomized, open-label, parallel-group, multicenter trial conducted in Japan. Participating institutions include Institute of Science Tokyo, Tokyo Metropolitan Tama-Nambu Chiiki Hospital, Japanese Red Cross Oomori Hospital, Showa General Hospital, Kohnodai Hospital, National Center for Global Health and Medicine, Saitama Red Cross Hospital, Soka Municipal Hospital, Tsuchiura Kyodo General Hospital, Tokyo Metropolitan Ohtsuka Hospital, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, and the JA Toride Medical Center.

Patients with OAB who did not respond adequately to the initial 4-week antimuscarinics treatment will be randomized in a 1:1 ratio into two groups: an add-on group in which vibegron 50 mg/day is added to the antimuscarinic drug they were taking, and a switch group in which the antimuscarinics they were taking is discontinued and replaced with vibegron 50 mg/day. A dynamic allocation method (i.e., minimization) with a random element in treatment assignment via an Interactive Web Response Systems is used with the following stratification factors: age (≥ 75 years, < 75 years), sex (men, women), and average daily urinary frequency (≥ 10 times, < 10 times). The primary endpoint is the inter-group comparison of changes in daily urinary frequency between the add-on group and the switch group at 12 weeks after the initiation of protocol treatment.

The study protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT: see Additional File 1). This trial has been reviewed and approved by the Institute of Science Tokyo Certified Clinical Research Review Board (approval number: NR2024-001) and was registered in the Japan Registry of Clinical Trials (jRCT) on June 3, 2024 (registration number: jRCTs031240134) [14].

Participants

The following inclusion criteria will be used for this trial:

- Patients are aged 18 years or older at the time of enrollment.

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- Patients have been 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 are willing and able to accurately complete the voiding diary/questionnaire, including measuring urine output over a 3-day period.
- Patients are willing and able to follow and comply with the study protocol, including study visits and tests.
- Patients fully understand the study content and have given their written consent.

The following exclusion criteria will be used for this trial:

- Patients have clinically significant bladder outlet obstruction.
- Patients have high residual urine volume (>150 ml).
- Patients have significant stress incontinence or mixed incontinence in which stress incontinence is the predominant factor.
- Patients use a continuously placed urinary catheter or clean intermittent catheterization.
- Patients are 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 are 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 intravesical botulinum toxin injection).

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- Patients have chronic inflammatory disease or malignant disease in the pelvic region.
- Patients 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 have a history of hypersensitivity to the components of vibegron.
- Patients are pregnant, potentially pregnant, or lactating.
- Patients are deemed ineligible by the principal investigator or co-investigator for medical, psychological, or other reasons.

Study population and recruitment

In accordance with the inclusion and exclusion criteria, we will enroll patients with OAB who have responded insufficiently to initial 4-week antimuscarinics. The physician in charge will obtain informed consent and written consent forms from patients prior to study enrollment. The consent forms and explanatory documents provided to the participants are shown in Additional File 2 and Additional File 3.

After inclusion, patients will be assigned randomly to either the add-on group (vibegron added to current antimuscarinic) or the switch group (switch to vibegron from current antimuscarinic) in a 1:1 ratio. This randomization will be based on the minimization method, using age (≥75 years/<75 years), sex (male/female), and mean daily urinary frequency (≥10 times/<10 times) as stratification factors. The process will be conducted in an open-label fashion, utilizing a computer-generated minimized randomization allocation sequence as part of the electronic data capture (EDC) system.

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Interventions

Figure 1 outlines the study procedures. Both groups will receive 50 mg of vibegron daily for OAB treatment. The add-on group will continue their current antimuscarinic alongside vibegron, while the switch group will discontinue their antimuscarinic and take only vibegron. This study does not use a placebo.

If a patient experiences an adverse reaction to vibegron administration and/or antimuscarinics administration, its severity will be assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [15]. The medication may be temporarily withdrawn or permanently discontinued based on this assessment. For grade 3 or higher constipation, dry mouth, or urinary tract infection, vibegron administration will be paused until the condition improves to grade 2 or lower. Treatment can then resume. However, if these adverse events persist for more than 14 days, vibegron will be discontinued.

Follow-up, data collection and data protection

Patients will be seen every 4 weeks for 3 months following trial enrollment. At each visit, a 3-day voiding diary, OABSS, International Prostate Symptom Score (IPSS), and residual urine volume will be evaluated (Fig. 2). Additionally, adverse events related to treatment will be assessed using CTCAE version 5.0. To enhance monitoring adherence, the physician in charge will explain the importance of follow-up tests during patient visits and encourage participation in the study's follow-up process. To ensure data quality, a clinical research coordinator will enter data from medical records, and central monitoring will be implemented. To safeguard patients' personal information, each patient will be assigned a unique identification code. All data will be stored as password-protected electronic files on the EDC system before, during, and after the study, with access restricted to investigators only.

Outcome Measures

Primary outcome measure

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The primary endpoint is the inter-group comparison of the change in daily voiding frequency between the add-on and switch groups at 12 weeks after initiating protocol treatment. Daily urinary frequency will be calculated as the average from 3-day urinary diaries immediately preceding the assessment date.

Secondary outcome measure

Secondary outcomes include:

1) Inter-group comparison of the change in daily urinary frequency between the add-on and switch groups at 4 and 8 weeks after protocol treatment initiation.
2) Inter-group comparison of the change in daytime urinary frequency between the add-on and switch groups at 4, 8, and 12 weeks after protocol treatment initiation.
3) Inter-group comparison of the change in nocturnal urinary frequency between the add-on and switch groups at 4, 8, and 12 weeks after protocol treatment initiation.
4) Inter-group comparison of the change in daily urinary incontinence frequency between the add-on and switch groups at 4, 8, and 12 weeks after protocol treatment initiation.
5) Inter-group comparison of the change in OABSS scores and total score between the add-on and switch groups at 4, 8, and 12 weeks after protocol treatment initiation.
6) Inter-group comparison of the changes in IPSS/QOL scores and total scores between the add-on and switch groups at 4, 8, and 12 weeks after protocol treatment initiation.
7) Intra-group comparison of the change in daily urinary frequency in both the add-on and switch groups at 4, 8, and 12 weeks after protocol treatment initiation.
8) Intra-group comparison of the change in daytime urinary frequency in both the add-on and switch groups at 4, 8, and 12 weeks after protocol treatment initiation.
9) Intra-group comparison of the change in nocturnal urinary frequency in both the add-on and switch groups at 4, 8, and 12 weeks after protocol treatment initiation.
10) Intra-group comparison of the change in daily urinary incontinence frequency in both the add-on and switch groups at 4, 8, and 12 weeks after protocol treatment initiation.

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11) Intra-group comparison of the change in OABSS scores and total score in both the add-on and switch groups at 4, 8, and 12 weeks after protocol treatment initiation.

12) Intra-group comparison of the change in IPSS/QOL scores and total score in both the add-on and switch groups at 4, 8, and 12 weeks after protocol treatment initiation.

Safety endpoints

The safety endpoints for this study are as follows:

1) Incidence and severity of adverse events. These will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) version 27.0 [16], with severity graded according to the CTCAE version 5.0 [15].
2) Incidence of serious adverse events.
3) The proportion of patients discontinuing treatment due to adverse events.

Research drug

The investigational drug is Beova®, with the identification code 2590017F1025 and the chemical name vibegron. This study is covered by clinical research insurance. Compensation may be provided for adverse effects caused by vibegron administration that are not listed among its known possible adverse effects.

Determination of sample size

The target sample size is calculated to confirm the non-inferiority of the switch group compared to the add-on group for the primary endpoint, which is the change in daily voiding frequency at 12 weeks after initiation of protocol treatment. A Bayesian mixed effects model for repeated measures (MMRM) is employed to evaluate non-inferiority, with the success criteria defined as a posterior probability of at least 80% that the between-group difference in change in daily voiding frequency (switch group – add-on group) at 12 weeks would be less than the non-inferiority margin of one-time. With reference to the clinical trial results of mirabegron, a β3 receptor agonists [9, 17], we

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assume that the change in daily voiding frequency at 4, 8, and 12 weeks would be −0.6, −1.25, and −1.9 times in the switch group, and −0.7, −1.4, −2.1 times in the add-on group, respectively. Additionally, we assume a common standard deviation of 2.1 and a correlation coefficient of 0.8. Under these assumptions, the required sample size to achieve an 80% or higher probability of meeting the non-inferiority criterion is 50 patients per group. To account for a 10% dropout rate, the target sample size is set at 55 patients per group (110 patients in total).

Statistical analysis

All analyses for efficacy endpoints will be performed in the full analysis set (FAS), with the per protocol set (PPS) as a reference analysis population. The FAS will include all randomized patients excluding: 1) patients who have never received any protocol treatment; 2) patients who do not have any post-randomization data; and 3) patients who violate the well-defined and objectively determinable selection and exclusion criteria. The PPS will consist of the population from which the following patients are excluded from the FAS: 1) patients who were unable to properly complete the voiding diary, 2) patients that were retrospectively found to meet any of the exclusion criteria, and 3) patients found to have serious protocol violations. The analysis methods for each efficacy endpoint are as follows:

1) Analysis for the primary outcome

The primary analysis will employ a Bayesian MMRM including the treatment group, the interaction between treatment group and time point, and the interaction between baseline value and time point as fixed effects. The covariance structure for repeated measurements within each patient will initially be specified as unstructured; however, if convergence issues arise, it will be adjusted to a first-order autoregressive or compound symmetry structure in that order. Non-informative priors will be used for all parameters, and no imputation will be applied for missing data.

Using this model, the maximum a posteriori estimator (MAP) and 95% highest posterior density (HPD) intervals for changes in daily voiding frequency at 4, 8, and 12 weeks will be derived for each group. Additionally, the MAP and 95% HPD intervals for the differences in changes between

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the treatment groups at these time points will be estimated. The posterior distribution of the difference in the change in daily voiding frequency at 12 weeks will be evaluated to determine whether the non-inferiority criterion is met.

2) Analysis for the secondary outcomes

For the secondary outcomes 1) to 6), the same analysis will be conducted using Bayesian MMRM as for the primary outcome. However, non-inferiority will be evaluated only for the secondary outcome 1), and the posterior probability of the difference in the change in daily voiding frequency between the treatment groups (switch group – add-on group) at 4 and 8 weeks is lower than the non-inferiority margin of one-time will be evaluated.

For the secondary outcomes 7) to 12), a frequency-based MMRM will be performed. The model includes the treatment group, the interaction between treatment group and time point, and the interaction between baseline value and time point as fixed effects. The covariance structure for repeated measurements within each patient will initially be specified as unstructured; however, if convergence issues arise, it will be modified to a first-order autoregressive or compound symmetry structure in that order. No imputation will be performed for missing data.

Using this model, the least-squares mean, 95% confidence interval, and p-value for outcomes at weeks 4, 8, and 12 will be calculated for each group.

3) Analysis for the safety outcomes

The safety analysis will be performed in the safety analysis set (SAS) which is defined the population will be randomized and will receive the protocol treatment. The data from the SAS will be analyzed by the actual treatment that subject received. Adverse event data will be listed individually and summarized by the number and proportion of patients for each treatment group in the SAS. The number and proportion of patients discontinuing treatment due to adverse events alse summarized in the SAS.

No interim analysis will be performed in this study.

Patient and public involvement

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Patients or the public will not be involved in the design, or conduct, or reporting, or dissemination plans of our research.

Dissemination

The study results will be submitted for publication in a peer-reviewed journal and presented at national and international scientific conferences.

Discussion

This study presents the protocol for an open-label randomized trial comparing vibegron with or without antimuscarinics in patients with OAB who have responded insufficiently to initial treatment. To our knowledge, this randomized trial is the first assessing the non-inferiority of switching to vibegron following antimuscarinic in patients with OAB. The study's significance lies in its scientific evaluation of secondary treatment options' effectiveness for OAB.

The efficacy of vibegron monotherapy in patients with OAB is well-documented, with Phase III comparative studies demonstrating a significant reduction in mean daily urinary frequency compared with placebo (imidafenacin 0.2 mg/day) [12]. However, research on combination therapy with antimuscarinics is scarce, highlighting the need for further investigation in this area. While mirabegron, another β3 receptor agonist, has shown promising effects, studies on vibegron as a secondary treatment for OAB patients already using antimuscarinics remain limited [13].

In this study, we aim to evaluate the efficacy and safety of two treatment approaches: adding vibegron to antimuscarinics and switching from antimuscarinics to vibegron. By comparing these two groups, we can determine which treatment option offers the best balance of benefits and risks. If we can demonstrate that vibegron is non-inferior as a secondary treatment for OAB, it could help address the growing issue of polypharmacy in older people. This, in turn, may significantly improve patients' QOL and reduce healthcare costs. As an open-label randomized controlled trial with unblinded participants and therapists, this study has an inherent risk of selection bias. This limitation requires careful consideration when interpreting the results.

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The frequentist approach, which evaluates treatment effects using observed data and quantifies certainty through confidence intervals and *p*-values, is a standard method for evaluating efficacy and safety. The ADVISR trial, unlike conventional OAB clinical trials, adopts Bayesian statistical analysis. Bayesian methods offers a valuable option for quantitatively assessing the certainty of results through the posterior distribution of the treatment effect, especially in small-scale clinical trials where hypothesis testing based on frequentist methods may be less interpretable. However, caution is needed in interpreting Bayesian results due to potential subjectivity in setting prior probabilities. The ADVISR trial addresses this using noninformative prior distributions, determining the posterior distribution primarily based on observed data. This minimizes arbitrariness in prior distribution selection while enabling efficacy evaluation. The adoption of Bayesian statistics in the ADVISR trial is expected to provide deeper insights into OAB treatment and more precise treatment effect evaluation. This innovative approach could transform the entire process from clinical research design to result interpretation and clinical decision-making, potentially setting a new standard for more patient-centered, effective, and efficient clinical trial designs.

Conclusion

This protocol describes the design of a randomized, open-label, parallel-group, multicenter trial that will evaluate the efficacy of vibegron in patients with OAB insufficiently responding to initial 4-week antimuscarinics. The results of this study are expected to provide a solid foundation for future large-scale prospective randomized trials.

List of abbreviations

AUA, American Urological Association; CTCAE, Common Terminology Criteria for Adverse Events; EDC, electronic data capture; FAS, full analysis set; ICIQ-SF, International Consultation On Incontinence Questionnaire-Short Form; IPSS, International Prostate Symptom Score; JCOG, Japan Clinical Oncology Group; JMO, Japanese Maintenance Organization; jRCT, Japan Registry of Clinical Trials; MedDRA, Medical Dictionary for Regulatory Activities; MMRM, mixed effects

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model for repeated measures; OAB, overactive bladder; OABSS, Overactive Bladder Symptom Score; PPS, per protocol set; QOL, quality of life; SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials; SUFU, the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction; UUI, urgency urinary incontinence.

Ethics and dissemination

The trial has been reviewed and approved by the Institute of Science Tokyo Certified Clinical Research Review Board (approval number: NR2024-001) and was registered in the Japan Registry of Clinical Trials (jRCT) on June 3, 2024 (registration number: jRCTs031240134) [14]. Participants will provide informed consent to participate before taking part in the study. Results will be reported in a separate publication.

Availability of data and materials

Data sharing is not applicable to this article because the current study is still open for inclusion of patients.

Competing interests

The authors have no competing interests.

Funding

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Author contributions

All authors contributed to the conception and conduct of this clinical trial. TY and SY designed and

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wrote the protocol and the manuscript. MI and HS designed and discussed the protocol. YM, TT, MT, KF, SU, SA, MI, SK, AY, NK, RT, YS, YO, TT, KN, HT and YF helped with implementation. MI will monitor the data set. RH and RK designed the statistical analysis. SY is the principal investigator. All authors contributed to and approved the final version of the manuscript.

Word counts

3857 words

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Figure legends

Figure 1 Design of the ADVISR trial.

Figure 2 Intervention and assessment schedule for the ADVISR trial according to the Recommendations for Interventional Trials (SPIRIT). Patients will visit the hospital every 4 weeks until approximately 12 weeks to collect data. *According to the Common Toxicity Criteria for Adverse Events (CTCAE v 5.0). Abbreviations: ICIQ-SF, International Consultation on Incontinence Questionnaire-Short Form; IPSS/QOL, International Prostate Symptom Score/quality of life; OABSS, Overactive Bladder Symptom Score.

Additional File 1. SPIRIT 2013 Checklist for the ADVISR trial.

Additional File 2. The explanatory document is translated into English (the original document was written in Japanese).

Additional File 3. The consent form is given to participants.

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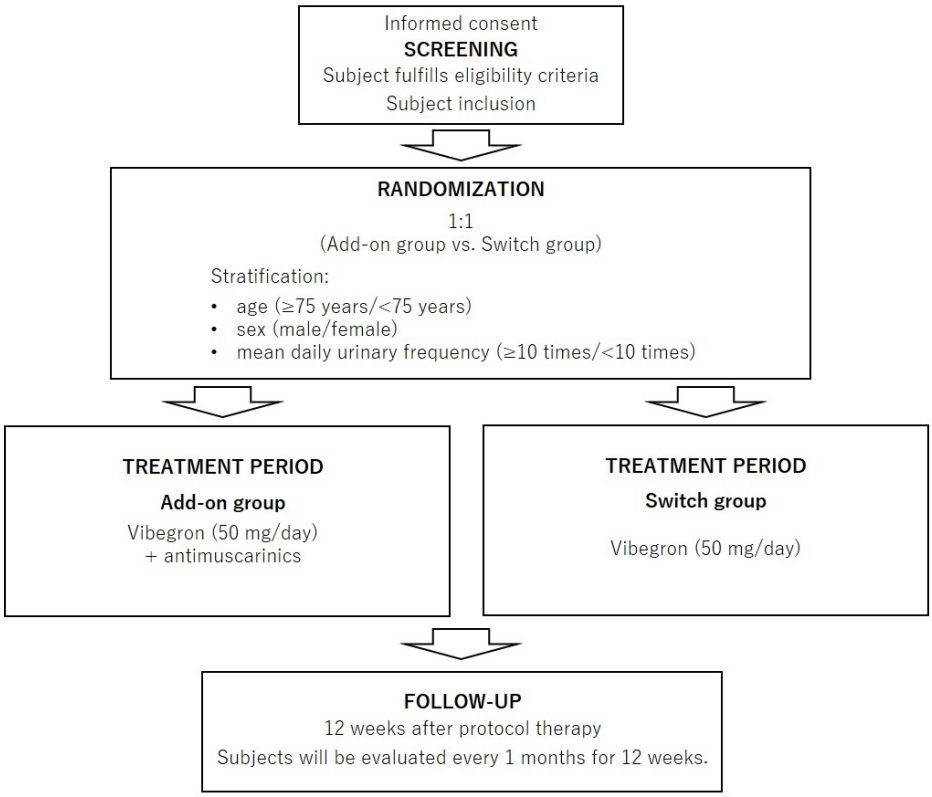

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	Screening period	Protocol therapy 4th week	Protocol therapy 8th week	Protocol therapy 12th week	Protocol therapy at discontinuation
Informed consent	×				
Hospital visit	×	×	×	×	×
Check patient background	×				
Voiding diary check	×	×	×	×	×
OABSS 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)

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	7
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	7
Protocol version	#3	Date and version identifier	7
Funding	#4	Sources and types of financial, material, and other support	17
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	17

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Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	17
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5-6
Objectives	#7	Specific objectives or hypotheses	5-6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic,	9

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		academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-9
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	10
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	10
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8-9
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10-12
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12-13
Recruitment	#15	Strategies for achieving adequate participant enrolment	12-13

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		to reach target sample size	
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known.	10

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		Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13-14
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13-14
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13-14
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	17
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Harms	#22	Plans for collecting, assessing, reporting, and managing	10

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		solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	7
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	7
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	10
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	10
Dissemination policy:	#31a	Plans for investigators and sponsor to communicate	14

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trial results		trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	17
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A, no granting public access is set up in this trial
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Additional file 2, Explanatory documents to the participants and Additional file 3, Consent form
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A, no biological samples collected.

Notes:

- 31c: N/A, no granting public access is set up in this trial
- 32: Additional file 2, Explanatory documents to the participants and Additional file 3, Consent form
- 33: N/A, no biological samples collected. The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative Commons Attribution License CC-BY-NC. This checklist was completed on 26. September 2024 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

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Add-on or switch to vibegron in patients with overactive bladder insufficiently responding to initial 4-week antimuscarinics: A randomized, parallel-group, multicenter trial (ADVISR) Protcol

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Primary Subject Heading:	Urology
Secondary Subject Heading:	Research methods

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Keywords:	UROLOGY, Bladder disorders < UROLOGY, Urinary incontinences < UROLOGY

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Title

Add-on or switch to vibegron in patients with overactive bladder insufficiently responding to initial 4-week antimuscarinics: A randomized, parallel-group, multicenter trial (**ADVISR**) **Protocol**

Takanobu Yamamoto[1], Soichiro Yoshida[2], Yuya Maezawa[3], Takashi Tamiya[4], Masahiro Toide[5], Hiroshi Fukushima[2], Sho Uehara[6], Saori Araki[7], Masaya Ito[5], Shuichiro Kobayashi[4], Atsushi Yoshinaga[8], Naoko Kawamura[9], Ryoji Takazawa[10], Yasuyuki Sakai[3], Yukihiro Ootsuka[11], Tetsuro Tsukamoto[6], Katsushi Nagahama[7], Hajime Tanaka[2], Ryo Kitabayashi[12], Ryoichi Hanazawa[12], Megumi Ishiguro[13], Hiroyuki Sato[12], Ryuji Koike[13], Yasuhisa Fujii[2]

[1] Department of Urology, Tokyo Metropolitan Tama-Nambu Chiiki Hospital, Tokyo, Japan.

[2] Department of Urology, Institute of Science Tokyo, Tokyo, Japan.

[3] Department of Urology, Tsuchiura Kyodo General Hospital, Ibaraki, Japan.

[4] Department of Urology, Japanese Red Cross Saitama Hospital, Saitama, Japan.

[5] Department of Urology, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan.

[6] Department of Urology, Showa General Hospital, Tokyo, Japan.

[7] Department of Urology, Kohnodai Hospital, National Center for Global Health and Medicine, Chiba, Japan.

[8] Department of Urology, Soka Municipal Hospital, Saitama, Japan.

[9] Department of Urology, JA Toride Medical Center, Ibaraki, Japan.

[10] Department of Urology, Tokyo Metropolitan Ohtsuka Hospital, Tokyo, Japan.

[11] Department of Urology, Japanese Red Cross Oomori Hospital, Tokyo, Japan.

[12] Department of Clinical Biostatistics, Institute of Science Tokyo, Tokyo, Japan.

[13] Health Science Research & Development Center, Institute of Science Tokyo, Tokyo, Japan.

Correspondence: Soichiro Yoshida, MD, PhD

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Department of Urology, Institute of Science Tokyo

1-5-45 Yushima, Bunkyo-Ku, Tokyo 113–8510, Japan.

Tel: +81 3-3813-6111; Fax: +81 3-3813-6111

Email: s-yoshida.uro@tmd.ac.jp

Keywords

Vibegron, β3 receptor agonists, antimuscarinics, OAB

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Abstract

Introduction

Overactive bladder (OAB) is a condition characterized by urinary urgency, often accompanied by frequency and nocturia. Antimuscarinics and β3 receptor agonists are first-line therapies that improve urinary symptoms and the quality of life. For insufficient antimuscarinic response, options include dose increase, switching medications, or combination therapy. However, evidence for these strategies, especially combinations with vibegron, is limited and needs further study.

Methods and Analysis

The study is designed as a randomized, open-label, parallel-group, multicenter trial conducted in Japan□. A total 110 patients with OAB who met the OAB criteria and did not respond adequately to the initial 4-week antimuscarinics treatment will be randomized in a 1:1 ratio into two groups: an add-on group in which vibegron 50 mg/day is added to the current antimuscarinic drug and a switch group in which the current antimuscarinics is discontinued and replaced with vibegron 50 mg/day□. The primary endpoint is the inter-group comparison of changes in daily urinary frequency between the add-on group and the switch group at 12 weeks after the initiation of protocol treatment□. The primary analysis aims to confirm the non-inferiority of the switch group compared to the add-on group using a Bayesian mixed model for repeated measures. Non-inferiority will be confirmed if the posterior probability that the difference in the change urinary frequency at 12 weeks between the two groups falls within the non-inferiority margin of one-time is 80% or greater.

Ethics and Dissemination

The trial has been reviewed and approved by the Institute of Science Tokyo Certified Clinical Research Review Board (approval number: NR2024-001)□. Participants will provide informed consent to participate before taking part in the study. Results will be reported in a separate publication.

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Trial Registration number

Japan Registry of Clinical Trials (jRCT) (jRCTs031240134).

Strengths and limitations of this study

⇒ The study is designed as a randomized, open-label, parallel-group, multicenter trial conducted to assess the non-inferiority of switching to vibegron following antimuscarinic therapy in patients with OAB.

⇒ The adoption of Bayesian statistics, an innovative approach in the ADVISR trial, is expected to provide deeper insights into OAB treatment and more precise treatment effect evaluation.

⇒ This open-label randomized controlled trial with unblinded participants and therapists study has an inherent risk of selection bias.

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Introduction

Overactive bladder (OAB) is a condition characterized by urinary urgency, often accompanied by frequency and nocturia, with or without urgency urinary incontinence (UUI). 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. OAB is diagnosed when urinary urgency occurs at least once a week and the total Overactive Bladder Symptom Score (OABSS) is 3 or higher. A comprehensive Japanese epidemiological study of patients aged 40 and above revealed that, in 2012, the prevalence of OAB symptoms and urinary urgency was 14.1% for both [1]. This study defined OAB symptoms as urinating eight or more times daily and experiencing urgency at least once weekly. Based on this research using Japan's 2012 population data, an estimated 10.4 million individuals were affected by OAB symptoms [1].

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. The 2024 guidelines from the American Urological Association (AUA) and the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU) recommend that clinicians offer antimuscarinics or β3 receptor agonists as evidence-level grade A to improve urinary urgency, frequency, and/or urgency incontinence in patients with OAB [2]. Clinical studies have also demonstrated that OAB agents significantly improve other outcomes of interest, including overall and disease-specific quality of life (QOL), treatment satisfaction, and work productivity [2].

When 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 [3]. In Japanese guidelines, switching from antimuscarinics to β3 receptor agonists is expected to reduce antimuscarinic-specific adverse effects such as dry mouth and constipation, and is recommended as grade B [4]. However, the efficacy of this switch in improving symptoms in patients who do not respond adequately to antimuscarinics is not yet well established and remains a grade C1 recommendation [4]. For patients who do not

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respond adequately to antimuscarinics, a combination therapy with β3 receptor agonists is also an option. The 2024 AUA/SUFU guidelines recommend the combination of antimuscarinics and β3 receptor agonists as a grade B recommendation for patients with OAB who do not achieve sufficient improvement with monotherapy [2]. In Japan, only the combination of antimuscarinics solifenacin succinate and β3 receptor agonists mirabegron is recommended for this combination therapy [4]. Several clinical trials have shown that this combination therapy significantly reduces daily urination frequency and urinary incontinence episodes in patients who did not respond adequately to the antimuscarinic drug solifenacin succinate alone [5-10]. However, evidence for the combination of other antimuscarinics and mirabegron is currently limited.

A Phase IIb clinical trial demonstrated that combining β3 receptor agonists vibegron 100 mg/day with antimuscarinic drug tolterodine 4 mg/day significantly reduced both the mean daily urination frequency and urinary urgency episodes compared with tolterodine alone [11]. However, the efficacy of combining antimuscarinics with the standard Japanese vibegron dose (50 mg/day) remains inadequately evaluated. In a Phase III long-term clinical trial conducted in Japan to evaluate the safety and efficacy of vibegron 50 mg/day for 52 weeks, antimuscarinics were concomitantly administered in some cases, but the efficacy and safety of these drugs have not been fully evaluated [12]. In other research, Tachikawa et al. reported real-world data on the efficacy and safety of vibegron, but cases of concomitant use with antimuscarinics were excluded from the analysis [13]. While numerous studies have reported on the efficacy and safety of mirabegron in combination with antimuscarinics for secondary OAB treatment, research on vibegron remains scarce, resulting in a significant evidence gap [5-10].

In this Phase II randomized trial—**AD**d-on or switch to **V**ibegron in patients with overactive bladder **I**n**S**ufficiently **R**esponding to initial 4-week antimuscarinics (**ADVISR** trial)—we will assess vibegron's efficacy and safety in two scenarios: as an adjunct to antimuscarinics and as their replacement.

Methods and analysis

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Trial design

This study is a randomized, open-label, parallel-group, multicenter trial conducted in Japan. Participating institutions include Institute of Science Tokyo, Tokyo Metropolitan Tama-Nambu Chiiki Hospital, Japanese Red Cross Oomori Hospital, Showa General Hospital, Kohnodai Hospital, National Center for Global Health and Medicine, Saitama Red Cross Hospital, Soka Municipal Hospital, Tsuchiura Kyodo General Hospital, Tokyo Metropolitan Ohtsuka Hospital, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, and the JA Toride Medical Center.

Patients with OAB who did not respond adequately to the initial 4-week antimuscarinics treatment will be randomized in a 1:1 ratio into two groups: an add-on group in which vibegron 50 mg/day is added to the antimuscarinic drug they were taking, and a switch group in which the antimuscarinics they were taking is discontinued and replaced with vibegron 50 mg/day. The definition of inadequate response was to meet the OAB criteria after initial 4-week antimuscarinics treatment. A dynamic allocation method (i.e., minimization) with a random element in treatment assignment via an Interactive Web Response Systems is used with the following stratification factors: age (≥ 75 years, < 75 years), sex (men, women), and average daily urinary frequency (≥ 10 times, < 10 times). The primary endpoint is the inter-group comparison of changes in daily urinary frequency between the add-on group and the switch group at 12 weeks after the initiation of protocol treatment.

The study protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT: see Additional File 1). This trial has been reviewed and approved by the Institute of Science Tokyo Certified Clinical Research Review Board (approval number: NR2024-001) and was registered in the Japan Registry of Clinical Trials (jRCT) on June 3, 2024 (registration number: jRCTs031240134) [14].

Participants

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The following inclusion criteria will be used for this trial:

- Patients are aged 18 years or older at the time of enrollment.
- Patients have been 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 are willing and able to accurately complete the voiding diary/questionnaire, including measuring urine output over a 3-day period.
- Patients are willing and able to follow and comply with the study protocol, including study visits and tests.
- Patients fully understand the study content and have given their written consent.

The following exclusion criteria will be used for this trial:

- Patients have clinically significant bladder outlet obstruction.
- Patients have high residual urine volume (>150 ml).
- Patients have significant stress incontinence or mixed incontinence in which stress incontinence is the predominant factor.
- Patients use a continuously placed urinary catheter or clean intermittent catheterization.
- Patients are 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 are determined by the principal investigator or co-investigator to have a history of

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disease or surgery that affects the assessment of OAB-related voiding (e.g., patients treated with intravesical botulinum toxin injection).

- Patients have chronic inflammatory disease or malignant disease in the pelvic region.
- Patients 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 have a history of hypersensitivity to the components of vibegron.
- Patients are pregnant, potentially pregnant, or lactating.
- Patients are deemed ineligible by the principal investigator or co-investigator for medical, psychological, or other reasons.

Study population and recruitment

In accordance with the inclusion and exclusion criteria, we will enroll patients with OAB who have responded insufficiently to initial 4-week antimuscarinics. The physician in charge will obtain informed consent and written consent forms from patients prior to study enrollment. The consent forms and explanatory documents provided to the participants are shown in Additional File 2 and Additional File 3.

After inclusion, patients will be assigned randomly to either the add-on group (vibegron added to current antimuscarinic) or the switch group (switch to vibegron from current antimuscarinic) in a 1:1 ratio. This randomization will be based on the minimization method, using age (≥75 years/<75 years), sex (male/female), and mean daily urinary frequency (≥10 times/<10 times) as stratification factors. The process will be conducted in an open-label fashion, utilizing a computer-generated minimized randomization allocation sequence as part of the electronic data

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capture (EDC) system.

Interventions

Figure 1 outlines the study procedures. Both groups will receive 50 mg of vibegron daily for OAB treatment. The add-on group will continue their current antimuscarinic alongside vibegron, while the switch group will discontinue their antimuscarinic and take only vibegron. This study does not use a placebo.

If a patient experiences an adverse reaction to vibegron administration and/or antimuscarinics administration, its severity will be assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [15]. The medication may be temporarily withdrawn or permanently discontinued based on this assessment. For grade 3 or higher constipation, dry mouth, or urinary tract infection, vibegron administration will be paused until the condition improves to grade 2 or lower. Treatment can then resume. However, if these adverse events persist for more than 14 days, vibegron will be discontinued.

Follow-up, data collection and data protection

Patients will be seen every 4 weeks for 3 months following trial enrollment. At each visit, a 3-day voiding diary, OABSS, International Prostate Symptom Score (IPSS), and residual urine volume will be evaluated (Fig. 2). Additionally, adverse events related to treatment will be assessed using CTCAE version 5.0. To enhance monitoring adherence, the physician in charge will explain the importance of follow-up tests during patient visits and encourage participation in the study's follow-up process. To ensure data quality, a clinical research coordinator will enter data from medical records, and central monitoring will be implemented. To safeguard patients' personal information, each patient will be assigned a unique identification code. All data will be stored as password-protected electronic files on the EDC system before, during, and after the study, with access restricted to investigators only.

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Outcome Measures

Primary outcome measure

The primary endpoint is the inter-group comparison of the change in daily voiding frequency between the add-on and switch groups at 12 weeks after initiating protocol treatment. Daily urinary frequency will be calculated as the average from 3-day urinary diaries immediately preceding the assessment date.

Secondary outcome measure

Secondary outcomes include:

1) Inter-group comparison of the change in daily urinary frequency between the add-on and switch groups at 4 and 8 weeks after protocol treatment initiation.
2) Inter-group comparison of the change in daytime urinary frequency between the add-on and switch groups at 4, 8, and 12 weeks after protocol treatment initiation.
3) Inter-group comparison of the change in nocturnal urinary frequency between the add-on and switch groups at 4, 8, and 12 weeks after protocol treatment initiation.
4) Inter-group comparison of the change in daily urinary incontinence frequency between the add-on and switch groups at 4, 8, and 12 weeks after protocol treatment initiation.
5) Inter-group comparison of the change in OABSS scores and total score between the add-on and switch groups at 4, 8, and 12 weeks after protocol treatment initiation.
6) Inter-group comparison of the changes in IPSS/QOL scores and total scores between the add-on and switch groups at 4, 8, and 12 weeks after protocol treatment initiation.
7) Intra-group comparison of the change in daily urinary frequency in both the add-on and switch groups at 4, 8, and 12 weeks after protocol treatment initiation.
8) Intra-group comparison of the change in daytime urinary frequency in both the add-on and switch groups at 4, 8, and 12 weeks after protocol treatment initiation.
9) Intra-group comparison of the change in nocturnal urinary frequency in both the add-on and switch groups at 4, 8, and 12 weeks after protocol treatment initiation.

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10) Intra-group comparison of the change in daily urinary incontinence frequency in both the add-on and switch groups at 4, 8, and 12 weeks after protocol treatment initiation.
11) Intra-group comparison of the change in OABSS scores and total score in both the add-on and switch groups at 4, 8, and 12 weeks after protocol treatment initiation.
12) Intra-group comparison of the change in IPSS/QOL scores and total score in both the add-on and switch groups at 4, 8, and 12 weeks after protocol treatment initiation.

Safety endpoints

The safety endpoints for this study are as follows:

1) Incidence and severity of adverse events. These will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) version 27.0 [16], with severity graded according to the CTCAE version 5.0 [15].
2) Incidence of serious adverse events.
3) The proportion of patients discontinuing treatment due to adverse events.

Research drug

The investigational drug is Beova®, with the identification code 2590017F1025 and the chemical name vibegron. This study is covered by clinical research insurance. Compensation may be provided for adverse effects caused by vibegron administration that are not listed among its known possible adverse effects.

Determination of sample size

The target sample size is calculated to confirm the non-inferiority of the switch group compared to the add-on group for the primary endpoint, which is the change in daily voiding frequency at 12 weeks after initiation of protocol treatment. A Bayesian mixed effects model for repeated measures (MMRM) is employed to evaluate non-inferiority, with the success criteria defined as a posterior probability of at least 80% that the between-group difference in change in daily voiding frequency

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(switch group – add-on group) at 12 weeks would be less than the non-inferiority margin of one-time. With reference to the clinical trial results of mirabegron, a β3 receptor agonists [9, 17], we assume that the change in daily voiding frequency at 4, 8, and 12 weeks would be −0.6, −1.25, and −1.9 times in the switch group, and −0.7, −1.4, −2.1 times in the add-on group, respectively. Additionally, we assume a common standard deviation of 2.1 and a correlation coefficient of 0.8. Under these assumptions, the required sample size to achieve an 80% or higher probability of meeting the non-inferiority criterion is 50 patients per group. To account for a 10% dropout rate, the target sample size is set at 55 patients per group (110 patients in total).

Statistical analysis

All analyses for efficacy endpoints will be performed in the full analysis set (FAS), with the per protocol set (PPS) as a reference analysis population. The FAS will include all randomized patients excluding: 1) patients who have never received any protocol treatment; 2) patients who do not have any post-randomization data; and 3) patients who violate the well-defined and objectively determinable selection and exclusion criteria. The PPS will consist of the population from which the following patients are excluded from the FAS: 1) patients who were unable to properly complete the voiding diary, 2) patients that were retrospectively found to meet any of the exclusion criteria, and 3) patients found to have serious protocol violations. The analysis methods for each efficacy endpoint are as follows:

1) Analysis for the primary outcome

The primary analysis will employ a Bayesian MMRM including the treatment group, the interaction between treatment group and time point, and the interaction between baseline value and time point as fixed effects. The covariance structure for repeated measurements within each patient will initially be specified as unstructured; however, if convergence issues arise, it will be adjusted to a first-order autoregressive or compound symmetry structure in that order. Non-informative priors will be used for all parameters, and no imputation will be applied for missing data.

Using this model, the maximum a posteriori estimator (MAP) and 95% highest posterior density

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(HPD) intervals for changes in daily voiding frequency at 4, 8, and 12 weeks will be derived for each group. Additionally, the MAP and 95% HPD intervals for the differences in changes between the treatment groups at these time points will be estimated. The posterior distribution of the difference in the change in daily voiding frequency at 12 weeks will be evaluated to determine whether the non-inferiority criterion is met.

2) Analysis for the secondary outcomes

For the secondary outcomes 1) to 6), the same analysis will be conducted using Bayesian MMRM as for the primary outcome. However, non-inferiority will be evaluated only for the secondary outcome 1), and the posterior probability of the difference in the change in daily voiding frequency between the treatment groups (switch group – add-on group) at 4 and 8 weeks is lower than the non-inferiority margin of one-time will be evaluated.

For the secondary outcomes 7) to 12), a frequency-based MMRM will be performed. The model includes the treatment group, the interaction between treatment group and time point, and the interaction between baseline value and time point as fixed effects. The covariance structure for repeated measurements within each patient will initially be specified as unstructured; however, if convergence issues arise, it will be modified to a first-order autoregressive or compound symmetry structure in that order. No imputation will be performed for missing data.

Using this model, the least-squares mean, 95% confidence interval, and p-value for outcomes at weeks 4, 8, and 12 will be calculated for each group.

3) Analysis for the safety outcomes

The safety analysis will be performed in the safety analysis set (SAS) which is defined the population will be randomized and will receive the protocol treatment. The data from the SAS will be analyzed by the actual treatment that subject received. Adverse event data will be listed individually and summarized by the number and proportion of patients for each treatment group in the SAS. The number and proportion of patients discontinuing treatment due to adverse events alse summarized in the SAS.

No interim analysis will be performed in this study.

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Patient and public involvement

Patients or the public will not be involved in the design, or conduct, or reporting, or dissemination plans of our research.

Dissemination

The study results will be submitted for publication in a peer-reviewed journal and presented at national and international scientific conferences.

Discussion

This study presents the protocol for an open-label randomized trial comparing vibegron with or without antimuscarinics in patients with OAB who have responded insufficiently to initial treatment. To our knowledge, this randomized trial is the first assessing the non-inferiority of switching to vibegron following antimuscarinic in patients with OAB. The study's significance lies in its scientific evaluation of secondary treatment options' effectiveness for OAB.

To evaluate OAB symptoms, OABSS and IPSS were used in this study in addition to the 3-day voiding diary; IPSS has been used to assess lower urinary tract symptoms and severity of benign prostatic obstruction in men, it is also useful to assess lower urinary tract dysfunction in women [18]. Hsiao et al. reported significantly higher IPSS storage subscore values were found in OAB patients with UUI, and it was well correlated with OABSS in women [19].

The efficacy of vibegron monotherapy in patients with OAB is well-documented, with Phase III comparative studies demonstrating a significant reduction in mean daily urinary frequency compared with placebo (imidafenacin 0.2 mg/day) [12]. However, research on combination therapy with antimuscarinics is scarce, highlighting the need for further investigation in this area. While mirabegron, another β3 receptor agonist, has shown promising effects, studies on vibegron as a secondary treatment for OAB patients already using antimuscarinics remain limited [13].

In this study, we aim to evaluate the efficacy and safety of two treatment approaches:

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adding vibegron to antimuscarinics and switching from antimuscarinics to vibegron. By comparing these two groups, we can determine which treatment option offers the best balance of benefits and risks. If we can demonstrate that vibegron is non-inferior as a secondary treatment for OAB, it could help address the growing issue of polypharmacy in older people. This, in turn, may significantly improve patients' QOL and reduce healthcare costs. As an open-label randomized controlled trial with unblinded participants and therapists, this study has an inherent risk of selection bias. This limitation requires careful consideration when interpreting the results.

The frequentist approach, which evaluates treatment effects using observed data and quantifies certainty through confidence intervals and *p*-values, is a standard method for evaluating efficacy and safety. The ADVISR trial, unlike conventional OAB clinical trials, adopts Bayesian statistical analysis. Bayesian methods offers a valuable option for quantitatively assessing the certainty of results through the posterior distribution of the treatment effect, especially in small-scale clinical trials where hypothesis testing based on frequentist methods may be less interpretable. However, caution is needed in interpreting Bayesian results due to potential subjectivity in setting prior probabilities. The ADVISR trial addresses this using noninformative prior distributions, determining the posterior distribution primarily based on observed data. This minimizes arbitrariness in prior distribution selection while enabling efficacy evaluation. The adoption of Bayesian statistics in the ADVISR trial is expected to provide deeper insights into OAB treatment and more precise treatment effect evaluation. This innovative approach could transform the entire process from clinical research design to result interpretation and clinical decision-making, potentially setting a new standard for more patient-centered, effective, and efficient clinical trial designs. The results of this study are expected to provide a solid foundation for future large-scale prospective randomized trials.

List of abbreviations

AUA, American Urological Association; CTCAE, Common Terminology Criteria for Adverse Events; EDC, electronic data capture; FAS, full analysis set; ICIQ-SF, International Consultation On

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Incontinence Questionnaire-Short Form; IPSS, International Prostate Symptom Score; JCOG, Japan Clinical Oncology Group; JMO, Japanese Maintenance Organization; jRCT, Japan Registry of Clinical Trials; MedDRA, Medical Dictionary for Regulatory Activities; MMRM, mixed effects model for repeated measures; OAB, overactive bladder; OABSS, Overactive Bladder Symptom Score; PPS, per protocol set; QOL, quality of life; SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials; SUFU, the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction; UUI, urgency urinary incontinence.

Ethics and dissemination

The trial has been reviewed and approved by the Institute of Science Tokyo Certified Clinical Research Review Board (approval number: NR2024-001) and was registered in the Japan Registry of Clinical Trials (jRCT) on June 3, 2024 (registration number: jRCTs031240134) [14]. Participants will provide informed consent to participate before taking part in the study. Results will be reported in a separate publication.

Availability of data and materials

Data sharing is not applicable to this article because the current study is still open for inclusion of patients.

Competing interests

The authors have no competing interests.

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Author contributions

All authors contributed to the conception and conduct of this clinical trial. TY and SY designed and wrote the protocol and the manuscript. MI and HS designed and discussed the protocol. YM, TT, MT, KF, SU, SA, MI, SK, AY, NK, RT, YS, YO, TT, KN, HT and YF helped with implementation. MI will monitor the data set. RH and RK designed the statistical analysis. SY is the principal investigator. TY is responsible for the overall content as guarantor. All authors contributed to and approved the final version of the manuscript.

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Figure legends

Figure 1 Design of the ADVISR trial.

Figure 2 Intervention and assessment schedule for the ADVISR trial according to the Recommendations for Interventional Trials (SPIRIT). Patients will visit the hospital every 4 weeks until approximately 12 weeks to collect data. *According to the Common Toxicity Criteria for Adverse Events (CTCAE v 5.0). Abbreviations: ICIQ-SF, International Consultation on Incontinence Questionnaire-Short Form; IPSS/QOL, International Prostate Symptom Score/quality of life; OABSS, Overactive Bladder Symptom Score.

Additional File 1. SPIRIT 2013 Checklist for the ADVISR trial.

Additional File 2. The explanatory document is translated into English.

Additional File 3. The consent form is given to participants.

Additional File 4. The original document of the explanatory document and the consent form written in Japanese.

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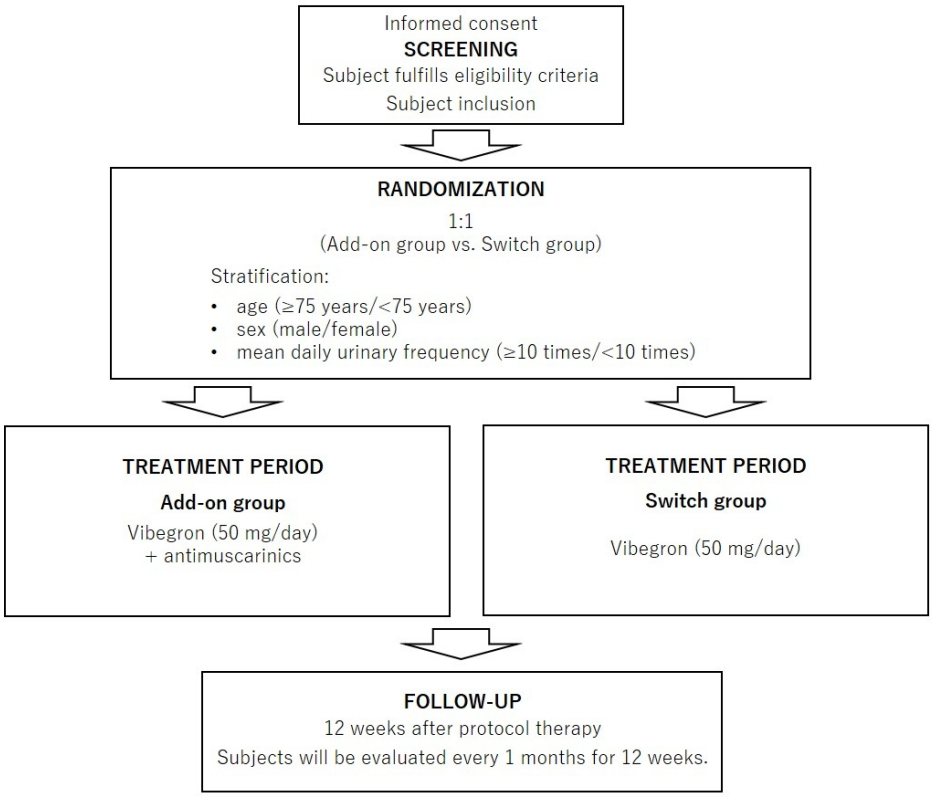

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	Screening period	Protocol therapy 4th week	Protocol therapy 8th week	Protocol therapy 12th week	Protocol therapy at discontinuation
Informed consent	×				
Hospital visit	×	×	×	×	×
Check patient background	×				
Voiding diary check	×	×	×	×	×
OABSS 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)

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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

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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:

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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%.

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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.

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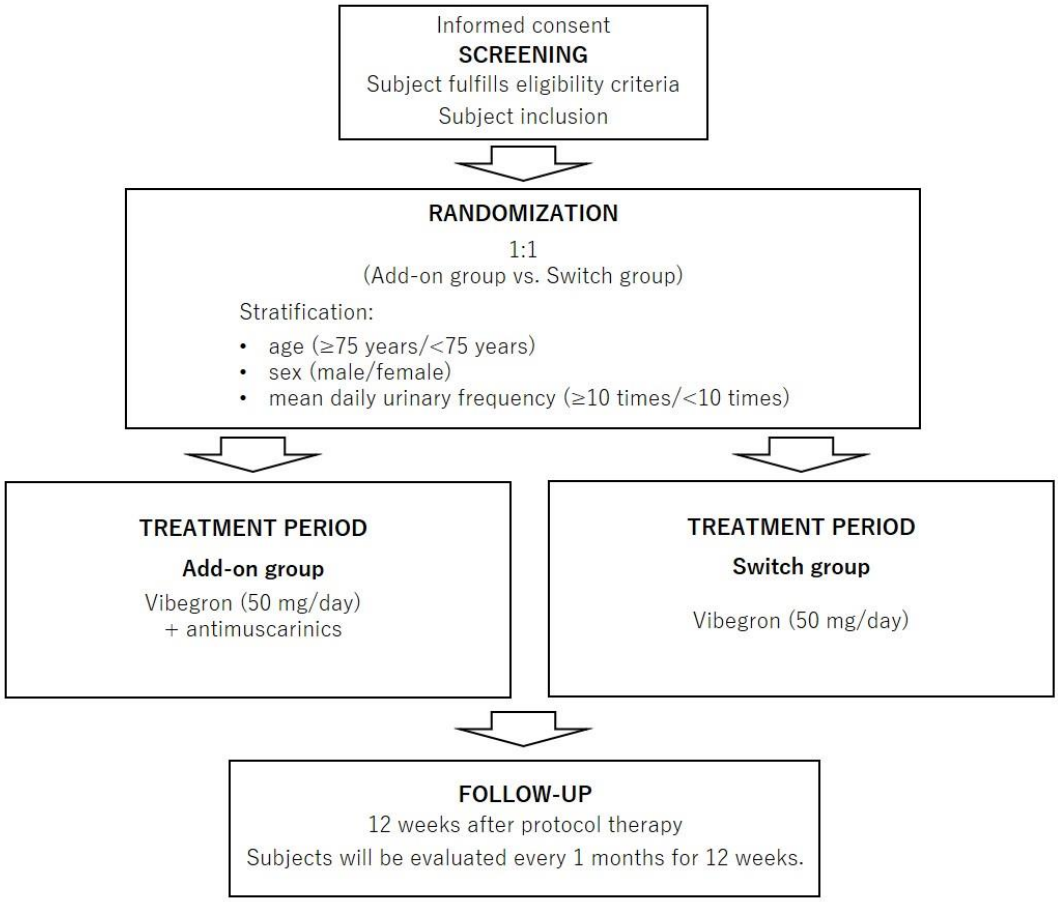
Flowchart of the tests



The flow chart of this study is shown above.

Schedule

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	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

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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.

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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

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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

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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.

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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.

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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

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(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.

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- 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)

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(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

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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)

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Consent Form

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

Instructions for use

□ Introduction: About independent clinical research (conflict of interest)

□ Purpose of this study

□ Methods of this study

□ Planned duration of participation in this study

□ Planned number of participants in this study

□ The expected effects of this treatment and the risks of adverse events that may occur.

□ Other treatment options if this treatment is not used.

□ What will happen to your health during this study (financial burden, compensation)?

□ Participation in this study is voluntary.

□ We will keep you informed about this treatment.

□ We may discontinue this treatment.

□ If you participate in this study, your medical records may be examined during or after the study.

□ Your medical records may be examined during or after the study.

□ If the results of this study are made public, your identity will not be revealed.

□ What you must do if you agree to participate in this study

□ About your cost burden

□ About your doctor

□ About the consultation service

[Patient's signature]

To participate in this study, I have received a full explanation of the above matters, received the consent document, and fully understood the contents.

I have received sufficient explanation on the above points, received the consent document, and fully understood the contents, and I agree to participate in this study.

Patient's name (Self-signed): _____

Name of substitute (signature) (relationship): _____

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(Signature of physician)

I have fully explained this voluntary clinical research to the above patient.

Date of explanation: / / (year/month/day)

Affiliation

Name (Self-signed): _____

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Withdrawal of Consent Form

Title of Clinical Research: **"A phase II randomized trial of metastasis-directed therapy with alpha emitter radium-223 in men with oligometastatic castration-resistant prostate cancer"**

I was fully informed about the "A phase II randomized trial of metastasis-directed therapy with alpha emitter radium-223 in men with oligometastatic castration-resistant prostate cancer" and agreed to cooperate in the study.

However, I would like to withdraw my consent and refuse any use of my personal data for research purposes unless there is a special reason and I give my consent after receiving an explanation.

(Patient's signature line)

Date of withdrawal of consent: / / (year/month/day)

Patient's name (Self-signed): _____

Name of substitute (signature) (relationship): _____

(Signature of physician)

Date of confirmation of withdrawal of consent: / / (year/month/day)

Affiliation

Name (Self-signed): _____

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患者さん用

同意撤回書

臨床研究課題名：「抗コリン薬に反応不良な過活動膀胱に対するビベグロンへの切り替えもしくは追加の有効性・安全性を評価する多施設共同無作為化並行群間比較試験」

私は、「抗コリン薬に反応不良な過活動膀胱に対するビベグロンへの切り替えもしくは追加の有効性・安全性を評価する多施設共同無作為化並行群間比較試験」について十分説明を受け、研究協力に同意しましたが、同意の撤回をすることを申し出ます。
これに伴い、特別な理由があり説明いただいた後に私が了承をしない限り、私の一切の個人データの研究目的での使用を拒否いたします。

【患者さんの署名欄】

同意撤回日：　　年　　月　　日

患者氏名：　（自署）＿＿＿＿＿＿＿＿＿＿＿＿

【医師の署名欄】

同意撤回確認日：　　年　　月　　日

所属：　＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

氏名：　（自署）＿＿＿＿＿＿＿＿＿＿＿＿

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同意撤回書

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患者さん用

同　意　書

東京科学大学病院　病院長 殿

臨床研究課題名：「抗コリン薬に反応不良な過活動膀胱に対するビベグロンへの切り替えもしくは追加の有効性・安全性を評価する多施設共同無作為化並行群間比較試験」

＜説明事項＞

1. はじめに
2. この研究の背景
3. この研究の目的
4. この研究に参加できる方
5. 研究参加人数と参加予定期間
6. この研究の方法
7. 研究参加中に守っていただきたいこと
8. 予想される利益と起こるかもしれない不利益
9. この研究中に、あなたの健康に被害が生じた場合について
10. この研究に参加しない場合の治療方法
11. この研究への参加は、あなたの自由意思によるものです
12. この研究に関する情報の公開
13. この研究への参加を中止させていただく場合があります
14. あなたのカルテなどが研究中あるいは研究終了後に調査されることがあります
15. 試料・情報等の保存について
16. 研究結果を公表する場合も、あなたの身元が明らかになることはありません
17. あなたの費用負担について
18. 研究資金と利益相反
19. この担当医師が、あなたを担当いたします
20. いつでも相談窓口にご相談下さい
21. 認定臨床研究審査委員会

私はこの研究に参加するにあたり、上記の事項について十分な説明を受け、同意説明文書を受け取り、内容等を十分理解いたしましたので、本研究に参加することに同意します。

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医療機関保管用

同　意　書

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患者さんへ

「抗コリン薬に反応不良な過活動膀胱に対するビベグロンへの切り替えもしくは追加の有効性・安全性を評価する多施設共同無作為化並行群間比較試験」についてのご説明

これから「臨床研究」についてご説明します。
臨床研究への参加に同意していただけるかどうかは、あなたの自由な意思によるもので、誰からも強要されるものではありません。臨床研究への参加に同意できない場合には、遠慮なく申し出てください。参加に同意していただけない場合でもあなたに不利益が生じることはありませんので、ご安心ください。
なお、この説明文書の内容でわからないことや疑問点などがありましたら、担当医師もしくは相談窓口へ遠慮なくお尋ねください。

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1．はじめに

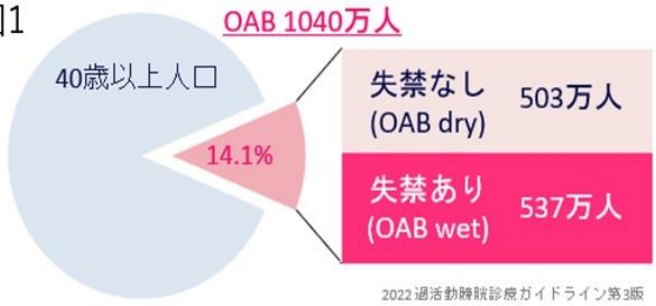
病気の予防や原因の解明、診断・治療方法の改善または有効性の検証などのために、人を対象として行われる研究を「臨床研究」といいます。その中でも、薬や医療機器等の効果や安全性を確認するための臨床研究は、法律で定められた規則に従って実施され、厚生労働省から薬・医療機器としての承認を得ることを目的として行うもの（治験）と、それ以外の大きく2種類に区分することが出来ます。今回参加をお願いする臨床研究は、後者（治験以外）の研究となり、「臨床研究法」という法律に従って、厚生労働省の認定した審査委員会である「東京科学大学臨床研究審査委員会」の承認を得た上で、研究を実施する病院の病院長の許可を得て実施されます。また厚生労働大臣に実施計画を提出しています。

臨床研究は通常の治療と異なり、研究の目的や計画に沿って薬や医療機器の評価をするものです。研究計画によって、来院の頻度が決められていたり、使用できない薬があるなど、日常診療にはない制限事項が決められていることもあります。研究に参加されるかどうかはあなたの自由意思で決めて下さい。参加されなくてもあなたが今後の治療を受ける上で不利益を被ることはありません。また参加されている途中でも、いつでも参加を取りやめることが出来ます。

2．この研究の背景

過活動膀胱（over active bladder：OAB）は、急に尿意を催して、トレイの回数が増えたり、トイレまで間に合わず、尿を漏らしてしまう状態を言います。週に１回以上の尿意切迫感（急に尿がしたくなり、我慢がむずかしいこと）がある、かつ、過活動膀胱症状スコア（over active bladder symptom score ：OABSS）の合計スコアが３点以上であることが、過活動膀胱の診断基準とされています。

図1



日本における40 歳以上の方を対象とした大規模疫学調査では、14.1%の方が過活動膀胱症状を有すると報告されており、2012 年の人口構成からは、その実数は 1040 万人に上ると推定されています。（図 1）

過活動膀胱は、加齢による膀胱機能の変化、膀胱や尿道などを支えている筋肉の衰えなどの他にも、前立腺肥大症、脳出血や脳梗塞の後遺症などさまざまな原因で起こり得ます。従来より「抗コリン薬」と呼ばれる「膀胱の収縮を抑える」効果をもった薬剤による治療が主に行われています（図 2）。抗コリン薬は、その有効性や安全性が確立した薬剤ではあるものの、口の渇きや便秘などの副作用があり、長く継続できない患者さんもいます。このような患者さんには薬剤の変更が必要になりますが、長いあいだ、抗コリン薬以外で同じような効果を持つ薬はありませんでした。しかし、現在はこの抗コリン薬のほかに「β３受容体作動薬」という「膀胱の筋肉の緊張を緩める」

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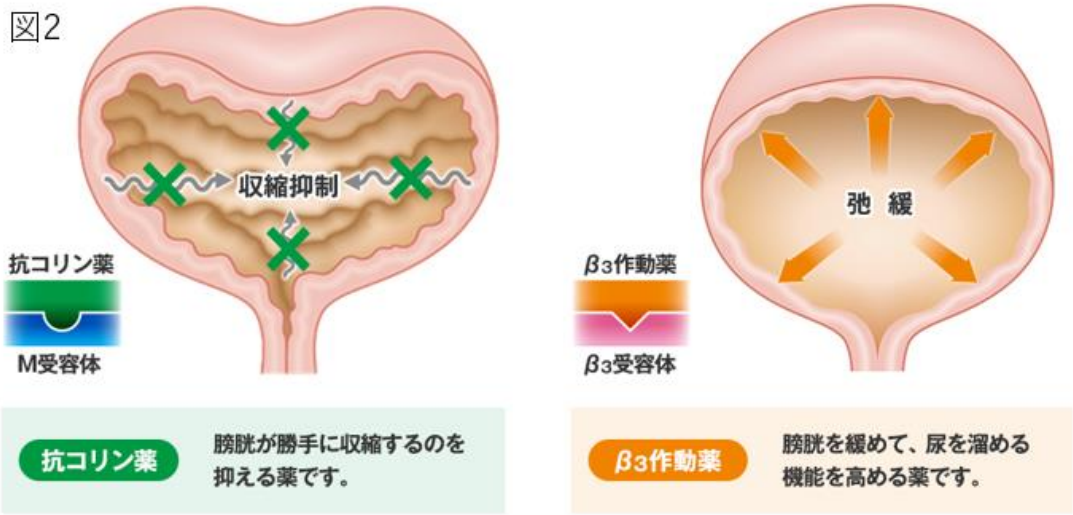
効果を持った薬剤が開発され（図２）、抗コリン薬以外の選択肢も生まれました。
β３受容体作動薬は、2011 年に発売された薬剤（ミラベグロン（販売名：ベタニス®）、と今回の研究で使用するビベグロン（販売名：ベオーバ®）の２種類のみが、日本で過活動膀胱に使用できる薬剤となっています。β３受容体作動薬は、抗コリン薬特有の口の渇きや便秘などの副作用が少ないことが報告されています。また、抗コリン薬のみで効果が不十分な患者さんには、抗コリン薬と「β３受容体作動薬」とを併用して内服することで、症状の改善につながるという報告もあります。しかし、今回この研究で使用するビベグロンは、2018 年に発売となった薬剤で、まだまだ十分な情報の集積ができていないのが現状です。

図2



３．この研究の目的

β３受容体作動薬であるビベグロンは過活動膀胱治療において効果のある薬剤と考えられております。今回の研究では、従来から行われている抗コリン薬を用いた過活動膀胱治療で、効果が不十分と思われる患者さんに対して、（A）抗コリン薬にビベグロンを追加する、もしくは（B）ビベグロンに切り替えることで、過活動膀胱の症状が改善するか、副作用の軽減につながるかを評価することを目的としています。（B）と比較して、（A）は効果が良好となる可能性がありますが、副作用の増加につながる可能性があります。そのため、（A）と（B）の治療法を比べることで、効果や副作用の面で、総合的により患者さんのメリットになる治療法を検討します。

４．この研究に参加できる方

この研究に参加していただくためには、いくつかの参加基準があります。研究に参加することに同意していただけましたら、あなたが参加基準に当てはまるか、決められた検査を行い、研究責任医師が最終的に判断します。
この研究に参加できる主な条件及び参加できない主な条件は以下のとおりです。以下の条件を満たしていても、問診の結果などから、参加いただけないこともあります。

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参加できる条件：

４週間以上の抗コリン薬の治療を行ったが、過活動膀胱の症状がある（過活動膀胱の診断基準を満たす）患者さんのうち、以下の基準のすべてに当てはまる方

（1）18 歳以上の方

（2）決められた調査時点の前の３日間の尿量測定を含む、排尿日誌・質問票に正確に記入する意思と能力がある方

（3）調査のための来院、検査を含む、この研究のスケジュールに従う意志があり、順守できる方

（4）本試験に関する情報に関して十分な説明を受け、同意書に署名した方

参加できない条件：以下のいずれかの基準に当てはまる方

（1）臨床的に膀胱出口部に閉塞がある方

（2）残尿量が多い方（残尿量＞150ml）

（3）日常生活の支障になるような、腹圧による尿失禁がある方

（4）尿道カテーテルを留置している方、または間欠的自己導尿を行っている方

（5）尿失禁に対して、仙骨神経刺激療法を含む薬物以外の治療を行っている方（研究開始の 30 日以上前に開始した膀胱訓練プログラムまたは骨盤底筋体操は含みません）

（6）過活動膀胱による排尿評価に影響を及ぼす疾患のある方や、手術を受けられた方（ボツリヌス毒素膀胱壁内注入療法を受けた患者さんなど）

（7）骨盤内の慢性炎症疾患または悪性腫瘍（がん）（※）を有している方

※12 か月以内に膀胱悪性腫瘍の膀胱内治療を行っている方、もしくは過去５年以内に悪性腫瘍（非浸潤性皮膚癌を除く）の既往歴がある方（悪性腫瘍の既往がある方でも治療を受け、５年間再発を認めない方は参加可能です）

（8）コントロールされていない狭隅角緑内障、尿閉または幽門狭窄、重症潰瘍性大腸炎、中毒性巨大結腸症、重症筋無力症、その他研究責任（分担）医師により抗コリン薬が禁忌と判断された方

（9）ビベグロンの成分に対して過敏症、アレルギーのある方

（10）妊娠中の方、妊娠している可能性がある方、授乳中の方

5．この研究への研究参加人数と参加予定期間

この研究には、全体で約110人の方に参加していただきます。

当院からは約10人の方に参加いただく予定です。

この研究に同意をいただいた後、研究のために来院していただく回数は３回です。個々の患者さんがこの研究に参加していただく期間は、同意をいただいてから約12週間です。

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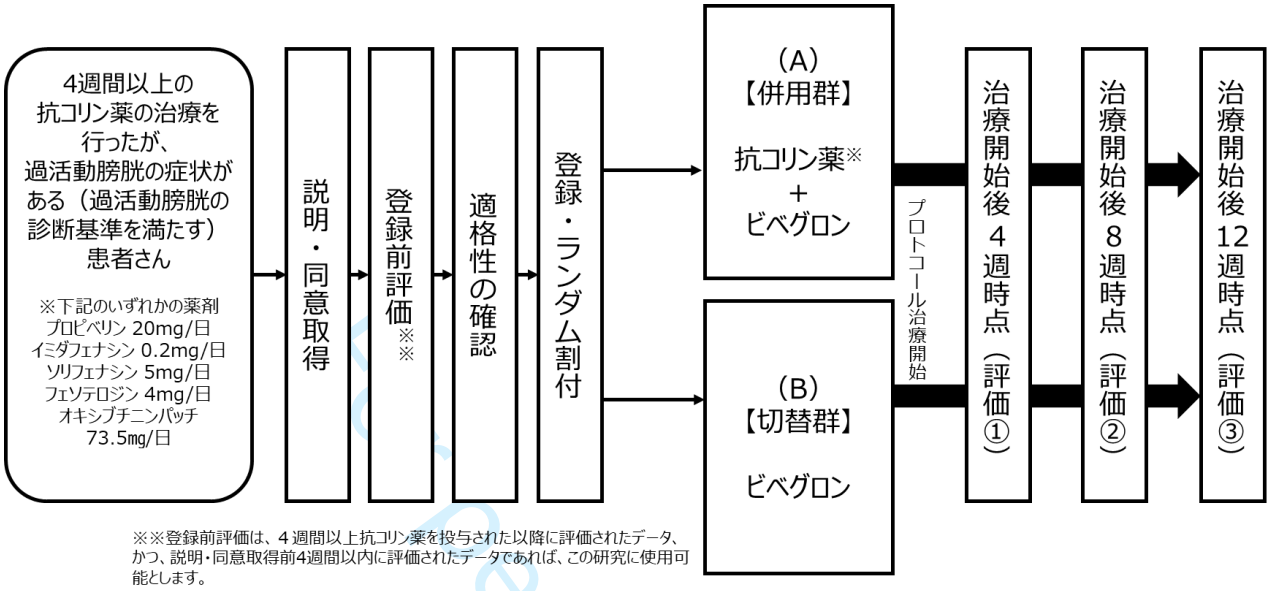
６．この研究の方法

研究の流れ



① 説明・同意取得～登録前評価～登録

この研究への参加について、文書で同意をいただいた後、この後の治療効果の評価の基準（ベースライン）となる排尿の状態を評価したり、研究に参加する条件を満たしていることを確認します。この時、登録前 30 日以内に実施している検査などがあれば、そのデータを使わせていただくことで、再度の検査等は不要となります。研究に参加する条件を満たしていることが確認されたら、本研究に登録されます。

② 治療法の割り振り

「ランダム割付」（※）という方法で、研究に参加いただいている方を、以下の（A）（B）の２つの治療法のグループに振り分けます。

（A）抗コリン薬にビベグロンを追加するグループ

（B）抗コリン薬からビベグロンに切り替えるグループ

（※）「ランダム割付」とは

臨床研究において、研究参加者を２つ以上のグループに振り分ける代表的な方法です。

振り分けは担当医師の判断やあなたの希望で決まるものではなく、治療法について適切な評価を行うために、それぞれのグループにランダムに振り分けられます。担当医師もあなたも、どちらのグループに振り分けられるかを選ぶことはできません。

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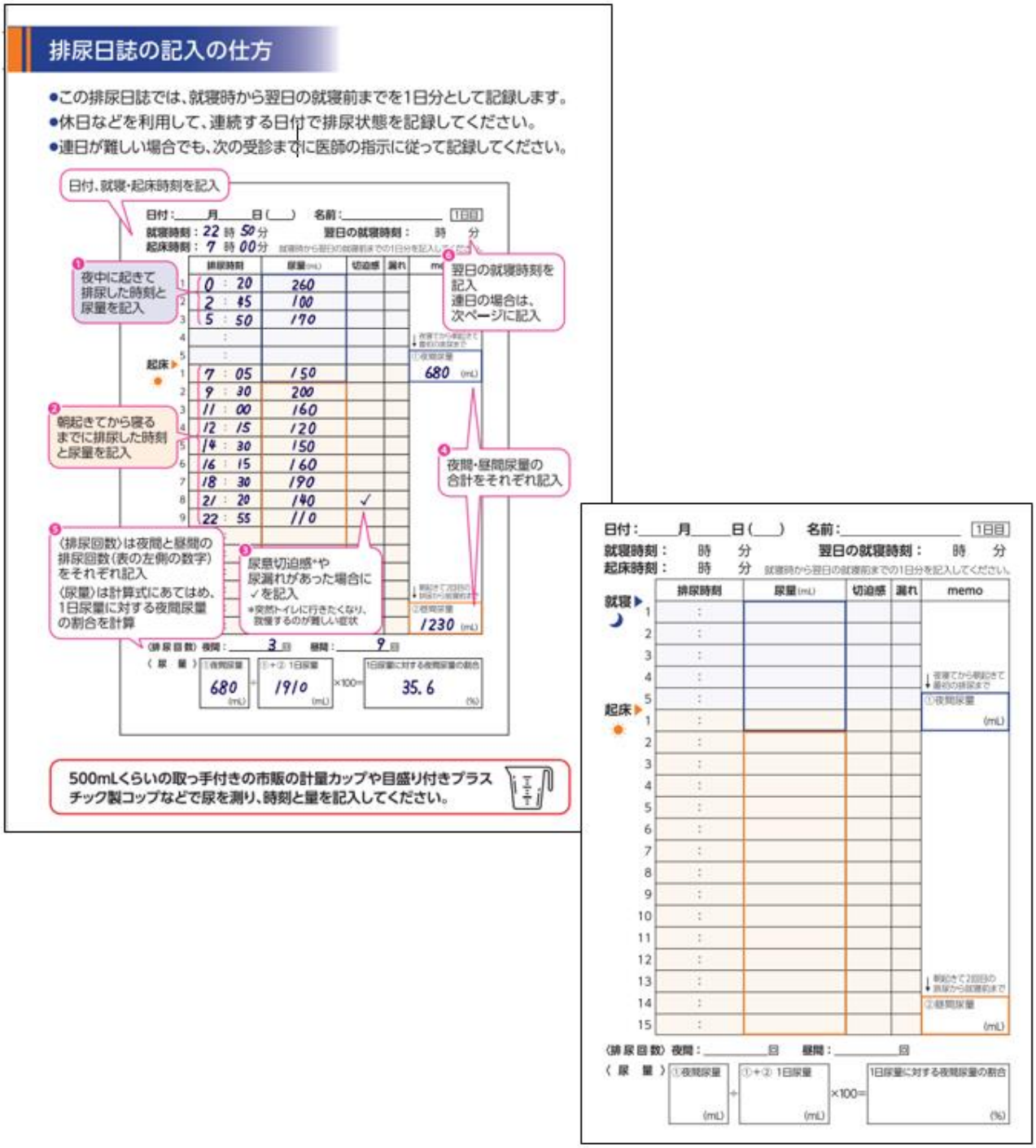
③ ４週後、８週後、12 週後の調査

ビベグロンが開始になった後の排尿状態を、４週後、８週後、12 週後に確認します。

- 受診日の前の３日間の排尿日誌を提出していただきます。
- 受診の際に、以下の２種類の質問票を記入していただきます。
  - ✓ 過活動膀胱症状スコア質問票（OABSS）
  - ✓ 国際前立腺症状スコア（IPSS）・生活の質（QOL）質問票
- 受診の際に、排尿後に膀胱内に残った尿量（残尿量）を、超音波を使用して測定します。また、問診や診察などにより、薬剤による副作用がないかなども確認します。



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この研究で行う検査について
スケジュール表

項目	説明・同意取得 ～登録前評価	登録・ ランダム割付	治療開始後 4週時点	治療開始後 8週時点	治療開始後 12週時点	プロトコール治療 中止時
同意取得	×					
登録・無作為化		×				
診察	×		×	×	×	×
患者背景情報	×					
排尿日誌	×		×	×	×	◇
OABSS質問票	×		×	×	×	◇
IPSS/QOL質問票	×		×	×	×	◇
ICIQ-SF質問票	×					
残尿量	×		×	×	×	◇
有害事象	×		×	×	×	×

◇：プロトコール治療を中止した場合、排尿日誌、OABSS質問票、IPSS/QOL質問票、残尿量など、可能な限り評価を行う。

《重要》他の病院に通院されている方はお知らせください

現在、あなたが他の病院に通院されている場合は、その病院と病名、使用しているお薬をお知らせ下さい。また、薬局などで購入して使用しているお薬やサプリメントがある場合もお知らせ下さい。これらは、研究を安全に行うために大切なことです。また、あなたが他の病院に通院されている場合は、この研究に参加していることをその病院にお知らせすることがありますので、ご了解ください。

7．研究参加中に守っていただきたいこと

1）研究に参加している間は、担当医師や研究協力者の指示に従ってください。もし、来院予定日に来院できない場合は、必ず担当医師または研究協力者にご連絡ください。

2）研究参加中に他の病院で治療を受ける場合や、新たに薬を使用される場合は、事前に担当医師または研究協力者にご相談ください。

3）何か身体に異常を感じたら、担当医師または研究協力者にお知らせください。

4）本研究に関する情報を、SNS等に公開しないようにしてください。

5）研究参加中にあなたが妊娠した場合、またはあなたのパートナーが妊娠した場合には、すみやかに担当医師にご連絡ください。

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8．予想される利益と起こるかもしれない不利益

この研究に参加することによりあなたに直接的な利益は生じませんが、研究の成果により将来の医療の進歩に貢献できる可能性があります。

この研究で使用されるビベグロンは、過活動膀胱の治療のための医薬品として承認されています。ビベグロンの副作用としては、便秘（1.6%）、口内乾燥（1.4%）、尿閉（頻度不明）などが報告されています。

（A）抗コリン薬にビベグロンを追加するグループでは、２種類の薬剤を併用することにより、副作用が増える可能性がありますが、ビベグロンと同様の作用機序の薬剤であるミラベグロンと抗コリン薬（ソリフェナシン）とを併用した際の副作用はいずれも軽度で、重大な副作用は認められなかったことが報告されています。そのため、抗コリン薬にビベグロンを追加することによるリスクは限定的と考えています。

（B）抗コリン薬からビベグロンに切り替えるグループでは、この研究に参加することにより、日常診療に比べて副作用のリスクが上昇することはないと考えられます。

この研究に参加している間に、何か気になる症状や変わったことに気付いたときは、担当医師や研究協力者（相談窓口）にご相談ください。

9．この研究中に、あなたの健康に被害が生じた場合について

この研究は、これまでの報告に基づいて科学的に計画され、慎重に行われます。もしこの研究の期間中あるいは終了後に患者さんに副作用などの健康被害が生じた場合には、医師が適切な診察と治療を行います。この研究で行われる治療は、ビベグロンの投与を含め保険診療の範囲内であるため、健康被害が生じた場合の診察や検査、入院にかかる費用については、あなたが加入されている健康保険に準じた自己負担額をお支払いいただきます。なお、副作用による一定の健康被害が生じた場合には、医薬品副作用被害救済制度の給付対象となる場合もあります。

10．この研究に参加しない場合の治療方法

この研究に参加されない場合には、現在一般的に使用されている過活動膀胱の治療の中から、担当医師とよく相談して治療を決めることになります。

研究に参加されないことによって、今後の治療を受ける上で不利益を被ることはありません。

11．この研究への参加は、あなたの自由意思によるものです

この説明文書は、あなたにこの研究の内容を正しく理解していただき、あなたの自由な意思に基づいて、この研究に参加するかどうかを判断していただくためのものです。この説明文書をお読みになり、研究責任医師または研究分担医師もしくは研究担当者からからの説明を聞かれた後、十分に考えてからこの研究に参加するかどうかを決めてください。同意した後でも、あなたの意思が変わった場

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合はいつでも同意を撤回することができます。同意しない場合や、途中で同意を撤回される場合でも、それを理由に今後治療を受ける上であなたが不利な扱いを受けることはありません。
不明な点があれば、どんなことでも気軽にお尋ねください。
なお、研究に参加されている間に安全性に関する新たな情報等、あなたの参加意思に影響を及ぼす可能性がある情報が得られた場合などには、研究への参加を継続するかどうか、再度あなたの意思を確認させていただくことがあります。

12. この研究に関する情報の公開

この臨床研究の概要は、厚生労働省の臨床研究等提出・公開システム「jRCT; Japan Registry of Clinical Trials（https://jrct.niph.go.jp/）」に登録されています。
あなたが、研究内容や方法についての情報を知りたいときには、担当医師や研究協力者にお知らせ下さい。支障がない範囲で、計画書や方法に関する資料を閲覧できるようにいたします。
また、研究期間中にこの研究で使用する医薬品に関して重要な知見が得られた場合には、すみやかにあなたにお知らせいたします。

13. この研究への参加を中止させていただく場合があります

あなたに研究参加の同意をいただいた後でも、次のような場合は研究へ参加していただけなかったり、研究を中止したりすることがありますのでご了承ください。中止が決まった場合、速やかにお知らせし、研究の中止と、必要な場合は中止後の経過観察を行います。

1）重い副作用がみられた場合
2）あなたの体の状態やその他の理由により、研究を止めた方がよいと担当医師が判断した場合
3）あなたが研究参加の同意を撤回した場合
4）研究への参加条件に合わないことが分かった場合
5）あなたが医師の指示通りに治療を行わなかったり、来院できなくなったりした場合
6）あなたの妊娠が判明した場合
7）この研究の治療の安全性に問題があることがわかったり、新たな情報が得られたりしたこと等により、研究全体が中止された場合

14. あなたのカルテなどが研究中あるいは研究終了後に調査されることがあります

患者さんの人権が守られながら、きちんとこの研究が行われているかを確認するために、この研究の関係者（この病院の職員、認定臨床研究審査委員会委員、厚生労働省等国内外の規制当局の関係者、この臨床研究のデータの確認を行う担当者等など）があなたのカルテなどの医療記録を見ることがあります。この研究への参加について同意をいただいた場合、これらの関係者による医療記録の閲覧についても承諾いただいたことになりますので、ご了承ください。なお、これらの関係者には国の法令によって守秘義務が課せられており、あなたの個人を特定する情報（氏名や住所等）が当院の外に持ち出されることはありません。

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15. 試料・情報等の保存について

・ 情報の保管と廃棄

この研究では、カルテや各種検査結果等の情報を研究データとして使用します。患者さんのお名前やカルテ ID など単体で個人を識別できる情報は研究データとして収集せず、別の研究用の番号を割り振って情報を管理いたします。患者さん個人と研究 ID を紐づける情報は、当院内で厳重に管理されます（情報保管責任者：各実施医療機関の研究責任医師）。

この研究で収集する情報(研究データ)は、Web を介して臨床研究データ管理システム「eACReSS」（イーアクレス）＊に入力されます。入力された情報は、東京科学大学病院内の「eACReSS」サーバ内に保管されます。その他、この研究にかかわる紙資料は、当院内の関係者のみがアクセスできる施錠可能な保管庫で厳重に保管されます。

＊臨床研究データ管理システム「eACReSS」は、大学病院臨床試験アライアンス事業にて整備された臨床研究データを管理する専用システムです。大学病院臨床試験アライアンスは、関東甲信越地区の８つの国立大学からなる治験・臨床研究のアライアンスです（東京大学、千葉大学、東京科学大学、筑波大学、群馬大学、新潟大学、信州大学、山梨大学）。

これらの情報は、研究終了後10年間保管し、その後、復元不可能な状態に処理して廃棄します。なお、研究への参加を同意撤回された場合は、既に収集された情報の利用について、あなたの意志を確認させていただきます。もしあなたの情報を使用してほしくない場合は、申し出ていただければ利用することはありません。ただし、同意撤回の時点ですでに論文などで成果を発表していた場合、それらは廃棄することができませんのでご了承ください。

＜データの二次利用について＞

この研究で得られたあなたの試料や情報は、将来計画・実施される別の医学研究にとっても大変貴重なものとなる可能性があります。あなたの同意が得られた場合に限り、この研究に提供いただいた試料や情報を、前述の期間を超えて保管し、別の研究に利用する可能性や、外部の研究機関に試料や情報を提供する可能性があります。試料や情報を新たな研究に利用する場合、新しく研究計画書を作成し、倫理審査委員会等で審査し、承認を受けた上で実施します。

16. 研究結果を公表する場合も、あなたの身元が明らかになることはありません

この研究で得られた成績は、東京科学大学をはじめとする研究実施医療機関や学会のWebサイト、医学雑誌などに公表されることがありますが、それらの情報にあなたのお名前などの個人的情報は含まれず、誰のデータか一切わからないように取り扱われます。たとえば、あなたの名前やイニシャルからまったく推定できない別の研究用番号をつけるなどを行いますので、プライバシーは守られます。

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17. あなたの費用負担について

この研究で使用するベオーバ®は、過活動膀胱治療に対して保険適用のある医薬品です。そのため、この研究で行われる薬剤、経過観察の来院や検査に関する医療費については、通常の保険診療として、あなたが加入されている健康保険に準じた自己負担額をお支払いいただきます。この研究に参加することによる追加の費用負担は生じません。副作用などにより診察や検査、入院をした場合も同様に、あなたが加入されている健康保険に準じた自己負担額をお支払いいただきます。
研究に参加することに伴う謝金などのお支払いはありません。

18. 研究資金と利益相反

本研究は、「ベオーバ®錠 50mg」を製造または販売している杏林製薬株式会社、キッセイ薬品工業株式会社から資金提供を受けて行われます。この研究の実施にあたっては、研究責任医師、研究分担医師、統計解析責任者は、利益相反を開示し、認定臨床研究審査委員会の審査を受け、承認を得ております。
※利益相反とは、外部との利害関係によって、臨床研究の実施や結果の公表に影響を与えうる状態のことをいいます。

19. この担当医師が、あなたを担当いたします

当院における 研究責任医師	東京科学大学病院　泌尿器科 医師名：吉田 宗一郎（准教授） 電話：03-5803-5680（泌尿器科外来）
担当医師 （研究分担医師）	医師名：＿＿＿＿＿＿＿＿　診療科：泌尿器科 連絡先：03-5803-5680（泌尿器科外来）

また、この研究全体の実施体制は以下の通りです。　◎：研究代表医師

実施医療機関名	研究責任医師
東京科学大学病院	◎ 吉田 宗一郎　（泌尿器科・准教授）
東京都立多摩南部地域病院	山本 卓宜　（泌尿器科）
大森赤十字病院	大塚 幸宏　（泌尿器科）
公立昭和病院	塚本 哲郎　（泌尿器科）
国立国際医療研究センター国府台病院	長濱 克志　（泌尿器科）
さいたま赤十字病院	小林 秀一郎　（泌尿器科）
草加市立病院	吉永　敦史　（泌尿器科）
土浦協同病院	酒井 康之　（泌尿器科）
都立大塚病院	高沢 亮治　（泌尿器科・尿路結石センター）
がん・感染症センター　都立駒込病院	伊藤　将也　（腎泌尿器外科）
JA とりで総合医療センター	川村　尚子　（泌尿器科）

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20. いつでも相談窓口にご相談下さい

この研究について何か知りたいことや心配なことがありましたら、遠慮なくあなたの担当医師または以下までお問い合わせください。

当院におけるお問い合わせ先

担当診療科	東京科学大学病院　泌尿器科 住所：東京都文京区湯島1-5-45 電話：03-5803-5680（泌尿器科外来）
当院における 相談対応窓口	東京科学大学病院　臨床試験管理センター 電話番号：03-5803-5612　平日（月～金）8:30～17:00
夜間・休日の 緊急連絡先	東京科学大学病院　救命救急センター 電話番号：03-3813-6111（代表） ※泌尿器科当直医が必ず院内に待機しており、対応可能です。

21. 認定臨床研究審査委員会

認定臨床研究審査委員会では、研究に参加される方の人権や安全性の保護、研究の科学性などについて問題がないかを審議する委員会です。本研究は以下の委員会で審査のうえ実施を承認され、病院長の許可を得ています。

名　称：東京科学大学臨床研究審査委員会
所在地：東京都文京区湯島1-5-45
Website：https://www.tmd-ac.jp/nin_r_irb/index.html

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NR2024-001
第1.3版 （2024年10月18日作成）

患者さん用

同意撤回書

臨床研究課題名：「抗コリン薬に反応不良な過活動膀胱に対するビベグロンへの切り替えもしくは追加の有効性・安全性を評価する多施設共同無作為化並行群間比較試験」

私は、「抗コリン薬に反応不良な過活動膀胱に対するビベグロンへの切り替えもしくは追加の有効性・安全性を評価する多施設共同無作為化並行群間比較試験」について十分説明を受け、研究協力に同意しましたが、同意の撤回をすることを申し出ます。
これに伴い、特別な理由があり説明いただいた後に私が了承をしない限り、私の一切の個人データの研究目的での使用を拒否いたします。

【患者さんの署名欄】

同意撤回日：　　年　　月　　日

患者氏名：　（自署）＿＿＿＿＿＿＿＿＿＿＿＿

【医師の署名欄】

同意撤回確認日：　　年　　月　　日

所属：　＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

氏名：　（自署）＿＿＿＿＿＿＿＿＿＿＿＿

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NR2024-001
第1.3版 （2024年10月18日作成）

医療機関保管用

同意撤回書

臨床研究課題名：「抗コリン薬に反応不良な過活動膀胱に対するビベグロンへの切り替えもしくは追加の有効性・安全性を評価する多施設共同無作為化並行群間比較試験」

私は、「抗コリン薬に反応不良な過活動膀胱に対するビベグロンへの切り替えもしくは追加の有効性・安全性を評価する多施設共同無作為化並行群間比較試験」について十分説明を受け、研究協力に同意しましたが、同意の撤回をすることを申し出ます。
これに伴い、特別な理由があり説明いただいた後に私が了承をしない限り、私の一切の個人データの研究目的での使用を拒否いたします。

【患者さんの署名欄】

同意撤回日：　　年　　月　　日

患者氏名：　（自署）＿＿＿＿＿＿＿＿＿＿＿＿

【医師の署名欄】

同意撤回確認日：　　年　　月　　日

所属：　＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

氏名：　（自署）＿＿＿＿＿＿＿＿＿＿＿＿

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第1.3版 （2024年10月18日作成）

患者さん用

同　意　書

東京科学大学病院　病院長 殿

臨床研究課題名：「抗コリン薬に反応不良な過活動膀胱に対するビベグロンへの切り替えもしくは追加の有効性・安全性を評価する多施設共同無作為化並行群間比較試験」

＜説明事項＞

1. はじめに
2. この研究の背景
3. この研究の目的
4. この研究に参加できる方
5. 研究参加人数と参加予定期間
6. この研究の方法
7. 研究参加中に守っていただきたいこと
8. 予想される利益と起こるかもしれない不利益
9. この研究中に、あなたの健康に被害が生じた場合について
10. この研究に参加しない場合の治療方法
11. この研究への参加は、あなたの自由意思によるものです
12. この研究に関する情報の公開
13. この研究への参加を中止させていただく場合があります
14. あなたのカルテなどが研究中あるいは研究終了後に調査されることがあります
15. 試料・情報等の保存について
16. 研究結果を公表する場合も、あなたの身元が明らかになることはありません
17. あなたの費用負担について
18. 研究資金と利益相反
19. この担当医師が、あなたを担当いたします
20. いつでも相談窓口にご相談下さい
21. 認定臨床研究審査委員会

私はこの研究に参加するにあたり、上記の事項について十分な説明を受け、同意説明文書を受け取り、内容等を十分理解いたしましたので、本研究に参加することに同意します。

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医療機関保管用

同　意　書

東京科学大学病院　病院長 殿

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【医師の署名欄】　説明日：　　年　　月　　日

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