An early phase II study of TAS-303 in female patients with stress urinary incontinence

TAS-303 [redacted] [investigational product]

PROTOCOL No.: 10060050 Ver.P02
FINALIZATION DATE: July 11, 2016
AMENDMENT: August 16, 2016

SPONSOR:

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This clinical study will be conducted in accordance with International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline on Good Clinical Practice (GCP) and the regulatory requirements in Japan.

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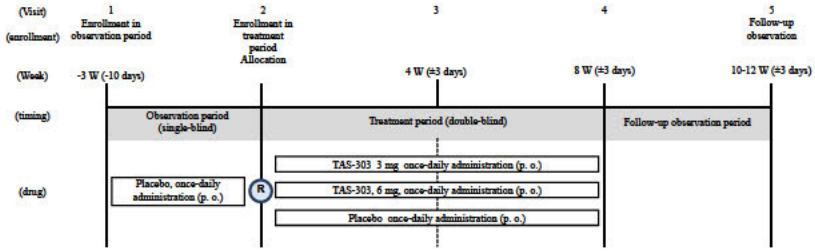
Abbreviations

Abbreviation	Definition
A/G	albumin/globulin ratio
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
$AUC_{0\text{-}24\ hr}$	area under the plasma concentration versus time curve from time zero to 24 hr
$AUC_{0\text{-}inf}$	area under the plasma concentration versus time curve from time zero to infinity
$AUC_{0\text{-}t}$	area under the plasma concentration-time curve from time zero to t (where t = the final time of detection)
BMI	body mass index
BUN	blood urea nitrogen
CI	confidence interval
CPK	creatine kinase, creatine phosphokinase
C_{max}	maximum plasma concentration
CRP	C-reactive protein
CYP	cytochrome P450
C_0	initial plasma concentration
EDC	Electronic Data Capture
FAS	Full Analysis Set
GCP	Good Clinical Practice
γ-GTP	γ-glutamyltransferase
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for human use
ICIQ-SF	International Consultation on Incontinence Questionnaire-Short Form
I-QOL	Incontinence-Quality of Life
INR	international normalized ratio
IRB	institutional review board
ISD	intrinsic sphincter deficiency
IWRS	Interactive Web Response System
LDH	lactate dehydrogenase
LOCF	last observation carried forward
LPP	leak point pressure
MMRM	mixed-effect models for repeated measures
MUI	mixed urinary incontinence

Abbreviation	Definition
NA	noradrenaline
6-OHF	6β-Hydroxycortisol
PGI-I	Patient Global Impression-Improvement
POP	pelvic organ prolapse
PPS	Per Protocol Set
PT-INR	prothrombin time-international normalized ratio
free Q_{ave}	Average urinary flow rate
free Q_{max}	Maximum urinary flow rate
QOL	quality of life
QTcF	QT corrected for heart rate by Fridericia's formula
SOP	standard operating procedure
SUI	stress urinary incontinence
$t_{1/2}$	elimination half-time
t_{max}	time to maximum plasma concentration
TOT	Trans-Obturator Tape
TVT	Tension-free Vaginal Tape
ULN	upper limit of normal
UUI	urgency urinary incontinence
VD	vaginal distention
Vdss	distribution volume at steady state
$X_{6\text{-}OHF}/X_F$	ratio of urinary 6β-hydroxycortisol to cortisol
$X_{6\text{-}OHF}/AUC_F$	ratio of urinary 6β-hydroxycortisol to cortisol area under the plasma concentration versus time curve (AUC)

Synopsis

Name of Sponsor:	Taiho Pharmaceutical Co., Ltd.
Name of Investigational Product:	TAS-303 [redacted]
Non-proprietary name:	-
Title of Study: An early phase II study of TAS-303 in female patients with stress urinary incontinence	
Protocol Number:	10060050
Phase of Development:	Phase IIa
Indication:	Stress urinary incontinence (SUI)
Background/Rationale:	SUI is a complaint of involuntary leakage of urine at the time of exertion or exercise, or during sneezing or coughing. According to Clinical Guideline for Female Lower Urinary Tract Symptoms, although anatomical factors of SUI cannot be improved by medication, resting urethral pressure has been reported to be lower in SUI patients than in women at the same age without urinary incontinence and therefore, theoretically, SUI can be treated by improving the low urethral closure pressure. [redacted]
Study Objective/Endpoints:	**Primary:** To examine the efficacy of TAS-303 using the rate of change in the number of urinary incontinence as an index and placebo as control in female patients with SUI **Secondary:** (1) To examine the efficacy of TAS-303 using changes in the variables including the International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) score or the Incontinence Quality of Life (I-QOL) score as indices and placebo as control in female patients with SUI (2) To examine the dose response of TAS-303 in improvement of urinary incontinence in female patients with SUI in an exploratory manner (3) To examine the safety of TAS-303 using the status of onset of adverse events and other indices in female patients with SUI **Primary Endpoint:** • Rate of change in mean number of urinary incontinence per 24 hours (Week 8 in treatment period) **Main Secondary Endpoints:** • Mean number of urinary incontinence per 24 hours

	• Amount of urinary incontinence by 1-hour pad test • Mean number of used pads per 24 hours • ICIQ-SF score • Patient Global Impression-Improvement: PGI-I • I-QOL score • Status of onset of adverse events and adverse reactions
Study Design:	This clinical trial is a multicenter randomized double-blind placebo-controlled parallel-group study with central enrollment for the examination of efficacy and safety of TAS-303 in female patients with SUI. The design of this study is shown in the following figure. This study consists of a single-blind observation period, a double-blind treatment period and a follow-up observation period. In the observation period, the study drug (placebo) is orally administered once daily for 3 weeks. Subjects are randomly assigned to the study drugs to be given during the treatment period with a ratio of TAS-303 3 mg group: TAS-303 6 mg group: Placebo group of 1:1:1. In the treatment period, the study drugs are orally administered once daily for 8 weeks. Patients are asked to visit the office 4 and 8 weeks after the start of the treatment period (enrollment in the treatment period) to perform specified observation and tests. Follow-up observation is performed 2 to 4 weeks after the last administration of the study drugs. 
Study Status	Study Completion Date (Anticipate): March, 2018 Region/Location: Japan
No. of Patients Planned:	In this study, central enrollment of 250 patients in the treatment period is planned.
Eligibility of patients:	**<u>Inclusion Criteria at the Time of Enrollment in Observation Period:</u>** • Female outpatients who gave written consent by themselves • Aged 20 years or older and younger than 80 years at the time of consent • Have symptoms of SUI for at least 12 weeks before enrollment in the observation period • Considered by the Investigator or Sub-investigator to be able to go to the bathroom and keep an accurate urination record by themselves • Meet all the following conditions for ICIQ-SF at the time of the enrollment in the observation period 1) Selection of the answer, "about once a day" (3 points), or those with higher scores for Q1 2) Selection of the answer, "small amount" (2 points), or those with higher scores for Q2 3) Selection of the answer, leaks "when I cough or sneeze" or leaks "while I am moving my body or exercising" for Q4

	• The amount of urinary incontinence exceeds 2.0 g in a 1-hour pad test at the time of the enrollment in the observation period. **Inclusion Criteria at the Time of Enrollment in Treatment Period:** • Fulfillment of all the following conditions has been indicated in the information in the urination record for 7 days immediately before the enrollment in the treatment period. 1) 1 or more mean number of urinary incontinence per 24 hours 2) Number of SUI > number of urgency urinary incontinence (UUI) 3) Ten or less mean number of daytime urination per day and 2 or less mean number of night-time urination per day 4) 70% or higher rate of entry in urination record (status of urinary incontinence) • Meet all the following conditions for ICIQ-SF at the time of the enrollment in the treatment period 1) Selection of the answer, "about once a day" (3 points), or those with higher scores for Q1 2) Selection of the answer, "small amount" (2 points), or those with higher scores for Q2 3) Selection of the answer, leaks "when I cough or sneeze" or leaks "while I am moving my body or exercising" for Q4 **Main Exclusion Criteria at the Time of Enrollment in Observation Period:** • Symptoms of UUI were considered by the Investigator or Sub-investigator to be more predominant than those of SUI • History of surgical treatment for urinary incontinence (Trans-Obturator Tape [TOT] procedure, Tension-free Vaginal Tape [TVT] procedure, etc.) • Have accompanying pelvic organ prolapse quantification (POP-Q) stage II or more severe pelvic organ prolapse (POP) or underwent surgical repair of POP within 180 days before the enrollment in the observation period • Accompanying lower urinary tract obstruction • Accompanying urinary tract infection (cystitis, etc.), urolithiasis (ureteral calculus, urethral calculus, vesical calculus, etc.), urethral diseases (urethral polyp, urethral diverticulum, etc.) or interstitial cystitis, or a history of recurrent urinary tract infection (3 or more incidents within 180 days before the consent) • Diagnosis of neurogenic bladder • Difficulty in undergoing pad test (going up and down stairs, etc.) • Accompanying central nervous system disorders (dementia, etc.) that make it impossible to answer the questionnaire • Accompanying angle-closure glaucoma • 100 mL or more residual urine volume measured at the time of the enrollment in the observation period • Delivery within 1 year before the enrollment in the observation period • Started physical therapy (pelvic floor muscle training, feedback training, biofeedback training, vaginal cone, bladder training, electric stimulation therapy, magnetic stimulation therapy, etc.) within 30 days before the enrollment in the observation period • Pregnant or nursing women, or women of childbearing potential with

	positive pregnancy test (urine or serum) within 7 days before the enrollment in the observation period • Fertile patients who do not agree to practice contraception during their participation in the study and for 40 days after the completion of the treatment with the study drugs **Main Exclusion Criteria at the Time of Enrollment in Treatment Period:** • Less than 80% compliance with the treatment with the study drugs during the observation period • Urinary incontinence symptoms at the time of enrollment in the treatment period were considered by the Investigator or Sub-investigator to have improved greatly compared with those at the time of the enrollment in the observation period (50% or greater improvement in the mean number of urinary incontinence per 24 hours, etc.). • Symptoms of UUI were considered by the Investigator or Sub-investigator to be more predominant than those of SUI based on the information in the urination record for 7 days immediately before the enrollment in the treatment period. • 100 mL or more residual urine volume measured at the time of the enrollment in the treatment period • Pregnant or nursing women, or women of childbearing potential with a positive pregnancy test (urine or serum) within 7 days before the enrollment in the treatment period
Administration Regimens:	**Observation Period:** Placebo is orally administered once daily for 3 weeks. **Treatment Period:** Three or 6 mg of TAS-303, or placebo is orally administered once daily for 8 weeks.
Study Participation Period:	**Study Participation Period:** Period from the acquisition of written consent to the completion of the follow-up observation period **Observation Period:** Period from the enrollment in the observation period up to the enrollment in the treatment period (the enrollment in the treatment period is implemented 3 weeks after the enrollment in the observation period) **Treatment Period:** Period from the enrollment in the treatment period to the visit at Week 8 in the treatment period **Follow-up Observation Period:** Period after the visit at Week 8 in the treatment period to the completion of the follow-up observation (implemented 2 to 4 weeks after the completion of Week 8 of the treatment period)

Statistical Methods:

Analysis Populations:

The analysis populations of this study are defined as follows:

Analysis Set	Definition
Screened Patients	A group of all patients who gave consent
Enrolled Patients in observation period	A group of all patients enrolled in the observation period of this study
Enrolled Patients in treatment period	A group of all patients enrolled in the treatment period of this study
All Treated Patients	A group of patients who took the study drugs at least once among those enrolled in the observation period
Full Analysis Set (FAS)	A group of patients who took the study drugs for the treatment period at least once and have at least 1 efficacy endpoint before the start of the treatment period and during the treatment period among those enrolled in the treatment period
Per Protocol Set (PPS)	A group of patients in FAS except for those who meet the following criteria (1) Shown not to meet inclusion criteria (2) Shown to meet exclusion criteria (criteria affecting efficacy evaluation) (3) Less than 80% compliance with the treatment during treatment period (4) Less than 70% entry rate in urination record (status of urinary incontinence) at Week 8 of the treatment period (5) Use of prohibited concomitant drugs or therapies considered to influence efficacy evaluation

Primary Endpoint:

The following analyses are performed regarding the rate of change in mean number of urinary incontinence per 24 hours at Week 8 of the treatment period from baseline, which is the primary endpoint.

(1) Main analysis

- In PPS, the difference between the TAS-303 6 mg group and the placebo group and the difference between the TAS-303 3 mg group and the placebo group are tested by t test using the two-sided significance level of the entire test of 5%. To consider multiplicity, the significance level for each comparison is adjusted by Hochberg's method.[14)]

(2) Sensitivity analysis of main analysis

- The evaluation in (1) is performed in FAS. Missing values are imputed using last observation carried forward (LOCF).

(3) Secondary analysis of primary endpoint
The following analyses are performed in FAS and PPS.

- Summary statistics are calculated for each treatment group. Missing values are not imputed.
- The rate of change from baseline in mean number of urinary

	incontinence per 24 hours for each week was analyzed using mixed-effect models for repeated measures (MMRM) to estimate the therapeutic effect of TAS-303 at Week 8 of the treatment period. - In PPS and FAS, intergroup comparison is performed by Wilcoxon rank sum test. Missing values are imputed by LOCF. (4) Analysis by allocation factor - The primary endpoint is analyzed for each condition of urinary incontinence (SUI and mixed urinary incontinence [MUI]). - The primary endpoint is analyzed for each category of mean number of urinary incontinence per 24 hours (less than 2/day and 2 or more/day).
Sample Size Justification:	Target number of patients: 250 to be enrolled in the treatment period This study is the first study that evaluates the efficacy of TAS-303 for the treatment of urinary incontinence. The number of subjects was determined, assuming that efficacy comparable to that of duloxetine can be expected based on the results of nonclinical studies. Based on the mean rate of change in the number of urinary incontinence of -62.28% in the duloxetine group and -41.86% in the placebo group from the data of a clinical trial of duloxetine, [redacted] the difference between the TAS-303 6 mg or 3 mg group and the placebo group in the rate of change in the number of urinary incontinence, which is the primary endpoint of the present study, was assumed to be -20%. From the standard deviation of 33.73% in the duloxetine group and 32.08% in the placebo group in the above study data, the standard deviation common in two groups was assumed to be 35%. Using the two-sided significance level of the entire test of 5% and the two-sided significance level of each test of 2.5% by Bonferroni's method, when the statistical power is specified as 90% and the rate of withdrawal in the treatment period as about 5%, the number of subjects necessary for the confirmation of a significant difference between the TAS-303 group and the placebo group is approximately 250 (83 per group).

Table 1　Evaluation and Test Items

Acquisition of consent			
Date of acquisition of consent			
Patient background			
Gender	Date of birth	Age[*1]	
Race	Height	Body weight	
BMI[*2]	History of clinical trial participation (within past 90 days)		
Past history (within past 180 days)	Complication		
Onset timing of SUI (year)	Condition of urinary incontinence (SUI/MUI)[*3]		
Presence or absence of menopause	Number of delivery (natural/cesarean section)		
History of previous treatment	Menstrual cycle		
Presence or absence of use of incontinence pad	History of POP surgical repair		
Patient enrollment			
Patient identification code	Patient number	Drug number	
Subjective and objective findings			
Vital signs			
Pulse rate	Blood pressure (systolic, diastolic)	Body temperature	
Compliance with treatment with study drugs			
Concomitant medications and therapies			
12-lead electrocardiography			
Heart rate	QTcF interval		
Hematological tests			
Red blood cell count	Hemoglobin	Hematocrit	Platelet count
White blood cell count	Neutrophil	Eosinophil	Basophil
Lymphocyte	Monocyte	PT-INR	
Serum chemistry			
AST	ALT	ALP	BUN
Albumin	Creatinine	Na	Cl
K	T-Bil	Direct bilirubin	Total protein
CRP	CPK	LDH	γ-GTP
Blood sugar	Triglyceride	Total cholesterol	A/G
Urinalysis			
Protein	Occult blood	Glucose	Urobilinogen
Pregnancy test[*4]			
Serum or urinary β-human chorionic gonadotropin			
Evaluation of symptom scores			
ICIQ-SF	PGI-I		
Evaluation of QOL score			
I-QOL			
Urination record			
Status of urinary incontinence, time and date	Presence or absence of pad change		
Urination time and date			
Pad test			
1-hour pad test			
Measurement of urinary flow			
Maximum urinary flow rate (free Q_{max})	Average urinary flow rate (free Q_{ave})		
Voided volume	Time of voiding		
Measurement of residual urine volume			
Evaluation of adverse events			

*1: Automatically calculated from date of birth

*2: Automatically calculated from height and body weight

*3: Determined from the content of Q4 of ICIQ-SF

*4: Required. When at least 1 year has passed after menopause or when the possibility of pregnancy is medically denied, the test is not necessary.

Table 2　Observation and Test Schedule

Timing	At enrollment in observation period	Observation period[5)]	At enrollment in treatment period	Treatment period[6)]				Follow-up observation[7)]	At discontinuation[8)]
		7 days before enrollment in treatment period		7 days before Week 4 visit	Week 4	7 days before Week 8 visit	Week 8		
Visit	1		2		3		4	5	
Week	-3		1		4		8	10 to 12	
Acquisition of consent	X[1)]								
Patient background survey	X		X						
Enrollment	X		X						
Study drugs　Prescription	X		X		X				
Collection of remaining drugs			X		X		X		X
Confirmation of compliance			X		X		X		X
Subjective and objective findings	X		X		X		X	X	X
Blood pressure, pulse rate and body temperature measurement	X[9)]		X		X		X	X	X
12-lead electrocardiography	X[9)]		X				X	X	X
Laboratory test[2)]	X[9)]		X		X		X	X	X
Pregnancy test[3)]	X		X					X	X
Urination record　Distribution	X		X		X				
Collection			X		X		X		X
Confirmation of entry			X		X		X		X
Record of status of urinary incontinence		←	→	←	→	←	→		
Record of number of used pads		←	→	←	→	←	→		
Record of number of urinations		←	→	←	→	←	→		
1-hour pad test	X		X				X		X
ICIQ-SF evaluation	X		X		X		X		X
PGI-I evaluation			X		X		X		X
I-QOL evaluation			X		X		X		X
Urinary flow test			X				X		X
Measurement of residual urine volume by ultrasonography	X[9)]		X				X		X
Concomitant drugs and therapies[4)]	←	←	←	←	←	←	←	→	X
Evaluation of adverse events[4)]	←	←	←	←	←	←	←	→	X

1. Acquisition of consent: Consent is obtained within 28 days before the enrollment in the observation period.
2. Laboratory test: Hematological tests, serum chemistry and urinalysis are performed.
3. Pregnancy test: Required. When at least 1 year has passed after menopause or when the possibility of pregnancy is medically denied, the test is not necessary. The pregnancy test (serum or urine) before the enrollment must be negative.

4. Concomitant drugs/therapies, evaluation of adverse events: Investigated from the acquisition of consent to the completion of the follow-up observation period.
5. Acceptable range of observation period: Observation period is 3 weeks in principle, but up to 4 weeks is permitted.
6. Acceptable range of timings of visits in treatment period: Week 4 and Week 8 visits ± 3 days from the scheduled dates are permitted.
7. Follow-up observation: Observation is performed 2 to 4 weeks after the completion of Week 8 of the treatment period. When the treatment is discontinued, it is performed 2 to 4 weeks after the last administration of the study drugs.
8. In cases of discontinuation: Specified observation and tests are performed as much as possible.
9. When the specified observation and tests were performed within 14 days before the enrollment, even if it was before the consent, the results can be used as the data at the time of the enrollment in the observation period.

1. Background Information

1.1 Introduction

Urinary incontinence is a complaint of involuntary leak of urine.[1)] When it becomes serious, urinary incontinence markedly lowers quality of life (QOL) by discouraging patients from going out or making them always concerned about urination. There are various types of urinary incontinence, which can be roughly divided into urgency urinary incontinence (UUI), stress urinary incontinence (SUI) and mixed urinary incontinence (MUI). UUI is a complaint of involuntary leak of urine at the same time or immediately after urgency.[1)] SUI is a complaint of involuntary leak of urine at the time of exertion or exercise, or during sneezing or coughing.[1)] MUI is a symptom in which UUI and SUI are observed. It is a complaint of involuntary leak of urine associated not only with urgency, but also with exercise, exertion, sneezing and cough.

No full-scale epidemiological survey of urinary incontinence has been conducted in Japan and therefore, exact prevalence is unknown. On urinary incontinence in women, some studies of its prevalence have been conducted and the results have been reported since around 1986. The prevalence of urinary incontinence in otherwise healthy women without disorders other than urinary incontinence has been reported to be 10% to 46%.[2),3),4),5)] SUI is more prevalent than UUI and the frequency of UUI increases with age. In Japan, MUI is observed in approximately 20% of women. Moreover, in an epidemiological study of people aged 40 years or older by the Japanese Continence Society, SUI occurred once a week or more frequently in 12.6% and 3.0% of women and men, respectively, confirming that SUI is more common in women. When women were analyzed by generation, SUI peaked in their forties and fifties and decreased after that.[6)] In contrast, the prevalence of MUI rose sharply at the age of no less than 60 years, at which SUI started to decrease.[6)] These results suggest that symptoms of SUI are universal among people aged 40 years or older. In addition, along with nocturia, SUI is considered to lower the QOL most greatly among urination disorders in women. This tendency is prominent in women in their forties to sixties.[6)] Therefore, women in these generations who are actively involved in the society are speculated to be bothered especially by SUI. As the society ages and women make more advances in society, treatment of SUI is considered to have a greater social significance.

The factor for onset of SUI is decrease in urethral resistance and resulting increase in intravesical pressure in response to abdominal pressure to the level exceeding urethral resistance. Thus, urine leaks without bladder contraction. The main pathological conditions that cause decrease in urethral resistance are urethral hypermobility and intrinsic sphincter deficiency (ISD). In urethral hypermobility, pelvic floor muscles that support pelvic viscera relax, the bladder neck droops down and the support by pubourethral ligament becomes insufficient. Therefore, urethra tends to dilate when there is abdominal pressure, resulting in urinary leak. In ISD, urinary sphincter itself becomes weak, bladder neck and proximal urethra dilate even at rest and mild increase in bladder pressure in response to abdominal pressure causes urinary incontinence. ISD may be caused by atrophy of urethral mucosa due to postmenopausal decrease in estrogen or changes in urethra due to surgical treatment of urinary incontinence or gynecological surgery. However, the causes are unknown in many cases. ISD is also considered to be caused by disorders of external urethral sphincter that are iatrogenic or based on traumas or neurological diseases.[5)] The smooth muscles in bladder

neck or proximal urethra that correspond to internal urethral sphincter contract when the sympathetic nerve (hypogastric nerve) is stimulated being mediated by α_1 receptor. Prostatic smooth muscles in men have a similar contraction mechanism mediated by α_1 receptor. The external urethral sphincter and pelvic floor muscles are predominantly innervated by somatic nerve (pudendal nerve) and their contraction is mediated by nicotinic acetylcholine receptor.

UUI is mainly treated by drug therapy. Anticholinergics or β_3 adrenergic receptor agonists are used. Therapeutic methods for SUI include physical therapy (pelvic floor muscle training), drug therapy (β_2 adrenergic receptor agonists) and surgical therapy (urethral sling surgery). Pelvic floor muscle training is expected to be effective when implemented for a long term. However, not so many patients continue it for a long term. Urethral sling surgery is widely performed for SUI in women and favorable results have been obtained. Nevertheless, its disadvantage is that it requires placement of a foreign object inside the body. Vaginal erosion and other conditions caused by the material of the foreign object, the sling, have been reported as complications.[7)] In drug therapy, a β_2 adrenergic receptor agonist, clenbuterol, is the only drug covered by insurance in Japan. Clenbuterol is rated as the recommendation grade B in Clinical Guideline for Female Lower Urinary Tract Symptoms.[8)] As it increases the contractility of external urethral sphincter and relaxes the detrusor muscle, it is expected to improve the symptoms of SUI. However, it needs to be administered carefully in patients with hypertension or heart disease. Thus, development of noninvasive and effective drugs for SUI is desired.

[redacted]

1.2 TAS-303 [redacted] [investigational drug]

The investigational drug is a white tablet containing 1 mg of TAS-303.

1.2.1 Mechanism of Action

[redacted]

1.3 Placebo [Comparator]

The placebo, which is the comparator, is a tablet that does not contain the active ingredient of the investigational drug and is indistinguishable from the investigational drug in appearance.

1.4 Known and Potential Benefits and Risks

1.4.1 TAS-303

1.4.1.1 Potential Benefits

In drug therapy for SUI, a β_2 adrenergic receptor agonist, clenbuterol, is the only drug covered by insurance in Japan. Clenbuterol is rated as the recommendation grade B in Clinical Guideline for Female Lower Urinary Tract Symptoms.[8)] As it increases the contractility of external urethral sphincter and relaxes the detrusor muscle, it is expected to improve the symptoms of SUI. However, it needs to be administered carefully in patients with hypertension or heart disease. Thus, development of noninvasive and effective drugs for SUI is desired.

[redacted]

Among clinical studies conducted so far, subjects of Study 10060010, Study 10060020

and Study 10060030 were healthy adults and therefore, benefits to subjects were not evaluated. Ongoing Study 10060040 is a Phase I study in patients with SUI and its objectives are pharmacodynamic and pharmacokinetic examination and evaluation of tolerability of TAS-303. The improvement of SUI symptoms by TAS-303 is not evaluated.

1.4.1.2 Possible Safety Risks

[redacted]

1.4.2 Drugs with Similar Mechanism of Action to That of TAS-303

As drugs with the same mechanism of action as that of TAS-303, which is an inhibitory action on NA reuptake, atomoxetine hydrochloride and amezinium metilsulfate are on the market. The main adverse reactions to atomoxetine hydrochloride are shown in Table 1.4.2-1 and the main adverse reactions to amezinium metilsulfate in Table 1.4.2-2. As serious adverse reactions to atomoxetine hydrochloride, hepatic function disorder, jaundice, hepatic failure (incidence unknown) and anaphylaxis (incidence unknown) have been reported.

Table 1.4.2-1 Main Adverse Reactions to Atomoxetine Hydrochloride

Category of adverse reactions	5% or higher	1% or higher and less than 5 %
Gastrointestinal	Nausea, decreased appetite, abdominal pain, vomiting, constipation, thirst	Diarrhoea, dyspepsia, dry mouth
Neuropsychiatric	Headache, somnolence, dizziness	Dizziness postural, sleep disorder, irritability, dysphoria, insomnia
Hypersensitivity	-	Pruritus
Cardiovascular	Palpitations	Tachycardia, blood pressure increased, heart rate increased
Dermatological	-	Hyperhidrosis
Urogenital	-	Dysuria, erectile dysfunction
Other	Weight decreased	Chest pain, asthenia, fatigue, hot flush, chills, dysgeusia

Table 1.4.2-2 Main Adverse Reactions to Amezinium Metilsulfate

Category of adverse reactions	0.1% or higher and less than 5 %
Gastrointestinal	Queasy/vomiting, abdominal pain
Neuropsychiatric	Giddiness, dizziness on standing up, headache, heaviness of head, feels poorly
Cardiovascular	Palpitations, tachycardia, blood pressure fluctuation, arrhythmia (eg., extrasystoles, atrial fibrillation), feeling of hot flushes, feeling of hot flash
Hepatic	Hepatic function abnormal including AST increased and ALT increased
Other	Urination impaired

1.4.3 Estimated Benefits and Risks for This Study

In the evaluation of the number of urinary incontinence, the amount of urinary incontinence, QOL and other parameters in this study, improvement of urinary incontinence by TAS-303 can be expected in participating patients. Additionally, safety and dose response in 8-week administration of TAS-303 at a dose of 3 mg or 6 mg can be discussed and the recommended dose can be estimated.

1.5 Key Findings and Experiences

1.5.1 Nonclinical Findings

Refer to the Investigator's Brochure.

1.5.2 Clinical Experiences

1.5.2.1 Phase I single-dose study (Study 10060010)

[redacted]

1.5.2.1.1 Pharmacokinetics

[redacted]

1.5.2.1.2 Safety

[redacted]

[redacted]

[redacted]

[redacted]

1.5.2.2 Phase I multiple-dose study (Study 10060020)

[redacted]

1.5.2.2.1 Pharmacokinetics

[redacted]

[redacted]

1.5.2.2.2 Safety

[redacted]

1.5.2.3 Drug Interaction Study with Simvastatin/Midazolam (Study 10060030)

[redacted]

[redacted]

1.5.2.3.1 Pharmacokinetics

[redacted]

1.5.2.3.2 Safety

[redacted]

[redacted]

1.5.2.4 Phase I Study in Patients with SUI (Study 10060040)

The study period was completed and the clinical study report is currently being prepared.

1.6 Rationale for Study and Selection

1.6.1 Study Population

The subjects of this study are female patients with SUI aged 20 years or older and younger than 80 years who present with a stable pathological condition, have subjective symptoms of SUI and were diagnosed with SUI objectively. To make the study population uniform as much as possible, the administration of placebo during the observation period using single-blind design and the exclusion of patients who responded considerably to placebo as ineligible at the time of enrollment in the treatment period were planned.

1.6.2 Study Design

[redacted]

[redacted]

1.6.3 Selection of TAS-303 Doses

As the doses of TAS-303 in this study, 3 mg and 6 mg were selected.

[redacted]

1.6.4 Selection of Placebo

Based on the high placebo effect in the treatment of SUI as is the case with the treatment of overactive bladder (OAB)[13)] and referring to the design of studies on duloxetine, an observation period for the administration of placebo using single-blind design was planned to exclude, as much as possible, the patients who respond considerably to placebo.

In order to objectively evaluate the efficacy and safety of TAS-303, the placebo group was formed for the treatment period. Use of placebo group is recommended in Guideline on the Clinical Investigation of Medicinal Products for the Treatment of Urinary Incontinence of EMA[11)] and FDA guidelines.[12)]

2. Objectives and Endpoints

2.1 Primary Objective

To examine the efficacy of TAS-303 using the rate of change in the number of urinary incontinence as an index and placebo as control, in female patients with SUI

2.2 Secondary Objectives

(1) To examine the efficacy of TAS-303 using the changes in the variables including ICIQ-SF score or I-QOL score as indices and placebo as control, in female patients with SUI

(2) To examine the dose response of TAS-303 in improvement of urinary incontinence in female patients with SUI in an exploratory manner

(3) To examine the safety of TAS-303 using the status of onset of adverse events and other indices in female patients with SUI

2.3 Endpoints

2.3.1 Primary Endpoint

Rate of change in mean number of urinary incontinence per 24 hours (Week 8 in treatment period)

2.3.2 Secondary Endpoints

2.3.2.1 Efficacy

(1) Mean number of urinary incontinence per 24 hours

1) Rate of change (Week 4 in treatment period)

2) Amount of change (Week 4 and Week 8 in treatment period)

3) Proportion of subjects with 50% or greater improvement (Week 4 and Week 8 in treatment period)

4) Value at each evaluation time point (at the time of enrollment in treatment period, Week 4, Week 8)

(2) Amount of urinary incontinence by 1-hour pad test

1) Proportion of subjects with continence (2.0 g or less) (Week 8 in treatment period)

2) Proportion of subjects with 50% or greater improvement (Week 8 in treatment period)

3) Value at each evaluation time point (at the time of enrollment in observation period, at the time of enrollment in treatment period, Week 8)

4) Rate of change (Week 8 in treatment period)

5) Amount of change (Week 8 in treatment period)

(3) Mean number of used pads per 24 hours

1) Value at each evaluation time point (at the time of enrollment in treatment period, Week 4, Week 8)

2) Rate of change (Week 4 and Week 8 in treatment period)

3) Amount of change (Week 4 and Week 8 in treatment period)

(4) ICIQ-SF score

1) Total score at each evaluation time point (at the time of enrollment in observation period, at the time of enrollment in treatment period, Week 4, Week 8)

2) Score for each item at each evaluation time point (at the time of enrollment in observation period, at the time of enrollment in treatment period, Week 4, Week 8)

(5) Patient Global Impression-Improvement (PGI-I)

1) Proportion for 7-point scale evaluation at each evaluation time point (at the time of enrollment in treatment period, Week 4, Week 8)

2) Proportion of improvement ("very much better", "much better", "a little better") at each evaluation time point (at the time of enrollment in treatment period, Week 4, Week 8)

(6) I-QOL score

1) Total score at each evaluation time point (at the time of enrollment in treatment period, Week 4, Week 8)

2) Score of each area at each evaluation time point (at the time of enrollment in treatment period, Week 4, Week 8)

2.3.2.2 Safety

(1) Status of onset of adverse events and adverse reactions

(2) Vital signs (blood pressure, pulse rate, body temperature), 12-lead electrocardiogram, laboratory tests

(3) Urinary flow test parameters

Maximum urinary flow rate: Free Q_{max}, average urinary flow rate: free Q_{ave}, voided volume, time of voiding (at the time of enrollment in treatment period, Week 8)

(4) Residual urine volume (at the time of enrollment in observation period, at the time of enrollment in treatment period, Week 8)

(5) Mean number of urinations per 24 hours in urination record (at the time of enrollment in treatment period, Week 4, Week 8)

3. Overview of Study Design

This clinical trial is a multicenter randomized double-blind placebo-controlled parallel-group study with central enrollment for the examination of efficacy and safety of TAS-303 in female patients with SUI. The design of this study is shown in Figure 3-1. This study consists of a single-blind observation period, a double-blind treatment period and a follow-up observation period.

The procedures of the observation period are implemented in patients considered to be eligible in the enrollment in the observation period after written consent. Single-blind design is used for the administration of the study drug during the observation period. In the observation period, the study drug (placebo) is orally administered once daily for 3 weeks. After the completion of the observation period, the patients considered to be eligible in the enrollment in the treatment period are shifted to the treatment period. Double-blind design is used for the administration of the study drugs during the treatment period. Subjects are randomly assigned to the study drugs to be given during the treatment period with a ratio of TAS-303 3 mg group: TAS-303 6 mg group: Placebo group of 1:1:1. In order to achieve a balance among groups, dynamic allocation is performed using allocation factors (mean number of urinary incontinence per 24 hours [less than 2/day, 2 or more/day] and condition of urinary incontinence [SUI, MUI]). In the treatment period, the study drugs (3 mg of TAS-303, 6 mg of TAS-303 or placebo) are orally administered once daily for 8 weeks. Patients are asked to visit the office 4 and 8 weeks after the start of the treatment period (enrollment in the treatment period) to perform specified observation and tests. Follow-up observation is performed 2 to 4 weeks after the last administration of the study drugs. When an adverse event is considered to be an adverse reaction at the time of the follow-up observation, follow-up investigation is performed as much as possible until the symptoms (including abnormal laboratory test values) are confirmed to have resolved to achieve the condition before the onset or to be resolving.

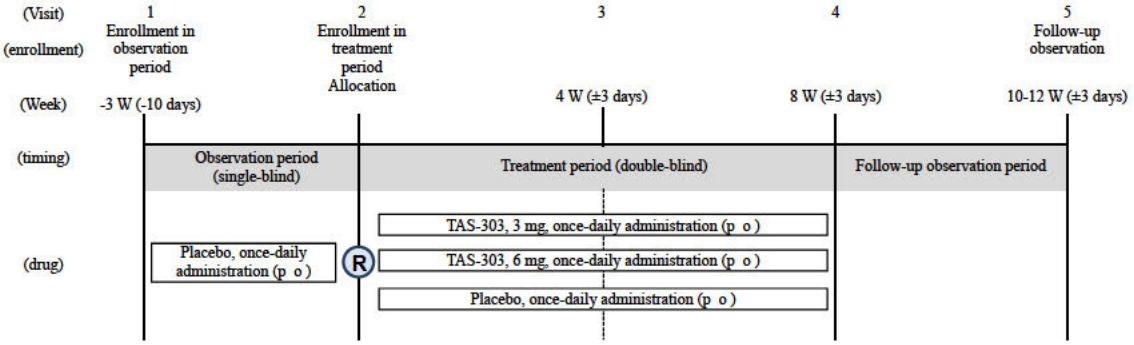


Figure 3-1 Study Design

3.1 Study Status

Study Start Date (Anticipated): September, 2016

Study Completion Date (Anticipated): March, 2018

[Region/Location]: Japan

3.1.1 Definition of Each Period for Each Patient

Each period specified in the protocol of this study is defined as follows:

Study participation period:	Period from the acquisition of written consent to the completion of the follow-up observation
Observation period:	Period from the enrollment in the observation period up to the enrollment in the treatment period (the enrollment in the treatment period is implemented 3 weeks after the enrollment in the observation period)
Treatment period:	Period from the enrollment in the treatment period to the visit at Week 8 in the treatment period
Follow-up observation period:	Period after the visit at Week 8 in the treatment period to the completion of the follow-up observation (implemented 2 to 4 weeks after the completion of Week 8 of the treatment period)

3.2 Randomization and Blinding

3.2.1 Randomization

This study is a randomized study to be conducted by central enrollment using an interactive web response system (IWRS). Data are entered in accordance with the written procedures for IWRS.

The Investigator or Sub-investigator obtains written consent after providing an explanation to the patients. Patient numbers are 6-digit (eg., 500101). The first digit represents the protocol number (5). The following 3 digits indicate a healthcare facility code. The last 2 digits represent the order of consent at each healthcare facility. These patient numbers are used throughout the entire study. The Investigator or Sub-investigator confirms that the subjects meet the inclusion criteria and do not meet the exclusion criteria for the enrollment in the observation period. Then, the patients concerned are enrolled in the observation period through IWRS. Similarly, for the enrollment in the treatment period, the patients concerned are enrolled in the treatment period through IWRS after the confirmation that they meet the inclusion criteria and do not meet the exclusion criteria for the enrollment in the treatment period. At the time of enrollment in the treatment period, subjects are randomly assigned to 3 mg of TAS-303, 6 mg of TAS-303 or placebo with a ratio of 1:1:1 through IWRS based on the stochastic minimization method.

Patients are stratified using the following allocation adjustment factors.

- Mean number of urinary incontinence per 24 hours at the time of enrollment in the treatment period (less than 2/day and 2 or more/day)
- Condition of urinary incontinence (SUI/MUI)

Through IWRS, a study drug is assigned to each patient, the study site is informed of the drug number assigned to the patient and the instructions regarding the prescription of the study drug are given. For details, see written procedures for IWRS.

If by any chance the study drug different from the drug number assigned by IWRS is dispensed to a patient, the Sponsor must be contacted immediately. The study site must record the cause of the error in prescription or dispensing of the study drug. If administration of the study drug was started in the group different from the assigned one, the administration is continued.

When the "Section 4.3 Patient Discontinuation Criteria" are met, the items related to the discontinuation are promptly entered into IWRS.

3.2.2 Blinding

This study is a double-blind study. All patients, Investigator, Sub-investigator, Clinical Research Coordinator and Sponsor will remain blinded to treatment groups during the study. Key codes are prepared and the study treatment is unblinded in accordance with the written procedures for allocation of the study drugs. The person responsible for study drug assignment retains and manages the key codes until unblinding.

The following items are presented in the written procedures for allocation of study drugs, the written procedures for emergency unblinding, the written procedures for unblinding or other documents.

- Method for assuring indistinguishability (timing, person in charge, items, etc.)
- Method for storage, management and handling of key codes and emergency key codes and specification of the person in charge of storage
- Procedures for emergency unblinding
- Timing and procedures for unblinding after data lock

4. Eligibility and Patient Discontinuation Criteria

4.1 Inclusion Criteria

The patients who meet all the following inclusion criteria at the time of each enrollment are the subjects of this study.

The rationale for the criteria is presented in Section 14.3.

4.1.1 At the time of enrollment in observation period

(1) Female outpatients who gave written consent by themselves

(2) Aged 20 years or older and younger than 80 years at the time of consent

(3) Have symptoms of SUI for at least 12 weeks before enrollment in the observation period

(4) Considered by the Investigator or Sub-investigator to be able to go to the bathroom and keep an accurate urination record by themselves

(5) Meet all the following conditions for ICIQ-SF at the time of the enrollment in the observation period

1) Selection of the answer, “about once a day” (3 points), or those with higher scores for Q1

2) Selection of the answer, “small amount” (2 points), or those with higher scores for Q2

3) Selection of the answer, leaks “when I cough or sneeze” or leaks “while I am moving my body or exercising” for Q4

(6) The amount of urinary incontinence exceeds 2.0 g in a 1-hour pad test at the time of the enrollment in the observation period

4.1.2 At the time of enrollment in treatment period

(1) Fulfillment of all the following conditions has been indicated in the information in the urination record for 7 days immediately before the enrollment in the treatment period

1) 1 or more mean number of urinary incontinence per 24 hours

2) Number of SUI > number of UUI

3) Ten or less mean number of daytime urination per day and 2 or less mean number of night-time urination per day

4) 70% or higher rate of entry in urination record (status of urinary incontinence)

(2) Meet all the following conditions for ICIQ-SF at the time of the enrollment in the treatment period

1) Selection of the answer, “about once a day” (3 points), or those with higher scores for Q1

2) Selection of the answer, “small amount” (2 points), or those with higher scores for Q2

3) Selection of the answer, leaks “when I cough or sneeze” or leaks “while I am moving my body or exercising” for Q4

4.2 Exclusion Criteria

Patients who meet any of the following criteria at the time of each enrollment are excluded from this study.

The rationale for the criteria is presented in Section 14.3.

4.2.1 At the time of enrollment in observation period

(1) Symptoms of UUI were considered by the Investigator or Sub-investigator to be more predominant than those of SUI

(2) History of surgical treatment for urinary incontinence (Trans-Obturator Tape [TOT] procedure, Tension-free Vaginal Tape [TVT] procedure, etc.)

(3) Have accompanying pelvic organ prolapse quantification (POP-Q) stage II or more severe pelvic organ prolapse (POP) or underwent surgical repair of POP within 180 days before the enrollment in the observation period

(4) Accompanying lower urinary tract obstruction

(5) Accompanying urinary tract infection (cystitis, etc.), urolithiasis (ureteral calculus, urethral calculus, vesical calculus, etc.), urethral diseases (urethral polyp, urethral diverticulum, etc.) or interstitial cystitis, or a history of recurrent urinary tract infection (3 or more incidents within 180 days before the consent)

(6) Diagnosis of neurogenic bladder

(7) Accompanying overflow incontinence

(8) Absence of urge to urinate

(9) Difficulty in undergoing pad test (going up and down stairs, etc.)

(10) Accompanying central nervous system disorders (dementia, etc.) that make it impossible to answer the questionnaire

(11) Accompanying angle-closure glaucoma

(12) Clinically problematic complications (including symptoms and findings) including severe liver diseases (viral hepatitis, chronic hepatic failure, hepatic cirrhosis, etc.), renal and urologic disease (acute renal failure, glomerulonephritis, interstitial nephritis, etc.), cardiovascular diseases (congestive cardiac failure, angina pectoris, serious arrythmia, etc.), hematologic diseases (pancytopenia, leukopenia, etc.), respiratory diseases (serious bronchial asthma, chronic bronchitis, etc.), gastrointestinal disease (serious peptic ulcer, reflux esophagitis, etc.), neuropsychiatric diseases (schizophrenia, dementia, etc.), immune diseases (collagen

disorder, etc.), metabolic and endocrine system diseases or malignant tumors

(13) History of hypersensitivity to the ingredients of the investigational products

(14) 100 mL or more residual urine volume measured at the time of the enrollment in the observation period

(15) Fulfillment of the following conditions in laboratory tests performed within 14 days before the enrollment in the observation period

1) Aspartate aminotransferase (AST) > 3 × upper limit of normal (ULN)

2) ALT >3×ULN

3) T-Bil >2×ULN

4) Serum creatinine > 2.0 mg/dL

(16) Delivery within 1 year before the enrollment in the observation period

(17) The following surgery or therapy within 180 days before the enrollment in the observation period

1) Surgery of pelvic viscera that damages hypogastric nerve and pudendal nerve (radical hysterectomy, radical operation for rectal cancer, extensive dissection of pelvic lymph nodes, etc.)

2) Radiation therapy that may influence urinary function

(18) Treatment with other investigational products within 90 days before the enrollment in the observation period

(19) Started physical therapy (pelvic floor muscle training, feedback training, biofeedback training, vaginal cone, bladder training, electric stimulation therapy, magnetic stimulation therapy, etc.) within 30 days before the enrollment in the observation period

(20) Pregnant or nursing women, or women of childbearing potential with positive pregnancy test (urine or serum) within 7 days before the enrollment in the observation period

Note) Women without childbearing potential are those who underwent hysterectomy or postmenopausal women who did not have menstruation for 1 year or longer without medical reasons including use of contraceptive drugs.

(21) Fertile patients who do not agree to practice contraception during their participation in the study and for 40 days after the completion of the treatment with the study drugs

Note) The Investigator or Sub-investigator instructs practicing contraception using the double barrier method (condom and diaphragm), intrauterine device or other methods during the study participation period and the contraception

period. Because the possibility that the study drugs inhibit the metabolism of oral contraceptive drugs cannot be denied, use of oral contraceptive drugs is not considered appropriate.

(22) Other patients considered by the Investigator or Sub-investigator to be inappropriate as subjects of this study

4.2.2 At the time of enrollment in treatment period

(1) Less than 80% compliance with the treatment with the study drugs during the observation period

(2) Urinary incontinence symptoms at the time of enrollment in the treatment period were considered by the Investigator or Sub-investigator to have improved greatly compared with those at the time of the enrollment in the observation period (50% or greater improvement in the mean number of urinary incontinence per 24 hours, etc.).

(3) Symptoms of UUI were considered by the Investigator or Sub-investigator to be more predominant than those of SUI based on the information in urination record for 7 days immediately before the enrollment in the treatment period

(4) Accompanying POP-Q Stage II or more severe POP

(5) Accompanying lower urinary tract obstruction

(6) Accompanying urinary tract infection (cystitis, etc.), urolithiasis (ureteral calculus, urethral calculus, vesical calculus, etc.), urethral diseases (urethral polyp, urethral diverticulum, etc.) or interstitial cystitis

(7) Diagnosis of neurogenic bladder

(8) Accompanying overflow incontinence

(9) Absence of urge to urinate

(10) Difficulty in undergoing pad test (going up and down stairs, etc.)

(11) Accompanying central nervous system disorders (dementia, etc.) that make it impossible to answer the questionnaire

(12) Accompanying angle-closure glaucoma

(13) Clinically problematic complications (including symptoms and findings) including severe liver diseases (viral hepatitis, chronic hepatic failure, hepatic cirrhosis, etc.), renal and urologic disease (acute renal failure, glomerulonephritis, interstitial nephritis, etc.), cardiovascular diseases (congestive cardiac failure, angina pectoris, serious arrythmia, etc.), hematologic diseases (pancytopenia, leukopenia, etc.), respiratory diseases (serious bronchial asthma, chronic bronchitis, etc.), gastrointestinal disease (serious peptic ulcer, reflux esophagitis, etc.), neuropsychiatric diseases (schizophrenia, dementia, etc.), immune diseases (collagen disorder, etc.), metabolic and endocrine system diseases or malignant tumors

(14) 100 mL or more residual urine volume measured at the time of the enrollment in the

treatment period

(15) Fulfillment of the following conditions in laboratory tests performed within 14 days before the enrollment in the treatment period

1) AST >3×ULN

2) ALT >3×ULN

3) T-Bil >2×ULN

4) Serum creatinine > 2.0 mg/dL

(16) Pregnant or nursing women, or women of childbearing potential with positive pregnancy test (urine or serum) within 7 days before the enrollment in the treatment period

Note) Women without childbearing potential are those who underwent hysterectomy or postmenopausal women who did not have menstruation for 1 year or longer without medical reasons including use of contraceptive drugs.

(17) Other patients considered by the Investigator or Sub-investigator to be inappropriate as subjects of this study

4.3 Patient Discontinuation Criteria

When patients meet the following conditions, administration of the study drugs is discontinued. Discontinuation criteria for individual patients are shown below.

(1) When continuation of treatment is difficult because of onset of an adverse event

(2) When the patient requested the withdrawal of consent

(3) When a serious noncompliance with the study implementation procedures was noted

(4) When continuation of the study became impossible due to a move, transfer to another hospital, busy schedule or other reasons of the patient

(5) When a patient was found not to fulfill the criteria for subjects of this study (not meeting the inclusion criteria or meeting the exclusion criteria)

(6) When the following liver damage for which a causal relationship with the study drugs of this study cannot be denied occurred

1) AST (glutamic oxaloacetic transaminase [GOT]) or ALT (glutamic pyruvic transaminase [GPT]) > 8 × ULN

2) AST (GOT) or ALT (GPT) > 5 × ULN persisting for 2 weeks or longer

3) AST (GOT) or ALT (GPT) > 3 × ULN with total bilirubin (T-Bil) > 2 × ULN or international normalized ratio (INR) > 1.5

4) AST (GOT) or ALT (GPT) > 3 × ULN and onset of malaise, nausea, vomiting,

right upper quadrant pain/tenderness, pyrexia, rash or eosinophilia (> 5%)

(7) When a patient became pregnant

(8) When the effect of the study drugs was insufficient or symptoms were exacerbated and the Investigator or Sub-investigator considered that the study should be discontinued

(9) Other cases in which the Investigator or Sub-investigator considered the discontinuation of the study necessary

5. Study Assessments

The evaluation and test items performed in this study are shown in Table 5-1 and the details of the implementation schedule in Table 5-2.

All information specified in the protocol must be recorded. When the specified observation and tests were performed within 14 days before the enrollment, even if it was before the consent, the results can be used as the data at the time of the enrollment in the observation period.

Table 5-1 Evaluation and Test Items

Acquisition of consent			
Date of acquisition of consent			
Patient background			
Gender	Date of birth		Age*[1]
Race	Height		Body weight
BMI*[2]	History of clinical trial participation (within past 90 days)		Past history (within past 180 days)
Complication	Onset timing of SUI (year)	Condition of urinary incontinence (SUI/MUI)*[3]	
Presence or absence of menopause	Number of delivery (natural/cesarean section)		History of previous treatment
Menstrual cycle	Presence or absence of use of incontinence pad		History of POP surgical repair
Patient enrollment			
Patient identification code	Patient number		Drug number
Subjective and objective findings			
Vital signs			
Pulse rate	Blood pressure (systolic, diastolic)		Body temperature
Compliance with treatment with study drugs			
Concomitant medications and therapies			
12-lead electrocardiography			
Heart rate	QTcF interval		
Hematological tests			
Red blood cell count	Hemoglobin	Hematocrit	Platelet count
White blood cell count	Neutrophil	Eosinophil	Basophil
Lymphocyte	Monocyte	Prothrombin time-international normalized ratio (PT-INR)	
Serum chemistry			
AST	ALT	ALP	BUN
Albumin	Creatinine	Na	Cl
K	T-Bil	Direct bilirubin	Total protein
CRP	CPK	LDH	γ-GTP
Blood sugar	Triglyceride	Total cholesterol	A/G
Urinalysis			
Protein	Occult blood	Glucose	Urobilinogen
Pregnancy test*[4]			
Serum or urinary β-human chorionic gonadotropin			
Evaluation of symptom scores			
ICIQ-SF	PGI-I		
Evaluation of QOL score			
I-QOL			
Urination record			
Status of urinary incontinence, time and date	Presence or absence of pad change	Urination time and date	
Pad test			
1-hour pad test			
Measurement of urinary flow			
Maximum urinary flow rate (free Q_{max})		Average urinary flow rate (free Q_{ave})	
Voided volume		Time of voiding	
Measurement of residual urine volume			
Evaluation of adverse events			

*1: Automatically calculated from date of birth

*2: Automatically calculated from height and body weight

*3: Determined from the content of Q4 of ICIQ-SF

*4: Required. When at least 1 year has passed after menopause or when the possibility of pregnancy is medically denied, the test is not necessary.

Table 5-2 Observation and Test Schedule

Timing	At enrollment in observation period	Observation period[5)]	At enrollment in treatment period	Treatment period[6)]				Follow-up observation[7)]	At discontinuation[8)]
		7 days before enrollment in treatment period		7 days before Week 4 visit	Week 4	7 days before Week 8 visit	Week 8		
Visit	1		2		3		4	5	
Week	-3		1		4		8	10 - 12	
Acquisition of consent	X[1)]								
Patient background survey	X		X						
Enrollment	X		X						
Study drugs Prescription	X		X		X				
Collection of remaining drugs			X		X		X		X
Confirmation of compliance			X		X		X		X
Subjective and objective findings	X		X		X		X	X	X
Blood pressure, pulse rate and body temperature measurement	X[9)]		X		X		X	X	X
12-lead electrocardiography	X[9)]		X				X	X	X
Laboratory test[2)]	X[9)]		X		X		X	X	X
Pregnancy test[3)]	X		X					X	X
Urination record Distribution	X		X		X				
Collection			X		X		X		X
Confirmation of entry			X		X		X		X
Record of status of urinary incontinence		←	→	←	→	←	→		
Record of number of used pads		←	→	←	→	←	→		
Record of number of urinations		←	→	←	→	←	→		
1-hour pad test	X		X				X		X
ICIQ-SF evaluation	X		X		X		X		X
PGI-I evaluation			X		X		X		X
I-QOL evaluation			X		X		X		X
Urinary flow test			X				X		X
Measurement of residual urine volume by ultrasonography	X[9)]		X				X		X
Concomitant drugs and therapies[4)]	←	←	→	←	→	←	→	→	X
Evaluation of adverse events[4)]	←	←	→	←	→	←	→	→	X

1. Acquisition of consent: Consent is obtained within 28 days before the enrollment in the observation period.
2. Laboratory test: Hematological tests, serum chemistry and urinalysis are performed.

3. Pregnancy test: Required. When at least 1 year has passed after menopause or when the possibility of pregnancy is medically denied, the test is
before the enrollment must be negative.
4. Concomitant drugs/therapies, evaluation of adverse events: Investigated from the acquisition of consent to the completion of the follow-up obs
5. Acceptable range of observation period: Observation period is 3 weeks in principle, but up to 4 weeks is permitted.
6. Acceptable range of timings of visits in treatment period: Week 4 and Week 8 visits ± 3 days from the scheduled dates are permitted.
7. Follow-up observation: Observation is performed 2 to 4 weeks after the completion of Week 8 of the treatment period. When the treatment is d
administration of the study drugs.
8. In cases of discontinuation: Specified observation and tests are performed as much as possible.
9. When the specified observation and tests were performed within 14 days before the enrollment, even if it was before the consent, the results ca
the observation period.

5.1 All Study Procedures

The following evaluation and tests must be recorded as source documents of each patient.

5.1.1 Informed Consent

Consent is obtained within 28 days before the enrollment in the observation period and subsequently, eligibility is confirmed.

5.1.2 Patient Background

All the items of patient background information shown in Table 5-1 are collected.

5.1.3 Patient enrollment

Unique patient identification codes are assigned for screening at study sites and patient numbers are assigned by the time of enrollment in the observation period. At the time of enrollment in the treatment period, drug numbers are obtained. The allocation method is shown in Section 3.2.

5.1.4 Subjective and Objective Findings

Subjective and objective findings are evaluated at the timing shown in Table 5-2. The information regarding signs and symptoms observed at the time of enrollment in the treatment period is collected as the information regarding baseline signs and symptoms. All the abnormal findings considered to be clinically significant compared with baseline must be recorded as adverse events. The evaluation methods of adverse events shown in Section 12 are used.

5.1.5 Vital Signs

As vital signs, blood pressure (systolic and diastolic), pulse rate and body temperature are measured at the timings shown in Table 5-2. At all measurement timings, they should be measured keeping the patients at rest, using the same site and method in each patient.

The Investigator or Sub-investigator is responsible for assessing the changes in vital signs. If an abnormal result is obtained, measurement should be performed again immediately. Changes that are considered clinically significant based on the comparison with baseline must be recorded as adverse events. The evaluation methods of adverse events shown in Section 12 are used.

5.1.6 Compliance with treatment with study drugs

Compliance with treatment with the study drugs is confirmed in every visit by checking the treatment diary and empty sheet of used study drugs, asking subjects questions and other methods from the start of the treatment with the study drugs to the completion of the treatment.

5.1.7 Concomitant medications and therapies

The status of concomitant medications and therapies is confirmed and related information is collected at least in every visit by asking subjects questions or by other methods from the start of the treatment with the study drugs to the completion of the study participation period.

The information regarding all the concomitant medications (prescription drugs and over-the-counter drugs) and therapies is collected from the time of consent to the completion

of the study participation period and the status of their use is recorded in the source documents. The concomitant medications and therapies include the therapeutic agents used to treat adverse events or serious adverse events. For the concomitant medications and therapies for the adverse events the observation of the course of which is required at the time of the follow-up observation, information is collected until the completion of the observation of the course and the status of their use is recorded in the source documents. However, test agents, diagnostic agents or fluids for the administration of injections do not have to be recorded in the case report form (eCRF).

5.1.8 12-lead Electrocardiography

Twelve-lead electrocardiography is performed at the timings shown in Table 5-2. It should be performed keeping patients at rest, using the same method for each patient.

The Investigator or Sub-investigator is responsible for assessing the results of electrocardiography. All the abnormal findings considered to be clinically significant compared with baseline must be recorded as adverse events. The evaluation methods of adverse events shown in Section 12 are used.

5.1.9 Laboratory Findings

In laboratory tests, the items shown in Table 5-1 are evaluated.

The Investigator or Sub-investigator must evaluate all the laboratory test values as to whether they are clinically significant events. When an event was considered to be a clinically significant event, its course must be observed as specified in the protocol and the event must be recorded as an adverse event. The evaluation methods of adverse events shown in Section 12 are used. When liver damage is suspected, hepatic function tests are performed. When the tests showed AST (GOT) > 3 × ULN, ALT (GPT) > 3 × ULN or T-Bil > 2 × ULN, at least AST (GOT), ALT (GPT), alkaline phosphatase (ALP) and T-Bil are tested once every 2 to 3 days and the condition of the patient is observed in detail.

5.1.9.1 Hematology

Blood samples for hematology will be collected at the time points shown in Table 5-2.

5.1.9.2 Serum chemistry

Blood samples for serum chemistry will be collected at the time points shown in Table 5-2.

5.1.9.3 Urinalysis

Urine samples for urinalysis will be collected at the time points shown in Table 5-2.

5.1.10 Pregnancy Test

Serum or urinary β-human chorionic gonadotropin is tested at the timings shown in Table 5-2 in patients with childbearing potential to confirm that they are not pregnant. The test is unnecessary for patients without childbearing potential.

Note) Women without childbearing potential are those who underwent hysterectomy or postmenopausal women who did not have menstruation for 1 year or longer without medical reasons including use of contraceptive drugs.

5.1.11 Evaluation of symptom scores

5.1.11.1 ICIQ-SF

As the evaluation of a symptom score, patients are asked to answer ICIQ-SF at the timings shown in Table 5-2.

5.1.11.2 PGI-I

As the evaluation of patients' impression of improvement of urinary incontinence, patients are asked to evaluate PGI-I at the timing shown in Table 5-2.

5.1.12 Evaluation of QOL Scores

As the evaluation of QOL score, patients are asked to evaluate I-QOL at the timings shown in Table 5-2.

5.1.13 Urination Record (Bladder Diary)

Urination record (bladder diary) is issued to patients and collected at the timings shown in Table 5-2 and the entry is confirmed.

5.1.14 Pad Test

One-hour pad test is performed at the timings shown in Table 5-2 and the amount of urinary incontinence is evaluated. The test is performed in accordance with the written procedures for pad test.

5.1.15 Urinary Flow Test

Urinary flow test is performed at the timings shown in Table 5-2 and the maximum urinary flow rate (free Q_{max}), average urinary flow rate (free Q_{ave}), voided volume and time of voiding are evaluated. The test is performed in accordance with the written procedures for urinary flow test.

5.1.16 Measurement of Residual Urine Volume

Residual urine volume is measured at the timings shown in Table 5-2.

5.1.17 Evaluation of Adverse Events

As shown in Table 5-2, it is checked whether there are untoward medical occurrences (adverse events or serious adverse events) including adverse reactions on each day of visit from the time of consent to the completion of study participation period. The evaluation methods of adverse events shown in Section 12 are used.

5.2 Assessments by Visit

The evaluation and tests shown in Table 5-1 are performed according to the schedule shown in Table 5-2.

6. Study Drugs

The Sponsor will supply TAS-303 [redacted] and placebo until the completion of study participation period.

6.1 Overview of the Study Drugs

Physical and chemical characteristics of the investigational drug and the comparator are shown in Table 6.1-1 and Table 6.1-2.

Table 6.1-1 Overview of TAS-303 [redacted] [Investigational Drug]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Table 6.1-2 Overview of placebo [Comparator]

Formulation	Tablet that does not contain the active ingredient of the investigational drug and is indistinguishable from the investigational drug in appearance
[redacted]	[redacted]
Expiration date	Specified in the written procedures for management and handling of study drugs

6.2 Packaging and Labeling

The following information is printed on the outer boxes and aluminum pouches of the study drugs. The details are specified in the written procedures for management and handling of study drugs.

(1) Sponsor name

(2) Address

(3) Storage conditions

(4) Quantity

(5) Lot number

(6) Production date

6.3 Accountability

The head of the study site or the person in charge of management of the study drugs manages all study drugs received at the study site in accordance with the written procedures for management and handling of study drugs. The details are specified in the written procedures for management and handling of study drugs. The entire history of prescription of study drugs is recorded in the table for management of study drugs.

No study drug is to be used outside of this study.

6.4 Patients Instruction on Proper Using

The Investigator or Sub-investigator instructs patients to handle the study drugs using specified methods and record compliance with the treatment with study drugs in the treatment diary. The details of the instructions are specified in the written procedures for management and handling of study drugs and the treatment diary. When a patient does not comply with the specified methods, the Investigator or Sub-investigator can discontinue the study in the patient. Compliance is confirmed by checking the entry in the table for management of study drugs, the treatment diary and consistency with the source documents.

6.5 Implementation of Allocation Confirmation Study

This study is a double-blind controlled study. In order to confirm that the subjects are appropriately allocated to each treatment group (TAS-303 6 mg group, TAS-303 3 mg group and placebo group) after the allocation, the allocation confirmation study is conducted.

7. Study Drug Regimens

The entire status of administration is recorded in the source documents for patients. Instructions for the administration method are given to patients in accordance with the written procedures for management and handling of study drugs and the treatment diary.

7.1 Administration Procedure

7.1.1 Administration Regimens

7.1.1.1 Observation period

In the observation period, placebo is orally administered once daily for 3 weeks, using a single-blind design. The number of tablets of the study drug taken per administration is shown in Table 7.1.1.1-1.

Table 7.1.1.1-1 Number of Tablets of Study Drug Taken per Administration (observation period)

Treatment group	Number of tablets taken per administration
Placebo	Placebo × 6 tablets

7.1.1.2 Treatment period

In the treatment period, the study drugs (TAS-303 [redacted] or placebo) are orally administered once daily for 8 weeks, using double-blind design. The number of tablets of the study drug taken per administration is shown in Table 7.1.1.2-1.

Table 7.1.1.2-1 Number of Tablets of Study Drug Taken per Administration (treatment period)

Treatment group	Number of tablets taken per administration	TAS-303 equivalent
TAS-303 3 mg	TAS-303 [redacted] × 3 tablets and Placebo × 3 tablets	3 mg
TAS-303 6 mg	TAS-303 [redacted] × 6 tablets	6 mg
Placebo	Placebo × 6 tablets	-

7.2 Total Blood Volume

The volume of blood collected in this study is shown in Table 7.2-1. The total volume of blood collected from each patient is approximately 90 mL.

Table 7.2-1 Volume of Blood Collected during Study Participation Period

Item	Number of blood collection	Volume of blood collected per collection	Total volume of collected blood
Laboratory test	5	Approximately 15 mL	Approximately 75 mL
Pregnancy test	3 (for blood test)	Approximately 5 mL	Approximately 15 mL
Total	5	-	Approximately 90 mL

7.3 Restrictions

7.3.1 Contraception

Patients practice contraception during the study participation period and for 40 days after the completion of the treatment with the study drugs. The Investigator or Sub-investigator instructs practicing contraception using the double barrier method (condom and diaphragm), intrauterine device or other methods during the study participation period and the contraception period. Because the possibility that the study drugs inhibit the metabolism of oral contraceptive drugs cannot be denied, use of oral contraceptive drugs is not considered appropriate.

7.3.2 Food and Drink

During the treatment with the study drugs, patients should be instructed not to ingest food and beverages containing grapefruit or St. John's wort. Because ingestion of these food and beverages during the treatment with the study drugs may enhance or diminish the action of TAS-303, presence or absence of adverse events should be checked in cases of ingestion.

7.4 Concomitant medications and therapies

7.4.1 Prohibited Concomitant Medications and Therapies

The following concomitant medications and therapies are prohibited after the enrollment in the observation period until the day of Week 8 visit in the treatment period or the day of completion of treatment with the study drugs. The rationale is presented in Section 14.4.

(1) Drugs and therapies for SUI

- Clenbuterol hydrochloride
- Chinese herbal medicine or other related products (Hochuekkito, processed food containing medicinal Cucurbita pepo seed extract and soy germ extract [PEP])
- Tricyclic antidepressants (imipramine hydrochloride, amitriptyline hydrochloride, clomipramine hydrochloride, etc.)
- Estrogen
- α adrenergic receptor agonists (ephedrine, phenylpropanolamine, midodrine, methoxamine, etc.)
- Duloxetine
- Surgical treatment (TOT procedure, TVT procedure, etc.)
- Physical therapy (pelvic floor muscle training, feedback training, biofeedback training, vaginal cone, electric stimulation therapy, magnetic stimulation therapy, etc.)

(2) Drugs and therapies for overactive bladder (OAB)

- Anticholinergics (oxybutynin hydrochloride, propiverine hydrochloride, tolterodine tartrate, solifenacin succinate, imidafenacin, fesoterodine fumarate,

propantheline bromide, etc.)

- β_3 receptor agonist (mirabegron)
- Flavoxate hydrochloride
- Tricyclic antidepressants (imipramine hydrochloride, amitriptyline hydrochloride, clomipramine hydrochloride, etc.)
- Chinese medicine (Goshajinkigan, etc.)
- Estrogen
- Botulinum toxin
- Resiniferatoxin, capsaicin
- Antidiuretic hormone (desmopressin, etc.)
- Physical therapy (pelvic floor muscle training, feedback training, biofeedback training, bladder training, electric stimulation therapy, magnetic stimulation therapy, etc.)

(3) Drugs and therapies for voiding dysfunction

- Bethanechol chloride, distigmine bromide
- α adrenergic receptor antagonists (urapidil, naftopidil, terazosin hydrochloride, etc.)

(4) Other drugs speculated to affect the urinary function

(5) Drugs that inhibit NA reuptake

- Atomoxetine hydrochloride
- Amezinium metilsulfate
- Milnacipran hydrochloride
- Venlafaxine hydrochloride
- Maprotiline hydrochloride

(6) Other investigational drugs

7.4.2 Concomitant Medications and Therapies Requiring Precautions

Concomitant medications and therapies requiring precautions are specified as follows for the period after the enrollment in the observation period until the day of Week 8 visit in the treatment period or the day of completion of treatment with the study drugs. The rationale is presented in Section 14.5.

(1) Drugs with potent inhibitory action on CYP3A (itraconazole, voriconazole, clarithromycin, etc.)

[redacted]

(2) Drugs with potent CYP3A4-inducing action (carbamazepine, phenobarbital, phenytoin, rifabutin, rifampicin, etc.)

[redacted]

(3) The following drugs requiring caution in concomitant use with grapefruit juice

1) AT_1 receptor antagonist/calcium blocker combination drugs (azilsartan/amlodipine besylate, irbesartan/amlodipine besylate, olmesartan medoxomil/azelnidipine, candesartan cilexetil/amlodipine besylate, telmisartan/amlodipine besylate, valsartan/cilnidipine, valsartan/amlodipine besylate)

2) Calcium blockers (felodipine, nisoldipine, azelnidipine, nifedipine, aranidipine, efonidipine hydrochloride ethanolate, cilnidipine, nicardipine hydrochloride, nitrendipine, amlodipine besylate, nilvadipine, barnidipine hydrochloride, manidipine hydrochloride, verapamil hydrochloride, cinacalcet hydrochloride, benidipine hydrochloride)

3) HMG-CoA reductase inhibitor (atorvastatin calcium hydrate, simvastatin)

4) Drugs for orthostatic hypotension and vascular headache (dihydroergotamine mesilate)

5) Antipodagric (colchicine)

6) Endothelin receptor antagonist (bosentan hydrate)

7) Drug for migraine (eletriptan hydrobromide)

[redacted]

8. Pharmacokinetics and Pharmacodynamics

Pharmacokinetics and pharmacodynamics are not evaluated in this study.

9. Pharmacogenomic Analysis

Pharmacogenomic investigation is not performed in this study.

10. Discontinuation and Study Completion

10.1 Criteria for Discontinuation of the Study at Individual Study Sites

The Sponsor or Investigator may discontinue the study at a study site where major or continuous non-compliance with Good Clinical Practice (GCP) or the study protocol by the Investigator or Sub-investigator is found to have interfered or may have interfered with the proper conduct of the study. In such a case, the Sponsor or Investigator should promptly notify the IRB in writing, according to the standard operating procedure (SOP) of the study site.

10.2 Criteria for Termination of the Entire Study

The Sponsor reserves the right to discontinue the study for administrative reasons at any time. If the Sponsor should discover conditions arising during the clinical study that indicate it should be terminated, an appropriate schedule for termination of the entire or part of the study will be instituted. In such a case, the Sponsor will promptly notify the study site(s) lead with the reasons for study termination. Study site leads will promptly inform, in writing, the IRB and the Investigator. The Investigator or Sub-investigator should immediately advise the patients of the termination of the study and change the study treatment to other treatments. The Sponsor will promptly notify the Regulatory Authorities of the premature termination of the study.

11. Efficacy Evaluation

11.1 Evaluation of symptom scores

11.1.1 ICIQ-SF

The subjective symptoms of SUI (frequency of urine leakage, volume of urine leakage, impact on living and reason for urine leakage) are evaluated using ICIQ-SF. The content of ICIQ-SF is shown in APPENDIX 1 ICIQ-SF.

The total score of ICIQ-SF is defined as the sum of the scores for Q1, Q2 and Q3.

The Investigator or Sub-investigator instructs patients to enter the score corresponding to each subjective symptom at the evaluation time point. The Investigator or Sub-investigator should be careful not to bias the evaluation by, for example, being close to patients or talking to them while they are evaluating.

11.1.2 PGI-I

The patients' impression of improvement of urinary incontinence is evaluated using PGI-I. The content of PGI-I is shown in APPENDIX 2 Patient Global Impression-Improvement: PGI-I.

The improvement of PGI-I is defined as the selection of "very much better", "much better" or "a little better".

The Investigator or Sub-investigator instructs patients to evaluate the improvement of urinary incontinence at the evaluation time point using the following 7-point scale. The Investigator or Sub-investigator should be careful not to bias the evaluation by, for example, being close to patients or talking to them while they are evaluating.

- Very much better
- Much better
- A little better
- No change
- A little worse
- Much worse
- Very much worse

11.2 Evaluation of QOL Scores

QOL associated with urinary incontinence is evaluated using I-QOL. The content of I-QOL is shown in APPENDIX 3 I-QOL.

The total score of I-QOL is defined as the sum of the scores for all questions. In the evaluation of I-QOL scores for individual areas, 1) the score for "avoidance and limiting behavior" is defined as the sum of the scores for Questions 1, 2, 3, 4, 10, 11, 13 and 20, 2) the score for "psychosocial impacts" is defined as the sum of the scores for Questions 5, 6, 7, 9,

15, 16, 17, 21 and 22, and 3) the score for “social embarrassment” is defined as the sum of the scores for Questions 8, 12, 14, 18 and 19.

The Investigator or Sub-investigator instructs patients to enter the score corresponding to each subjective symptom at the evaluation time point. The Investigator or Sub-investigator should be careful not to bias the evaluation by, for example, being close to patients or talking to them while they are evaluating.

11.3 Urination Record (Bladder Diary)

Time of voiding, presence or absence of urgency, time of urinary incontinence, reason for leakage and status of use of pads are evaluated using the urination record (bladder diary).

The Investigator or Sub-investigator explains how to fill out the urination record (bladder diary) to patients. The details of the entry method are shown in the urination record (bladder diary). Patients are instructed to enter the time of voiding, presence or absence of urgency, time of urinary incontinence and reason for leakage during the 7 days before the day of the next visit in the urination record.

The urination record is issued to patients at every visit and they are instructed to bring it in the next visit. The urination record is collected in the subsequent visit, in principle.

11.4 1-hour Pad Test

Amount of urinary incontinence is evaluated by 1-hour pad test. The details of the 1-hour pad test are shown in APPENDIX 4 1-hour Pad Test.

The Investigator or Sub-investigator explains a 1-hour pad test to patients. The details of the method are shown in the written procedures of pad test. While patients are performing the pad test, it should be confirmed that they are carrying out the movements specified in the procedures.

12. Safety Evaluation

12.1 Adverse Events

12.1.1 Definition of Adverse Events

An AE is any untoward medical condition that occurs in a patient while participating in a clinical study and does not necessarily have a causal relationship with the study drug.

A complete and specific clinical diagnosis should be provided as an AE term. If a diagnosis is not available, then report signs and symptoms.

Symptoms or laboratory abnormalities associated with a pre-existing medical condition, SUI or other disease, should not be considered an AE. However, occurrences of new symptoms as well as worsening of pre-existing medical conditions are considered AEs.

Any laboratory abnormality that is clinically significant or medically important must be reported as an AE, unless it is a result considered to be supporting a clinical diagnosis that is already reported as an AE.

When a laboratory test value is handled as an adverse event:

- When intervention is required.
- When interruption or discontinuation of treatment with the study drugs or other measures are required.
- Additional tests were performed for diagnosis
- Any other events that are considered as medically important by the Investigator or Sub-investigator occur.

The details of the entry method are presented in the guide for preparation, change and correction of case report form (CRF).

Pregnancy and medication errors are described in Section 12.5.

12.1.2 Severity of Adverse Events

The severity of adverse events is rated as one of the following (";" means "or").

(1) Mild

Mild; asymptomatic or mild symptoms; clinical or examination findings only; intervention not indicated

(2) Moderate

Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activity of daily living (ADL)*

(3) Severe

Severe or medically significant but not immediately life-threatening; hospitalization of prolongation of hospitalization indicated; disabling; limiting self-care ADL**

Moreover, life-threatening events, events requiring emergency treatment and deaths due to adverse events are included in severe events.

*: Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**: Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications and not bedridden.

12.1.3 Causal Relationship with the Study Drug

Causal relationship between AE and the study drug will be assessed using the following 2-point scale, taking into consideration factors including the patient's condition, medical history, concomitant medications, and temporal relationship between study drug administration and onset of the AE. When the causal relationship with study drug was rated as being "No reasonable possibility", the reason is entered in the CRF.

(1) Select "**Reasonable possibility (<u>Related</u>)**" if the event follows a reasonable temporal sequence from study drug administration and any of the following conditions are true:

- A positive Dechallenge. This means that the event improves or resolves after the study drug is stopped (temporarily or permanently).
- A positive Rechallenge. This means that the event reappears after the study drug is restarted.
- The event cannot be reasonably explained by the patient's clinical state and/or other therapies administered.
- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (eg, angioedema, Stevens-Johnson syndrome).

(2) Select "**No reasonable possibility (<u>Not related</u>)**" if there is no evidence to suggest a causal relationship between study drug and the AE.

No reasonable possibility is selected if:

- The event occurred prior to the study drug administration.
- When the adverse event was possibly caused by the primary disease, complications, concomitant medications, predisposition of the patient or other factors

12.1.4 Outcome of Adverse Events

Record the outcome of AEs as follows:

(1) Recovered/resolved

Symptom or finding disappeared or returned to the previous condition.

(2) Recovering/resolving

Symptom or finding almost disappeared or almost returned to the previous condition.

(3) Not recovered/not resolved

Symptom or finding neither resolved nor changed.

(4) Recovered/resolved with sequelae

Symptom resolved, but dysfunction that interferes with daily life is considered to have been caused by the adverse event.

(5) Fatal

The patient died because of the adverse event.

12.1.5 Reporting of Adverse Events

Adverse events are reported for the period from the acquisition of consent to the completion of the follow-up observation. All adverse events are entered in the source documents. In CRF, the adverse events that occurred in relation to this study from the acquisition of consent up to the start of the treatment with study drugs and the adverse events that have occurred since the start of the treatment with the study drugs are entered.

When serious medical occurrences including adverse events and deaths were reported or observed by the Investigator or Sub-investigator after the completion of the follow-up observation and the causal relationship between these occurrences and the study drugs cannot be denied, the Investigator or Sub-investigator reports them to the Sponsor.

12.1.6 Follow-up of Adverse Events

When an AE occurs, the Investigator or Sub-investigator will promptly provide appropriate measures and follow up the patient until the AE is confirmed to have resolved. If it is not possible to follow up an AE for any of the following reasons, this should be documented fully in the CRF as follows:

- Another treatment is provided and it is therefore impossible to evaluate a causal relationship with the study drug.
- It is difficult to follow up the patient due to transfer to another hospital.
- The patient refuses follow up.
- The patient dies.
- Although the AE has not yet resolved, the Investigator or Sub-investigator considers that the AE is stable or no further improvement is expected.

12.2 Serious Adverse Events

12.2.1 Definition of Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

(a) Results in death.

(b) Is life-threatening.

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

(c) Requires inpatient hospitalization or prolongation of existing hospitalization. The following are not considered hospitalizations for the purposes of assessing seriousness:

- Emergency room visits <24 hours.
- Hospitalizations for preplanned procedures.
- Hospitalization for study-related treatment and procedures.

(d) Results in persistent or significant disability or incapacity.

(e) Is a congenital anomaly/birth defect (if exposure to product just before conception or during pregnancy resulted in an adverse outcome in the child).

(f) Other important medical event
Note: That may not be immediately life-threatening, result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.
Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

12.2.2 Reporting of Serious Adverse Events

SAEs must be reported to the Sponsor **within 24 hours** from the time the Investigator or Sub-investigator first becomes aware of the SAE. Comprehensive information available at the time of initial reporting (eg, narrative description, medical history, concomitant medications) should be provided with careful consideration regarding causal relationship and serious criterion. The contact information for reporting the SAE are provided below.

After the initial SAE notification to the Sponsor, follow up SAE information will be submitted each time that important follow-up information (eg, diagnosis, outcome, assessment of causal relationship, results of specific investigations) becomes available.

The Investigator also must submit further information if it is required by the Sponsor, the director of study site or IRB.

All the SAEs that occurred from the time of consent to the completion of the follow-up observation are reported to the Sponsor. When SAEs (including deaths) occurred outside the study participation period specified in the protocol, these SAEs are reported to the Sponsor only if the Investigator suspects a relationship between them and the study drugs.

SAEs should be reported to:

Clinical Development Division, Taiho Pharmaceutical Co., Ltd.

1-2-4 Uchikanda, Chiyoda-ku, Tokyo 101-0047

Phone 03-3293-2455 (direct number), Fax 03-3293-1271

(from 8:40 a.m. to 5:30 p.m. except Saturdays, Sundays and national holidays and the period from December 29 to January 4)

Outside the above time frame, the product leader or the clinical team leader should be

contacted.

For the contact information of the product leader and the clinical team leader, see the document attached to the protocol.

12.2.3 Follow-up of Serious Adverse Events

SAEs are followed up in the same way as the follow-up of adverse events. Follow-up of adverse events is described in Section 12.1.6. When the follow-up of SAEs cannot be continued, the reason is reported in the reports of SAEs.

12.2.4 Possibility of Prediction of Serious Adverse Events in Use of Study Drugs

It is determined based on the description in the investigator's brochure whether or not a serious adverse event can be predicted in association with the study drugs (known, unknown). When the characteristics and severity are consistent with the description, the event is considered to be "known". Even if the event is listed in the brochure, its characteristics and severity are inconsistent with the description (acute kidney failure and nephritis interstitial, hepatitis and hepatitis fulminant, etc.), the event is considered to be "unknown".

Because SAEs for which a causal relationship cannot be denied have not occurred in the use of TAS-303, all SAEs that occurred in this study are handled as "unknown" events.

12.3 Adverse Events of Special Interest

12.3.1 Definition of Adverse Events of Special Interest

In this study, adverse events of special interest are not defined.

12.4 Adverse Reactions

12.4.1 Definition of Adverse Reactions

Among the adverse events that occurred during or after the treatment period, those for which a causal relationship with the study drugs was rated as being "reasonably possible" by the Investigator or Sub-investigator (including abnormal laboratory test values) are considered to be adverse reactions.

12.5 Other Information

12.5.1 Pregnancy

In this study, contraception during the study participation period and for 40 days after the completion of the treatment with the study drugs is required.

If by any chance a patient becomes pregnant during the specified period for contraception, the Investigator or Sub-investigator reports the information about pregnancy of this patient **within 24 hours** from the time the Investigator or Sub-investigator first becomes aware of the pregnancy or its outcome. Information regarding pregnancy is entered in the Pregnancy Form and sent to the Sponsor by e-mail, fax or other methods. New and/or corrected information regarding the pregnancy obtained after submitting the Pregnancy Form must be submitted by emailing or faxing an updated Pregnancy Form to the Sponsor.

The Investigator or Sub-investigator will follow the pregnancy and report the outcome. If

the outcome of the pregnancy is a stillbirth, congenital anomaly/birth defect, or a serious event in the mother, report as an SAE to the Sponsor. Live births will be followed up by the Investigator or Sub-investigator and any information that may be associated with the study drug should be reported to the Sponsor even after study completion.

12.5.2 Medication Errors

A medication error is defined as any unintentional error in the prescribing, dispensing or administration of the study drug while the study drug is in the control of the healthcare professional or patient. The error may be related to the administration of a wrong drug, nature of the medication, route of administration, dosage or frequency of the treatment as specified in this protocol.

The following procedures should be followed:

- Medication errors with the study drugs regardless of whether it is associated with an AE (even if not fulfilling a definition of SAE) are to be promptly reported to the Sponsor.
- No antidote that can be used for the overdose of the study drugs is known. While carefully monitoring the patient, proactive treatment is provided by prophylactic and symptomatic methods to prevent or treat possible adverse reactions.

13. Statistical Analysis

Statistical analysis is performed following the plan described below. Details are specified in the separately prepared statistical analysis plan. The first version of the statistical analysis plan is prepared before the database lock. When the statistical analysis plan is changed, time of change, changed content and the reason are recorded.

13.1 Statistical Plan

13.1.1 Timing of Statistical Analysis

Statistical analysis is performed after the completion of all patients' study. Before unblinding, preliminary examination (blinded review) of the measurement of efficacy and safety, distribution of endpoints, relationship among items and other aspects is performed to make decisions regarding the handling of patient data, statistical analysis methods and other points.

13.1.2 Analysis Populations and Criteria for Handling Patient Data

13.1.2.1 Analysis Population

The analysis populations of this study are defined as follows:

Table 13.1.2.1-1 Definitions of Analysis Populations

Analysis Set	Definition
Screened Patients	A group of all patients who gave consent
Enrolled Patients in observation period	A group of all patients enrolled in the observation period of this study
Enrolled Patients in treatment period	A group of all patients enrolled in the treatment period of this study
All Treated Patients	A group of patients who took the study drugs at least once among those enrolled in the observation period
Full Analysis Set (FAS)	A group of patients who took the study drugs for the treatment period at least once and have at least 1 efficacy endpoint before the start of the treatment period and during the treatment period among those enrolled in the treatment period
Per Protocol Set (PPS)	A group of patients in FAS except for those who meet the following criteria (1) Shown not to meet inclusion criteria (2) Shown to meet exclusion criteria (criteria affecting efficacy evaluation) (3) Less than 80% compliance with the treatment during the treatment period (4) Less than 70% entry rate in urination record (status of urinary incontinence) at Week 8 of the treatment period (5) Use of prohibited concomitant drugs or therapies considered to influence efficacy evaluation

Handling of the patients who are in circumstances not specified in the definition of analysis populations is determined before database lock through discussion by the Sponsor, the medical experts and other personnel.

13.1.2.2 Criteria for Handling of Patient Data

The criteria for handling of patient data in the study are described below.

For problematic cases the Sponsor and the Medical Experts will discuss and determine an approach prior to database lock.

(1) Handling of missing values and abnormal values

- Handling of missing values in efficacy endpoints is specified for each analysis.
- Missing values in safety endpoints are not imputed. The proportion including that of subjects with adverse events is calculated using the analysis population as the denominator for the observation period and using the number of subjects who took the study drugs for the treatment period at least once among those in the analysis population as the denominator for the treatment period.
- The analyses will include all measured data unless the laboratory tests (eg, the effect of hemolysis during blood collection, showed obvious abnormal values). If abnormal values are excluded from the analysis, they should be specified and the reasons for exclusion should be stated.

(2) Handling of data of patients treated by study drug different from the assigned one

- In the analysis of the subjects treated with the study drugs or PPS, the data of patients treated with the study drug of the treatment group different from the group they are allocated to are handled as the data of the treatment group for the study drug they actually received.
- In the analysis of FAS, the data of these subjects are handled as the data in the allocated group.

13.1.3 Statistical Analysis Methods

The main statistical methods to evaluate the primary and secondary objectives of this study are described below.

13.1.3.1 Patient Disposition and Demographic Characteristics

(1) Patient disposition

- The number of patients enrolled will be counted so that their attribution to each analysis population can be seen, and patients excluded from the analysis populations will be listed with the reasons.

(2) Demographic characteristics of patients

- Distribution of the main patient background, disease characteristics and other characteristics in PPS is summarized.

13.1.3.2 Primary Endpoint Analysis

The following analyses are performed regarding the rate of change in mean number of urinary incontinence per 24 hours at Week 8 of the treatment period from baseline, which is the primary endpoint.

(1) Main analysis

- In PPS, the difference between the TAS-303 6 mg group and the placebo group and the difference between the TAS-303 3 mg group and the placebo group are

tested by t test using the two-sided significance level of the entire test of 5%. To consider multiplicity, the significance level for each comparison is adjusted by Hochberg's method.[14)]

(2) Sensitivity analysis of main analysis

- The evaluation in (1) is performed in FAS. Missing values are imputed using last observation carried forward (LOCF).

(3) Secondary analysis of primary endpoint

The following analyses are performed in FAS and PPS.

- Summary statistics are calculated for each treatment group. Missing values are not imputed.
- The rate of change from baseline in mean number of urinary incontinence per 24 hours for each week was analyzed using mixed-effect models for repeated measures (MMRM) to estimate the therapeutic effect of TAS-303 at Week 8 of the treatment period.
- In PPS and FAS, intergroup comparison is performed by the Wilcoxon rank sum test. Missing values are imputed by LOCF.

(4) Analysis by allocation factor

- The primary endpoint is analyzed for each condition of urinary incontinence (SUI and MUI).
- The primary endpoint is analyzed for each category of mean number of urinary incontinence per 24 hours (less than 2/day and 2 or more/day).

13.1.3.3 Secondary Endpoint Analysis

13.1.3.3.1 Efficacy Analysis

The following analyses are performed for each treatment group in FAS and PPS.

(1) Mean number of urinary incontinence per 24 hours

- Summary statistics of measured values, rate of change from baseline and amount of change at each evaluation time point are calculated.
- The rate of change from baseline is analyzed using MMRM and the therapeutic effect of TAS-303 at all evaluation time points is estimated.
- The proportion of subjects with 50% or greater improvement in the rate of change from baseline and 95% CI at each evaluation time point are calculated.

(2) Amount of urinary incontinence by 1-hour pad test

- Summary statistics of measured values, rate of change from baseline and amount of change at each evaluation time point are calculated.
- The proportion of subjects with 2.0 g or less measured values at Week 8 of the treatment period and 95% CI are calculated.
- The proportion of subjects with 50% or greater improvement in the rate of change from baseline at Week 8 of the treatment period and 95% CI are

calculated.

(3) Mean number of used pads per 24 hours (only in patients who used incontinence pads)

- Summary statistics of measured values, rate of change from baseline and amount of change at each evaluation time point are calculated.

(4) ICIQ-SF score

- Summary statistics of total score and amount of change from baseline at each evaluation time point are calculated.
- Summary statistics of the score for each item and amount of change from baseline at each evaluation time point are calculated.

(5) Patient Global Impression-Improvement (PGI-I)

- Proportion for each rating on 7-point scale at each evaluation time point is calculated.
- Proportion of improvement ("very much better", "much better", "a little better") at each evaluation time point and 95% CI are calculated.

(6) I-QOL score

- Summary statistics of total score and amount of change from baseline at each evaluation time point are calculated.
- Summary statistics of the score of each area and amount of change from baseline at each evaluation time point are calculated.

(7) Analysis by allocation factor

- The secondary endpoints are analyzed for each condition of urinary incontinence (SUI and MUI).
- The secondary endpoints are analyzed for each category of mean number of urinary incontinence per 24 hours (less than 2/day and 2 or more/day).

(8) Mean number of SUI per 24 hours

Among the incidents of urinary incontinence recorded in the urination record (bladder diary), the data of the incidents excluding those that occurred because patients "could not hold it in" are used in the following analyses.

- Summary statistics of measured values, rate of change from baseline and amount of change at each evaluation time point are calculated.
- The rate of change from baseline is analyzed using MMRM and the therapeutic effect of TAS-303 at all evaluation time points is estimated.
- The proportion of subjects with 50% or greater improvement in the rate of change from baseline and 95% CI at each evaluation time point are calculated.

(9) Mean number of UUI per 24 hours

Among the incidents of urinary incontinence recorded in the urination record (bladder

diary), the data excluding those that occurred “while coughing, laughing, sneezing, movements including standing up or engaging in sports” are used in the following analyses.

- Summary statistics of measured values, rate of change from baseline and amount of change at each evaluation time point are calculated.
- The rate of change from baseline is analyzed using MMRM and the therapeutic effect of TAS-303 at all evaluation time points is estimated.
- The proportion of subjects with 50% or greater improvement in the rate of change from baseline and 95% CI at each evaluation time point are calculated.

13.1.3.3.2 Administration Status

In the subjects treated with the study drugs, the following analyses are performed for the observation period and the treatment period separately, and for each treatment group.

(1) Administration status

- The administration status (total dose and total duration of administration) for each patient is summarized.

(2) Status of administration completion

- Summary statistics of compliance with treatment with the study drugs are calculated for each patient.

- Presence or absence of study discontinuation (including timing) and its reason are tabulated.

13.1.3.3.3 Safety Analysis

In the subjects treated with the study drugs, the following analyses are performed for each treatment group. The analysis for the treatment period is performed in subjects treated in the treatment period.

(1) AEs

The following analyses are performed for the observation period and for the treatment period, separately.

- The incidence of AEs is calculated.
- The number of patients and the incidence are calculated for each adverse event for each severity.
- The incidence of adverse events for each timing (Weeks 4 and 8 and follow-up observation) in the treatment period is calculated.
- For all adverse events that occurred from the start of the treatment with the study drugs to the completion day of the follow-up observation, name of the event, severity, onset date, treatment, outcome, causal relationship with study drugs and comments are listed for each adverse event in each patient.

(2) Adverse reactions

- Analyses similar to those for adverse events are performed for adverse reactions

(except preparation of the list).

(3) Blood pressure, pulse rate and body temperature

- Summary statistics of blood pressure, pulse rate and body temperature are calculated for each evaluation time point.
- Summary statistics of the amount of change in measured values of blood pressure and pulse rate from the values immediately before the start of the treatment with the study drugs are calculated for each evaluation time point.
- For blood pressure and pulse rate, the amount of change in measured values at each evaluation time point from the values immediately before the start of the treatment with the study drugs is categorized and the frequency for each category is calculated.

(4) 12-lead Electrocardiography

A test item based on 12-lead electrocardiogram, QT interval corrected using Fridericia's formula (QTcF) is used.

- Summary statistics of measured values of QTcF and heart rate are calculated for each evaluation time point.
- Summary statistics of the amount of change in measured values of QTcF and heart rate from the values immediately before the start of the treatment with the study drugs are calculated for each evaluation time point.
- For QTcF, measured values at each evaluation time point are categorized and the frequency for each category is calculated.
- For QTcF and heart rate, the amount of change in measured values at each evaluation time point from the values immediately before the start of the treatment with the study drugs is categorized and the frequency for each category is calculated.
- Subjects with abnormal changes in 12-lead electrocardiogram are listed.

(5) Laboratory test values

- Summary statistics of each laboratory test item are calculated for each evaluation time point.

(6) Urinary flow test

- Summary statistics of each item of urinary flow test (maximum urinary flow rate [free Q_{max}], average urinary flow rate [free Q_{ave}], voided volume and time of voiding) are calculated for each evaluation time point.
- Summary statistics of the amount of change in measured values of each urinary flow test item from the values immediately before the start of the treatment with the study drugs are calculated for each evaluation time point.

(7) Residual urine volume

- Summary statistics are calculated for each evaluation time point.
- Summary statistics of the amount of change in measured values from the values

immediately before the start of the treatment with the study drugs are calculated for each evaluation time point.

(8) Mean number of urinations per 24 hours

- Summary statistics are calculated for each evaluation time point.
- Analyses are performed for each condition of urinary incontinence (SUI and MUI).

13.1.4 Target Number of Patients and Sample Size Justification

Target number of patients: 250 to be enrolled in the treatment period

14. Rationales

14.1 Rationale for Endpoints

14.2 Rationale for Administration Methods

In Study 10060010, the effects on the pharmacokinetics of TAS-303 were evaluated in an exploratory manner and meals were considered not to affect greatly on the pharmacokinetics of TAS-303 based on the results. In addition, from the results of Study 10060020, once-daily multiple-dose administration of TAS-303 at doses up to 6 mg was determined to pose no safety problems and be tolerated.

Considering the above points and also compliance by the patients participating in this study, once daily administration was specified.

14.3 Rationale for Inclusion and Exclusion Criteria

14.3.1 Rationale for Inclusion Criteria

14.3.1.1 At the Time of Enrollment in Observation Period

(1) This criterion was specified to select female patients who can appropriately give consent in accordance with GCP and the spirit of the Declaration of Helsinki.

(2) This criterion was specified to avoid the impact of age-related impairment of physiological functions in participating patients on the efficacy of TAS-303.

(3) - (6) In order to achieve the objective of this study, these criteria were specified for the selection of patients who have stable symptoms of SUI.

14.3.1.2 At the Time of Enrollment in Treatment Period

These criteria were specified to exclude the patients who respond extensively to placebo and make the patient population as uniform as possible after confirming their eligibility once again as subjects for the evaluation of efficacy of TAS-303 based on the information in the urination record.

14.3.2 Rationale for Exclusion Criteria

14.3.2.1 At the Time of Enrollment in Observation Period

(1) - (10), (14), (16), (17), (19) These criteria were specified to exclude the patients for whom appropriate efficacy evaluation of TAS-303 may become impossible.

(11) This criterion was specified to ensure the safety of patients considering 1) mydriasis has been reported as an adverse reaction to atomoxetine, which has a selective inhibitory action on NA reuptake similar to that of TAS-303, and atomoxetine is contraindicated in patients with angle-closure glaucoma and 2) mydriasis has been observed in repeated-dose preliminary studies in rats and dogs.

(12) This criterion was specified because patients with accompanying severe diseases or malignant tumors may have unstable physiological functions and are considered inappropriate for safety evaluation of TAS-303.

(13) This criterion was specified to ensure the safety of patients.

(15) This criterion was specified because the safety and pharmacokinetics of TAS-303 in patients with liver damage or renal damage have not been evaluated.

(18) This criterion was specified because, in accordance with "General Considerations for Clinical Trials"[15], it is undesirable to enroll patients repeatedly into clinical studies without a sufficient washout period for the purposes of ensuring safety and eliminating carry-over effect.

[redacted]

(22) This criterion was specified to ensure the safety of patients or to exclude patients who may affect the results of this study by the requirement other than the specified criteria.

14.3.2.2 At the Time of Enrollment in Treatment Period

(1) This criterion was specified to exclude patients with low compliance and to appropriately evaluate the efficacy of the investigational product.

(2) This criterion was specified to exclude patients who extensively respond to the placebo and to appropriately evaluate the efficacy of the investigational product.

(3) - (17) As is the case with the exclusion criteria at the time of enrollment in the observation period, these criteria were specified to ensure the safety of patients and to exclude patients who may affect the efficacy and safety evaluation of TAS-303.

14.4 Rationale for Prohibited Concomitant Medications and Therapies

(1), (2), (3), (4) These criteria were specified because these drugs and therapies may affect the efficacy evaluation of TAS-303.

(5) This criterion was specified because drugs with inhibitory action on NA reuptake

similar to that of TAS-303 may affect the efficacy and safety evaluation of TAS-303.

(6) This criterion was specified because other investigational drugs have unclear drug profiles and may affect the efficacy and safety evaluation of TAS-303.

14.5 Rationale for Concomitant Medications and Therapies Requiring Precautions

[redacted]

14.6 Rationale for Contraception Period

[redacted]

14.7 Rationale for Restriction on Food and Beverages

[redacted]

15. Case Report Form (eCRF)

In this study, electronic case report form (eCRF) and Electronic Data Capture (EDC) system will be provided by the Sponsor. In order to protect eCRF data, eCRF data will be transmitted from study sites via SSL Internet communication, and access to the EDC system will be limited only to the Investigator, Sub-investigator and appropriate personnel authenticated by IDs and passwords unique to individuals, which should be maintained confidentially and never shared. Monitors will have the right to access to the EDC system for performing source data verification. Monitors, data managers, auditors and other relevant personnel of the Sponsor will receive a right to access to the EDC system according to their roles. These monitors, data managers, auditors or other relevant personnel will not have authority to enter or correct data or provide electronic signatures in eCRFs.

15.1 Recording of Case Report Forms

The eCRFs are prepared for the patients enrolled in the observation period. All the content except the special instructions is entered in English. The Investigator, Sub-investigator and Clinical Research Coordinators should input, change, correct or add data in eCRFs using the "eCRF Completion Guidelines" as a reference. In addition, the Investigator should check whether the contents of an eCRF are adequate and then electronically sign the eCRF.

After verification of the eCRF by the Sponsor, the Sponsor may make queries on additional check items. The Investigator, Sub-investigator and Clinical Research Coordinators should check the details of data required to be verified, correct as necessary and return to the Sponsor.

15.2 Completing Case Report Forms

When completing an eCRF, the following should be considered:

(1) The Sponsor should distribute the eCRF Completion Guidelines to the Investigator, Sub-investigator and Clinical Research Coordinators. The Investigator or Sub-investigator should enter, change, correct or add data in eCRFs in accordance with the Guidelines. The Clinical Research Coordinators may enter, change, correct or add data in eCRFs based on source documents prepared by the Investigator and Sub-investigator in accordance with the Guidelines.

(2) Information used for personal authentication in the EDC system (eg, ID and passwords) shall never be shared among the Investigator, Sub-investigator and Clinical Research Coordinators from the perspective of preparation of eCRFs based on proper personal authentication. This information shall be retained in such a manner that it will not be leaked to other people for preventing improper access to eCRFs by masquerading. The Sponsor, Investigator, Sub-investigator and Clinical Research Coordinators should as necessary check an audit trail of the EDC system to verify whether or not there is unauthorized access or data manipulation by masquerading.

(3) When corrections and/or changes are made, the reasons for the correction or change should be also entered. The reasons for corrections/changes will be recorded in an audit trail together with the details of the corrections/changes.

(4) When a section to be filled out remains blank, if necessary, an expression to differentiate it from input omission should be entered eg, “MS (No Data)”.

(5) The Investigator should check information entered in the eCRF against source data (eg, medical records [charts]), confirm the information and electronically sign the eCRF.

(6) The electronic signature must be personally affixed by the Investigator.

The Investigator should record all the data on eCRFs in accordance with time limit in the following items (Except the Sponsor request to stop recording the data):

- Patient background (condition of urinary incontinence, presence or absence of menopause, menstrual cycle): within 7 days after enrollment
- ICIQ-SF and I-QOL: within 7 days after they are recorded
- Urination record: within 7 days after collection day
- 1-hour pad test: within 7 days after it is performed
- Adverse events (as much information as possible): Within 7 days after the time point the Investigator or Sub-investigator first became aware of their onset
- Hematological tests, serum chemistry and urinalysis: Within 14 days after they are performed
- Other items: Within 14 days after the completion day of the follow-up observation

16. Protocol Compliance, Deviations and Amendments

16.1 Protocol Compliance

The Investigator will agree with the Sponsor on the details of the protocol and the sample CRF, and will sign or affix the signature and seal on and date the protocol or an alternative document as an evidence of the agreement that the protocol should be complied with.

In the case of amendment of the protocol and the sample CRF, and/or in the case of correction of the protocol and sample CRF by the direction of the Director of the study site based on the IRB, the same procedure should be followed.

16.2 Protocol Deviations

Severe protocol deviations are as follows:

(1) Failure to fulfill the inclusion criteria, which has a significant impact on the efficacy and safety evaluation of TAS-303

(2) Fulfillment of the exclusion criteria, which has a significant impact on the efficacy and safety evaluation of TAS-303

(3) Met the criteria for drug administration discontinuation, but did not discontinue

(4) Deviation that leads to significant noncompliance with GCP

To modify the protocol, the Investigator and the Sponsor must prepare a written agreement in advance and obtain the written approval of the IRB based on the prior review.

The Investigator should promptly provide written reports to the Sponsor, the director of study site, and the IRB via the director of study site on any change to the study that significantly affect the conduct of the study and/or increase the risk to patients.

However, where it is necessary for some unavoidable medical reason, eg, to eliminate an immediate hazard(s) to patients, deviation from or changes to the protocol may be implemented without prior written agreement with the Sponsor and prior approval by the IRB. In such a case, the Investigator should promptly report the details and the reason for the deviation or change to the Sponsor and the director of study site, and provide written reports to the IRB via the director of study site. The written approval of the IRB must be obtained.

The Investigator is to record any deviation from the protocol, irrespective of any reasons whatsoever.

16.3 Protocol Amendments

When the Sponsor considers that the protocol or the sample CRF requires an amendment, the Sponsor will submit the amended protocol or sample CRF to the Investigator. The Investigator will thoroughly review the details of amendment.

In the case of amendment of the protocol or sample CRF, the Sponsor will obtain agreement from the Investigator. For administrative amendments only (eg, change in the Sponsor's organization or system, change of name of the study site or department, change in the address or telephone number of the study site or the Sponsor, change of the Investigator's

title, change of monitors, change in CRF layout), no new agreement is required.

The Sponsor will submit the protocol or sample CRF to the director of study site, and obtain the approval of the IRB via the director of study site in a timely manner.

17. Direct Access to Source Documents

The Investigator and the director of study site must make all study-related records (eg, source documents) available for direct access for study-related monitoring, audit, IRB review, and regulatory inspection.

17.1 Source Documents

Source documents are original documents, data and records (eg., consent form, medical record, test notes, memos, record of prescription of drugs, data recorded by various automated instruments, patient files, list of names for screening, record of management of study drugs, medication diary, ICIQ-SF, PGI-I, I-QOL, urination record, record of 1-hour pad test, urinary flow test data and records retained at pharmacies, laboratories and medical technology departments involved in this study).

The following data will be recorded directly into the CRFs and will be considered source data:

- Previous and concurrent illnesses considered by the Investigator or Sub-investigator to have an important impact on the study
- Purpose of concomitant medications and therapies
- Names, purposes and treatment period of concomitant medications and therapies prescribed at other clinics
- Presence or absence, seriousness, severity and outcome of adverse events, reason for terminating follow-up investigation, causal relationship with the study drugs
- Presence or absence and reason of discontinuation and withdrawal
- Comments, reason for terminating the observation of course

17.2 Direct Access

The monitor of the Sponsor should cross-check the entries in the CRF and source documents to confirm that descriptions are accurate with regard to the following. If there are any discrepancies between the entries in CRF, etc., and source documents, the monitor will obtain from the Investigator records explaining such discrepancies.

- Data required by the protocol have been accurately recorded in the CRF and the report on SAEs, and are consistent with the descriptions in the source documents.
- All changes in dosage regimen or administration method, if any, have been recorded in the CRF for each patient.
- AEs have been recorded in the CRF in accordance with the protocol.
- All discontinued or drop-out cases among registered patients have been recorded in the CRF together with the reasons for discontinuation or drop-out.

18. Quality Control and Quality Assurance

The following quality control and quality assurance tasks are implemented in accordance with the SOP of the Sponsor.

18.1 Quality Control

The Sponsor is responsible for controlling the quality of the clinical study through, the following procedures according to individual SOPs related to study implementation and the Monitoring Plan for this study:

- The Sponsor will hold a meeting, etc. on the protocol to explain the study methodology (eg, patient selection, and investigation or assessment of the efficacy and safety to the Investigator, Sub-investigator or Clinical Research Coordinators).
- The Sponsor will conduct study monitoring of the study sites periodically to ensure that the study is performed in compliance with the protocol and GCP.
- The Sponsor will review the source documents to ensure that the entries in CRFs are accurate. In addition, the Sponsor will prepare the CRF Completion Guidelines and request the Investigator or Sub-investigator to make a correction in case that any change or correction is required.
- The Sponsor will check the items to be recorded in CRFs.
- The Sponsor will make sure that essential documents to be retained at the study sites are properly maintained.
- According to the Sponsor's SOPs, the Sponsor will complete recording and reporting pertaining to the operation of the study, data collection, DM, statistical analysis, and analyses of AEs, etc., and inspect them.

18.2 Sponsor’s Audits and Regulatory Inspections

For the purpose of ensuring compliance with the protocol, GCP and applicable regulatory requirements, the Investigator will permit auditing by the Sponsor and inspections by Regulatory Authorities.

The Investigator agrees to allow the auditors and inspectors to have direct access to the study records for review. The people performing these activities will not disclose any personal identity or personal medical information assessed.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data and documents pertaining to the clinical study. As soon as the Investigator is notified of a planned inspection by the Regulatory Authorities or IRB, the Investigator will inform the Sponsor. Any results arising from such inspections will be immediately communicated by the Investigator to the Sponsor. The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during audits and or inspections.

19. Data Handling and Recordkeeping

19.1 Data Handling

All information provided to the Investigator by the Sponsor, information produced during the clinical study included, but not limited to the protocol, CRF, investigator's brochure, and the results obtained during the course of the study is confidential. The members of the research team agree not to discuss such information in any way without prior written permission from the Sponsor.

The patient’s personal data and Investigator’s or Sub-investigator’s personal data which may be included in the Sponsor’s database shall be treated in compliance with all applicable laws and regulations.

When processing and archiving personal data pertaining to the Investigator, Sub-investigator and to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

19.2 Responsibilities of Recordkeeping

19.2.1 Investigator and Study Site

The Investigator and the study site are responsible for retaining all study documents in accordance with applicable regulatory requirements and GCP.

The Investigator and the study site agree to inform the Sponsor in writing of the intention to remove or destroy any study-related records. Prior to contacting the Sponsor, the Investigator and study site must ensure that the applicable regulatory requirements have been satisfied. The Sponsor will provide authorization for destruction of such records to the Investigator and study site in writing.

In the event that all retention of records requirements have been fulfilled, but the Sponsor requests that the Investigator and study site maintain the records for a longer period of time, additional arrangements will be made.

19.2.2 Sponsor

The Sponsor must retain all sponsor-specific essential documents in conformance with the applicable regulatory requirements of the countries where the product is approved, and where the Sponsor intends to apply for approvals.

If the Sponsor discontinues the clinical development of the study drug, the Sponsor must maintain all sponsor-specific essential documents in conformance with the applicable regulatory requirements.

20. Compensation for Health Injury

The clinical study is insured according to applicable regulatory requirements. A copy of the Compensation Policy Document will be provided to the study site by the Sponsor.

For the compensation claims associated with this study except for those based on medical malpractice or negligence, for which the Sponsor was clearly shown not to have any liability, the Sponsor specifies the compensation policy and payment procedure for health injuries related to the study in the Compensation Policy Document.

When patients receive compensation, the policies and payment procedure of compensation should comply with the Compensation Policy Document.

21. Publication Policy and Secondary Use of Data

21.1 Publication Policy

The Sponsor maintains the right to use the results of this study in their original form and/or in a global report for submission to governmental and Regulatory Authorities of any country.

The results of the study may be presented during scientific symposia or published in a scientific journal only after review by the Sponsor in accordance with the guidelines set forth in the applicable publication or financial agreement.

The timing, presenter and other matters are determined through discussion between the Coordinating Investigator and the Sponsor.

21.2 Secondary Use of Data

The Sponsor maintains the right to secondary use of data in this study. Secondary use of data describes the use of data from this study for other study/studies (including an external offering).

Specifically, secondary use of data may include:

- Use for analysis of other study.
- Use for integrated analysis with data from one or more associated study/studies.
- Utilization to regulatory authorities for their own analysis and the sharing of information with other regulatory authorities.
- Use for epidemiology study.

22. Ethics

22.1 Ethical Considerations

It is mandatory that all considerations regarding the protection of patients be carried out in accordance with the latest versions of the protocol, GCP, ICH Guidelines, the ethical principles that have their origin in the Declaration of Helsinki, and all applicable regulatory requirements.

22.2 Institutional Review Board

The study must be approved by an appropriately constituted IRB, as required in GCP or ICH E6 Guidelines. Prior to conduct, the study must be reviewed and approved by the IRB of the study site, and approved by the director of study site.

The Investigator is responsible for obtaining renewal of approval during the clinical study. Timeframes for renewal will be based on IRB requirements but renewal at least annually is required by regulations. At the end of the study, the Investigator will notify the IRB of the study site of the conclusion of the study and its outcome.

22.3 Informed Consent Procedure

Informed consent must be obtained in compliance with the guidelines provided in the GCP, Declaration of Helsinki, ICH E6 Guideline and local regulations.

The Investigator and Sub-investigator must fully inform patients of all pertinent aspects of the study. All participants should be informed to the fullest extent possible about the study in a language and in terms they are able to understand.

Prior to participation in the study, the written ICF is to be signed and personally dated by the patient and the person who provided the explanation for ICF. A copy of the signed and dated ICF must be given to the patient. The ICF used must have had prior approval by the IRB.

By signing and dating the ICF prior to the implementation of the study procedures set forth in this protocol, the patient is deemed to have consented to participate in the study.

Prior to the study enrollment, a copy of the ICF signed and dated by the patient must be given to him/her prior to any study-related procedures described in the ICF are undertaken.

The Investigator must prepare the ICF using a proposed ICF provided by the Sponsor as reference. When the ICF needs to be revised, the Investigator must discuss with the Sponsor, prepare a revised version and use the version approved by the IRB.

23. Study Administrative Structure

For details, see the attached document.

24. References

1. Homma Y, Nishizawa O, Yamaguchi, O. The Standardisation of Terminology of Lower Urinary Tract Function: Report from the Standardisation Sub-committee of the International Continence Society.J.Neurogenic Bladder Soc. 2003;14:278-289.
2. Kato K, Kondo A, Okamura K, Takaba H. Prevalence of Urinary Incontinence in Working Women. The Japanese Journal of Urology 1986;77:1501-1505.
3. Takai K, Miyashita A, Mochizuki K. Actual Conditions of Female Stress Incontinence.Japanese Journal of Clinical Urology 1987;41:393-396.
4. Umehara T, Matsukawa M, Tsukamoto T, Kumamoto Y. An incidence of stress urinary incontinence in healthy women-Analyses of 3020 questionares. Japanese Journal of Urological Surgery 1991;4:53-57.
5. The Study Group on Standardization of Treatment in the Urological Field. Guideline for Evidence-based Management of Urinary Incontinence. Tokyo: Jiho, Inc.; 2004. p. 9-11.
6. Homma Y, Kakizaki H, Goto M, Takei M, Yamanishi T, Hayashi K. Epidemiological survey on lower urinary tract symptoms in Japan. J Neurogenic Bladder Soc. 2003;14:266-277.
7. Edited by Kato K. Care for Urinary Incontinence and Female Urological Disease. Osaka: Medicus Shuppan Publishers Co., Ltd. 2008.; p. 230-231.
8. Committee for preparation of clinical guideline for female lower urinary tract symptoms, Ed. Clinical guideline for female lower urinary tract symptoms. Tokyo: RichHill Medical Inc. 2013. p. 128.
9. Shimazaki J, Yasuda K, Imabayashi K, Takimoto Y, Toyoshima A, Morita T, et al. Dose finding study on clenbuterol in stress in incontinence - a dose finding study -. Japanese Journal of Urological Surgery 1992;5:933-945.

[redacted]

11. European Medicines Agency. Guideline on the clinical investigation of medicinal products for the treatment of urinary incontinence. June 2013.
12. U.S. Department of Health and Human Services. Food and Drug Administration. Guidance for industry. Clinical investigations of devices indicated for the treatment of urinary incontinence. March 2011.
13. van Leeuwen JH, Castro R., Busse M, Bemelmans BL. The placebo effect in the pharmacologic treatment of patients with lower urinary tract symptoms. Eur Urol 2006;50:440–453.
14. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika. 1988;75:800-802.

15. General Considerations for Clinical Trials. PMSB/ELD Notification No. 380 (April 21, 1998)

25. Appendices