A Phase 2a Study of TAC-302 in Detrusor Underactivity Patients with Overactive Bladder

TAC-302 [test product]
Protocol Number: 10054040 Ver.P02
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Sponsor:
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This clinical study will be conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), Good Clinical Practice (GCP) Guidelines and applicable regulatory requirements in Japan.

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LIST OF ABBREVIATIONS

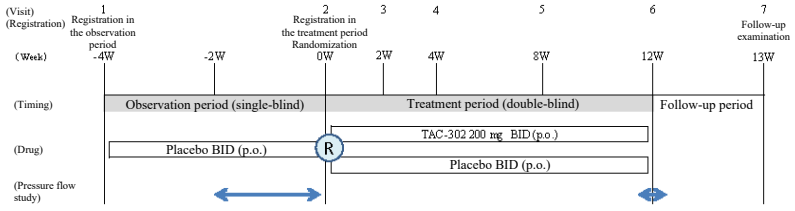
Term	Definition
ACTH	adrenocorticotrophic hormone
A/G	albumin/globulin ratio
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t (where t = the final time of detection)
BCI	bladder contractility index
BMI	body mass index
BOO	bladder outlet obstruction
BUN	blood urea nitrogen
BVE	bladder voiding efficiency
C_{max}	maximum plasma concentration
CRP	C-reactive protein
DU	detrusor underactivity
eCRF	electronic case report form
EDC	electronic data capture
FAS	full analysis set
free T_3	free triiodothyronine
free T_4	free thyroxine
GCP	Good Clinical Practice
γ-GTP	γ-glutamyltranspeptidase
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IPSS	International Prostate Symptom Score
IRB	institutional review board
IWRS	Interactive Web Response System
KHQ	King's Health Questionnaire
LDH	lactate dehydrogenase
LUTD	lower urinary tract dysfunction
LUTS	lower urinary tract symptoms
NAG	N-acetyl-β-D-glucosaminidase
OAB	overactive bladder
OABSS	overactive bladder symptom score
PFS	pressure flow study
PIP	projected isovolumetric pressure
PPS	per protocol set
free Q_{ave}	Average flow rate in uroflowmetry

Term	Definition
free Q_{max}	Maximum flow rate in uroflowmetry
QOL	quality of life
QTcF	QT corrected for heart rate by Fridericia's formula
SOP	standard operating procedure
TAC-302	[redacted]
T-Bil	total bilirubin
ULN	upper limit of normal
TSH	thyroid stimulating hormone
UAB	underactive bladder

SYNOPSIS

Sponsor:	Taiho Pharmaceutical Co., Ltd.
Test product:	TAC-302
Generic name	-
Title of Study: A Phase 2a Study of TAC-302 in Detrusor Underactivity Patients with Overactive Bladder	
Protocol Number:	10054040
Phase of Development:	Phase 2a
Indication:	Lower urinary tract symptoms (storage, voiding, and post-micturition symptoms) in detrusor underactivity and overactive bladder
Background/Rationale:	The lower urinary tract, which consists of the bladder and urethra, has a urine storage function, involving the storage of urine in the bladder, and a voiding function, involving the excretion of the stored urine. The general term for a condition where the urine storage function and urination function are impaired (storage disorder and urination disorder) is lower urinary tract dysfunction (LUTD). Symptoms caused by LUTD are called lower urinary tract symptoms (LUTS), which are classified into “storage symptoms,” “voiding symptoms,” and “post-micturition symptoms.” Each of these symptoms is a problem that greatly affects the patients’ activities of daily life and markedly impairs their quality of life (QOL). Recent clinical and basic research data have suggested that partial denervation of lower urinary tract organ tissues induced by various factors is importantly involved in the progression of impaired urinary function and serves as a key to the treatment of LUTS. [redacted]

	[redacted] Based on the background/rationale above, a phase 2a study in detrusor underactivity patients with overactive bladder has been planned to evaluate the efficacy of TAC-302 in these patients.
Study Objectives/Endpoints:	**<u>Primary Objective:</u>** To investigate the efficacy of TAC-302 in detrusor underactivity (DU) patients with overactive bladder (OAB), using evaluation of the bladder contractility index (BCI) (males) or projected isovolumetric pressure (PIP) 1 (females) at each time point as an indicator. **<u>Secondary Objectives:</u>** • To investigate the efficacy of TAC-302 in DU patients with OAB, using the changes in values including pressure flow study (PFS) parameters, uroflowmetry parameters, bladder voiding efficiency (BVE), the international prostate symptom score (IPSS) or the overactive bladder symptom score (OABSS) as indicators. • To investigate the efficacy of TAC-302 in DU patients with OAB in comparison with placebo. • To investigate the safety of TAC-302 in DU patients with OAB, using data including the incidence of adverse events and adverse reactions as indicators. **<u>Primary Endpoints:</u>** • BCI [maximum detrusor pressure at peak urine flow ($P_{det}Q_{max}$) + 5 × peak urine flow rate (Q_{max})] (males) • PIP1 ($P_{det}Q_{max}$ + Q_{max}) (females) [Evaluation time points: week 0, week 12] **<u>Secondary Endpoints:</u>** • PFS parameters (filling phase) • PFS parameters (voiding phase) • Uroflowmetry parameters • Post void residual measured by ultrasonography

	• BVE [voided volume / (voided volume + post void residual)] • IPSS • OABSS • Bladder diary record data • King's health questionnaire (KHQ) • Occurrence of adverse events and adverse reactions
Study Design:	This study is a central-registration, multi-center, double-blind, placebo-controlled, randomized parallel-group comparative study to investigate the efficacy and safety of TAC-302 in DU patients with OAB. The design of this study is shown in the figure below. This study is composed of a single-blind observation period, a double-blind treatment period, and a follow-up period. In the observation period, the investigational drug (placebo) will be administered orally twice daily after breakfast and dinner for 2 to 4 weeks. The investigational drug in the treatment period will be randomly assigned, with patients allocated to the TAC-302 and placebo group in a 2:1 ratio. In the treatment period, the investigational drug (TAC-302 200 mg or placebo) will be administered orally twice daily after breakfast and dinner for 12 weeks. After the start of the treatment period (registration in the treatment period), patients will make visits in weeks 2, 4, 8, and 12, and the designated observations and tests will be performed. A follow-up examination will be performed 1 week after the visit in week 12 of the treatment period.  Figure Study Design
Implementation Status:	Study completion date (planned): December 2019 Country: Japan
Planned Number of Patients:	In this study, 75 patients (48 men and 27 women) will be registered in the treatment period by central registration.
Patient Eligibility:	**<u>Inclusion criteria at registration in the observation period:</u>** (1) Provided written informed consent in person

	(2) Aged ≥ 20 years at the time of obtaining informed consent and able to receive treatment as an outpatient (irrespective of sex) (3) Being able to use the toilet himself/herself and make accurate bladder diary records, in the opinion of the principal investigator or subinvestigator (4) Having had lower urinary tract symptoms (storage symptoms, voiding symptoms, and post-micturition symptoms) for at least 12 weeks before registration in the observation period (5) Scoring ≥ 2 points on any of the following questions for the IPSS voiding symptoms score at registration in the observation period • Over the past month, how often have you found you stopped and started again several times when you urinated? • Over the past month, how often have you had a weak urinary stream? • Over the past month, how often have you had a push or strain to begin urination? (6) Scoring ≥ 2 points for the urinary urgency score (Question 3), and having an OABSS total score of ≥ 3 points in OABSS evaluation at registration in the observation period • Question 3: How often do you have a sudden desire to urinate, which is difficult to defer? (7) Post void residual ≤ 300 mL measured at registration in the observation period **<u>Inclusion criteria at registration in the treatment period:</u>** (1) Scoring ≥ 2 points on any of the following questions for the IPSS voiding symptoms score at registration in the observation period • Over the past month, how often have you found you stopped and started again several times when you urinated? • Over the past month, how often have you had a weak urinary stream? • Over the past month, how often have you had a push or strain to begin urination?

	(2) Meeting all of the following conditions based on information from bladder diary records in the 3 days directly before registration in the treatment period 1) Being able to use the toilet himself/herself and make accurate bladder diary records, in the opinion of the principal investigator or subinvestigator 2) An average of ≥ 8 urinations per 24 hours and meeting either of the following conditions • An average of ≥ 1 urinary urgency episodes per 24 hours • An average of ≥ 1 urgency urinary incontinence episode per 24 hours (3) Post void residual ≤ 300 mL measured at registration in the treatment period (4) Meeting the following criteria based on a urodynamic study (UDS) performed at registration in the treatment period [a, b: Calculated from PFS parameters, c: Calculated from uroflowmetry parameters and the measurement of the post void residual according to ultrasound] 1) Criteria for males a) BCI ($P_{det}Q_{max}+5Q_{max}$) < 100 b) Bladder outlet obstruction index ($BOOI=P_{det}Q_{max}-2Q_{max}$) < 40 c) BVE [voided volume / (voided volume + post void residual)] < 90% 2) Criteria for females a) $P_{det}Q_{max}$ < 20 b) Q_{max} < 15 c) BVE [voided volume / (voided volume + post void residual)] < 90% **<u>Exclusion criteria at registration in the observation period:</u>** (1) Having the following concurrent or historical conditions, and having been diagnosed with neurogenic bladder accompanied by obvious neurological abnormality associated with the following diseases 1) Cerebrovascular disorder (cerebral hemorrhage, cerebral infarction, etc.) 2) Parkinson's disease

	3) Alzheimer's disease 4) Multiple sclerosis 5) Spina bifida 6) Spinal cord disorder (spinal cord injury, etc.) (2) Concurrent urinary tract infection (prostatitis, cystitis, etc.) or historical recurrent urinary tract infection [occurring ≥ 3 times within a period of 168 days (24 weeks) before registration in the observation period]. Concurrent urinary disease impairing determination of the effect of the investigational drug, such as cystitis interstitial, urinary tract stenosis, urinary tract obstruction, calculus urinary (calculus ureteric, calculus urethral, calculus bladder, etc.), benign tumor of the urethra (urethral polyp, cyst, papilloma, etc.) and urethral diverticulum. (3) Concurrent bladder cancer or prostate cancer, or suspected bladder cancer or prostate cancer, or a history of these (4) Cystocele classified as stage III or higher according to the pelvic organ prolapse quantification (POP-Q) stage classification (females) (5) Prostate gland volume ≥ 30 mL (males) (6) Overflow urinary incontinence (7) Clinically significant concurrent conditions (including symptoms and findings) such as severe liver disease (hepatitis viral, drug-induced liver injury, etc.), severe renal disease (acute renal failure, glomerulonephritis, nephritis interstitial, etc.), severe cardiovascular disease (cardiac failure congestive, symptomatic unstable angina pectoris, poorly controlled arrhythmia, myocardial infarction, etc.), severe blood dyscrasia (pancytopenia, leukopenia, etc.), severe respiratory disease (bronchial asthma, bronchitis chronic, etc.), severe digestive disease (peptic ulcer, reflux esophagitis, Crohn's disease, colitis ulcerative, etc.), severe neuropsychiatric disease (schizophrenia, dementia, etc.), severe immune disease (collagen disorder, etc.), severe metabolic or endocrine disease or malignant tumor (8) Having received urethral catheter placement, or performing intermittent self-catheterization due to the inability to urinate spontaneously

	(9) Meeting the following conditions at laboratory tests performed in the period of 14 days before registration in the observation period 1) Aspartate aminotransferase (AST) > 3 × upper limit of normal (ULN) 2) Alanine aminotransferase (ALT) > 3 × ULN 3) Total bilirubin (T-Bil) > 1.5 × ULN 4) Serum creatinine > 1.5 × ULN (10) The following have been performed in the period of 154 days (22 weeks) before registration in the observation period. 1) Surgery of the pelvic organs (radical hysterectomy, radical surgery for rectal cancer, radical pelvic lymph node dissection, etc.) injuring the pelvic nerve or hypogastric nerve 2) Prostatectomy 3) Radiotherapy that may affect voiding function (11) Having received another investigational drug in the period of 90 days before registration in the observation period (12) Being pregnant, breastfeeding, or a female patient of childbearing potential with a positive (urine or serum) pregnancy test result in the period of 7 days before registration in the observation period Note) Women without childbearing potential are women who have undergone hysterectomy and postmenopausal women who have not experienced menstruation for at least 1 year with no associated medical reason such as administration of contraceptives (13) In the case of women with reproductive potential, not consenting to use contraception during the study period and for a period of 30 days after the end of administration of the investigational drug* (14) In the case of male patients, not consenting to use contraception during the study period and for a period of 90 days after the end of administration of the investigational drug* (15) Being determined to be ineligible for this study in the opinion of the principal investigator or subinvestigator * The principal investigator or subinvestigator will instruct patients to always perform contraception using a method such as the double-barrier method (a

	condom and pessary), an intrauterine device or oral contraceptives during the period of administration of the investigational drug and the period of contraception after the end of administration of the investigational drug. **Exclusion criteria at registration in the treatment period:** (1) A rate of compliance with administration of the investigational drug of < 80% in the observation period (2) Having the following concurrent conditions, and having been diagnosed with neurogenic bladder accompanied by obvious neurological abnormality associated with the following diseases 1) Cerebrovascular disorder (cerebral hemorrhage, cerebral infarction, etc.) 2) Parkinson's disease 3) Alzheimer's disease 4) Multiple sclerosis 5) Spina bifida 6) Spinal cord disorder (spinal cord injury, etc.) (3) Concurrent urinary disease impairing determination of the effect of the investigational drug, such as urinary tract infection (prostatitis, cystitis, etc.), cystitis interstitial, stenosis, urinary tract obstruction, calculus urinary (calculus ureteric, calculus urethral, calculus bladder, etc.), benign tumor of the urethra (urethral polyp, cyst, papilloma, etc.) and urethral diverticulum. (4) Concurrent bladder cancer or prostate cancer, or suspected bladder cancer or prostate cancer (5) Cystocele classified as stage III or higher according to the POP-Q stage classification (females) (6) Overflow urinary incontinence (7) Clinically significant concurrent conditions (including symptoms and findings) such as severe liver disease (hepatitis viral, drug-induced liver injury, etc.), severe renal disease (acute renal failure, glomerulonephritis, nephritis interstitial, etc.), severe cardiovascular disease (cardiac failure congestive, symptomatic unstable angina pectoris, poorly controlled arrhythmia, myocardial infarction, etc.), severe blood dyscrasia (pancytopenia, leukopenia, etc.), severe respiratory disease (bronchial asthma, bronchitis chronic, etc.), severe digestive disease (peptic ulcer, reflux esophagitis, Crohn's disease, colitis ulcerative, etc.), severe neuropsychiatric disease

<table>
<tr><td></td><td>(schizophrenia, dementia, etc.), severe immune disease (collagen disorder, etc.), severe metabolic or endocrine disease or malignant tumor
(8) Having received urethral catheter placement, or performing intermittent self-catheterization due to the inability to urinate spontaneously
(9) Being determined to be ineligible for this study in the opinion of the principal investigator or subinvestigator</td></tr>
<tr><td>Method of Administration:</td><td><u>Observation period:</u>
Placebo will be administered orally twice daily after breakfast and dinner for 2 to 4 weeks.
<u>Treatment period:</u>
TAC-302 200 mg or placebo will be administered orally twice daily after breakfast and dinner for 12 weeks.</td></tr>
<tr><td>Study Period:</td><td>Study Period:
From the time of obtaining informed consent to the end of the follow-up examination
<u>Observation period:</u>
From the time of registration in the observation period to the registration in the treatment period (registration in the treatment period will be performed between 2 to 4 weeks after registration in the observation period)
<u>Treatment period:</u>
From the time of registration in the treatment period to the end of week 12 of the treatment period
<u>Follow-up period:</u>
From the end of week 12 of the treatment period to the end of the follow-up examination (performed 1 week after the end of week 12 of the treatment period)</td></tr>
<tr><td>Analytical Methods:</td><td><u>Analysis sets:</u>
The definitions of the analysis sets in this study are as follows.<table><tr><th>Analysis set</th><th>Definition</th></tr><tr><td>Screening patients</td><td>The set of all patients who provided informed consent</td></tr><tr><td>All enrolled patients in the observation period</td><td>The set of all patients who were enrolled in the observation period</td></tr><tr><td>All enrolled patients in the treatment period</td><td>The set of all patients who were enrolled in the treatment period</td></tr></table></td></tr>
</table>

All treated patients in the observation period	The set of patients enrolled in the observation period who took the investigational drug at least once
All treated patients in the treatment period	The set of patients enrolled in the treatment period who took the investigational drug at least once
Full analysis set (FAS)	The set of patients enrolled in the treatment period who took the investigational drug for the treatment period at least once and who had at least 1 efficacy endpoint measurement before the start of the treatment period and in the treatment period
Per protocol set (PPS)	The set of patients in the full analysis set (FAS), excluding patients who met any of the following criteria: (1) Being discovered to have a violation of the inclusion criteria (2) Being discovered to meet any of the exclusion criteria (criteria affecting efficacy evaluation) (3) A compliance rate for the treatment period of < 80% (4) Being administered prohibited concomitant drugs or prohibited concomitant therapy considered likely to influence efficacy evaluation (5) No evaluation of the primary endpoint at week 12 of the treatment period

Primary Endpoints:

The primary endpoint, BCI (males) or PIP1 (females), will be analyzed as follows.

(1) Primary analysis

	- Summary statistics and 95% confidence intervals at each evaluation time point will be calculated by group in the per protocol set (PPS). (2) Sensitivity analysis of the primary analysis - (1) will be evaluated in the FAS. (3) Secondary analysis of the primary endpoint The following analysis will be performed in the FAS and PPS. - Time course plots at each evaluation time point will be prepared by group. - Paired t-tests for the values at baseline (week 0) and week 12 of the treatment period will be performed by group. - Summary statistics and 95% confidence intervals for the change and percentage change at week 12 of the treatment period relative to baseline (week 0) will be calculated by group. - The treatment effect in the TAC-302 group relative to the placebo group will be estimated using model analysis of the change and percentage change at week 12 of the treatment period relative to baseline (week 0).
Justification for the Sample Size:	[redacted]

Table 1 Evaluations and Examination Items

Obtaining informed consent			
Date of obtaining informed consent			
Patient backgrounds			
Sex	Date of birth		Age[*1]
Race	Height		Weight
BMI[*2]	History of participation in clinical studies (within the past 90 days)		Medical history (within the past 180 days)[*3]
Onset time of lower urinary tract symptoms (LUTS) (storage symptoms, voiding symptoms, and post-micturition symptoms)			
Concurrent conditions	History of prior treatment		
Patient registration			
Patient identification code	Drug number		
Symptoms and findings			
Blood pressure (systolic and diastolic)	Pulse rate		Body temperature
Compliance with administration of the investigational drug			
Concomitant medication and concomitant therapy			
12-lead electrocardiography			
Heart rate	QT interval	RR interval	QTcF interval[*4]
Hematology tests			
Red blood cell count	Hemoglobin	Hematocrit	Platelet count
White blood cell count	Neutrophils	Eosinophils	Basophils
Lymphocytes	Monocytes		
Biochemistry tests			
Total protein	Albumin	A/G	T-Bil
Direct bilirubin	AST(GOT)	ALT(GPT)	ALP
LDH	γ-GTP	BUN	Creatinine
Creatine kinase	Blood glucose	Amylase	Triglycerides
Total cholesterol	CRP	Na	K
Cl	Ca[*5]		
Endocrinological tests			
Thyroid stimulating hormone (TSH)	free T_3	free T_4	Cortisol
Adrenocorticotropic hormone (ACTH)			
Urinalysis			
Protein	Glucose	Urobilinogen	Urine NAG
Urine β_2-microglobulin	Urine sediment[*6]		
Pregnancy test[*7]			
Serum or urine human chorionic gonadotropin			
Prostate gland volume measurement			
PFS (filling phase)			
Volume at first desire to void	Maximum bladder volume	Bladder compliance	Appearance of bladder involuntary contraction
Bladder volume up to appearance of bladder involuntary contraction			
PFS (voiding phase)			
BCI ($P_{det}Qmax + 5Q_{max}$): males		PIP1 ($P_{det}Q_{max} + Q_{max}$): females	
Detrusor pressure at maximum flow ($P_{det}Q_{max}$)		Detrusor pressure at start of voiding ($P_{det\ open}$)	
Maximum detrusor pressure ($P_{det\ max}$)		Maximum flow rate (Q_{max})	
Average flow rate (Q_{ave})		Duration of bladder contraction	
Voided volume		Post void residual	
Uroflowmetry			
Maximum flow rate (free Q_{max})	Average flow rate (free Q_{ave})	Voided volume	Voiding time
Post void residual measured by ultrasound			
BVE [voided volume/(voided volume + post void residual)] Post void residual measured by ultrasound and voided volume measured by uroflowmetry			
Symptom score evaluation			
IPSS	OABSS		
QOL score evaluation			
KHQ			
Bladder diary records			
Dates and times of voiding and urinary incontinence	Urinary urgency	Voided volume	
Evaluation of adverse events			

*1: Automatically calculated from the date of birth. *2: Automatically calculated from height and weight.

*3: This is a medical history determined by the principal investigator or subinvestigator to be important in the conduct of this study (such as diseases related to urinary organs).

*4: Automatically calculated from the QT interval and RR interval.

*5: In the evaluation of adverse events, if albumin is < 4.0 g/dL, determinations will be made using values corrected by the following formula.

[Corrected calcium (mg/dL)] = [calcium (mg/dL)] – 0.8 × {[albumin (g/dL)] – 4}

*6: Urine sediment will only be examined at registration in the observation period and registration in the treatment period.

*7: Required for female patients with childbearing potential. However, a pregnancy test will not be required for patients more than 1 year after menopause or patients in whom the possibility of pregnancy is medically ruled out.

Table 2 Observation and Testing Schedule

Timing	Observation period		Treatment period								Follow-up period	At discontinuation[8]
	At registration	3 days before registration in the treatment period	At registration[5]	Week 2[6]	3 days before the visit for week 4	Week 4[6]	3 days before the visit for week 8	Week 8[6]	3 days before the visit for week 12	Week 12[6]	Follow-up examination[7]	
Visit	1		2	3		4		5		6	7	
Week	-4 to -2		0	2		4		8		12	13	
Obtaining informed consent	X[1]											
Assigning of patient identification codes[2]	X											
Patient backgrounds	X		X									
Registration	X		X									
Investigational drug dispensing	X		X	X		X		X				
Retrieving leftover drugs			X	X		X		X		X		X
Checking of drug compliance			X	X		X		X		X		X
Physical examination	X		X	X		X		X		X	X	X
Blood pressure, pulse rate, and body temperature	X[9]		X	X		X		X		X	X	X
12-lead electrocardiography	X[9]		X							X	X	X
Laboratory tests[3]	X[9]		X	X		X		X		X	X	X
Pregnancy tests[4]	X											
Bladder diary records: Supplied	X			X		X		X				
Filled in		←	→		←	→	←	→	←	→		
Collected			X			X		X		X		X
Checked			X			X		X		X		X
Symptom score (IPSS, OABSS) evaluation	X		X			X		X		X		X
KHQ evaluation			X							X		X
PFS[10]			X							X		X
Uroflowmetry			X[11]			X[11]		X[11]		X[11]		X[11]
Post void residual measured by ultrasound	X[9]		X[11]			X[11]		X[11]		X[11]		X[11]
Prostate gland volume measurement	X[9]											
Checking concomitant drugs/concomitant therapy[12]	←	←	←	←	←	←	←	←	←	←	→	X
Checking adverse events[12]	←	←	←	←	←	←	←	←	←	←	→	X

1) Obtaining informed consent: Obtained within the period of 28 days before registration in the observation period.
2) Assigning of patient identification codes: Assigned to patients providing informed consent.
3) Laboratory tests: Hematology tests, biochemistry tests, endocrinological tests and urinalysis will be performed. However, the urinalysis test urine sediment will only be performed at registration in the observation period and at registration in the treatment period.
4) Pregnancy tests: Required for female patients with childbearing potential. However, a pregnancy test will not be required for patients more than 1 year after menopause or patients in whom the possibility of pregnancy is medically ruled out. At tests before registration in the observation period, pregnancy tests (serum or urine) must be negative. The time window for performing the test is the period of 7 days before registration in the observation period.
5) Time window for registration in the treatment period: All observation and examination items at registration in the treatment period will be performed by registration in the treatment period, 2 to 4 weeks after registration in the observation period.
6) Time window for visits in the treatment period: Visits at weeks 2, 4, and 8 of the treatment periods will be allowed to be within the range of the standard date ±3 days. The visit at week 12 will be allowed to be within the range of the standard date −3 days to the standard date +7 days.
7) Time window for the follow-up examination: This will be performed 1 to 2 weeks after the end of week 12 of the treatment period. If the patient discontinued during the treatment period, it will be performed 1 to 2 weeks after the final dose of the investigational drug.
8) At discontinuation: The designated observations and examination items will be performed as far as possible. For patients providing informed consent but not enrolled in the treatment period, the observations and tests relating to safety evaluation will be performed as far as possible.
9) If the designated observations or tests are performed in the period of 14 days before registration in the observation period, even if this is before informed consent is obtained, these can be used as data at registration in the observation period.
10) PFS will be performed on the same date as uroflowmetry and measurement of the post void residual by ultrasound as far as possible.
11) For evaluating BVE, measurement of the post void residual by ultrasound will be performed after uroflowmetry.
12) Concomitant drugs/concomitant therapy and evaluation of adverse events: These will be investigated from informed consent to the end of follow-up.

1. BACKGROUND INFORMATION

1.1 Introduction

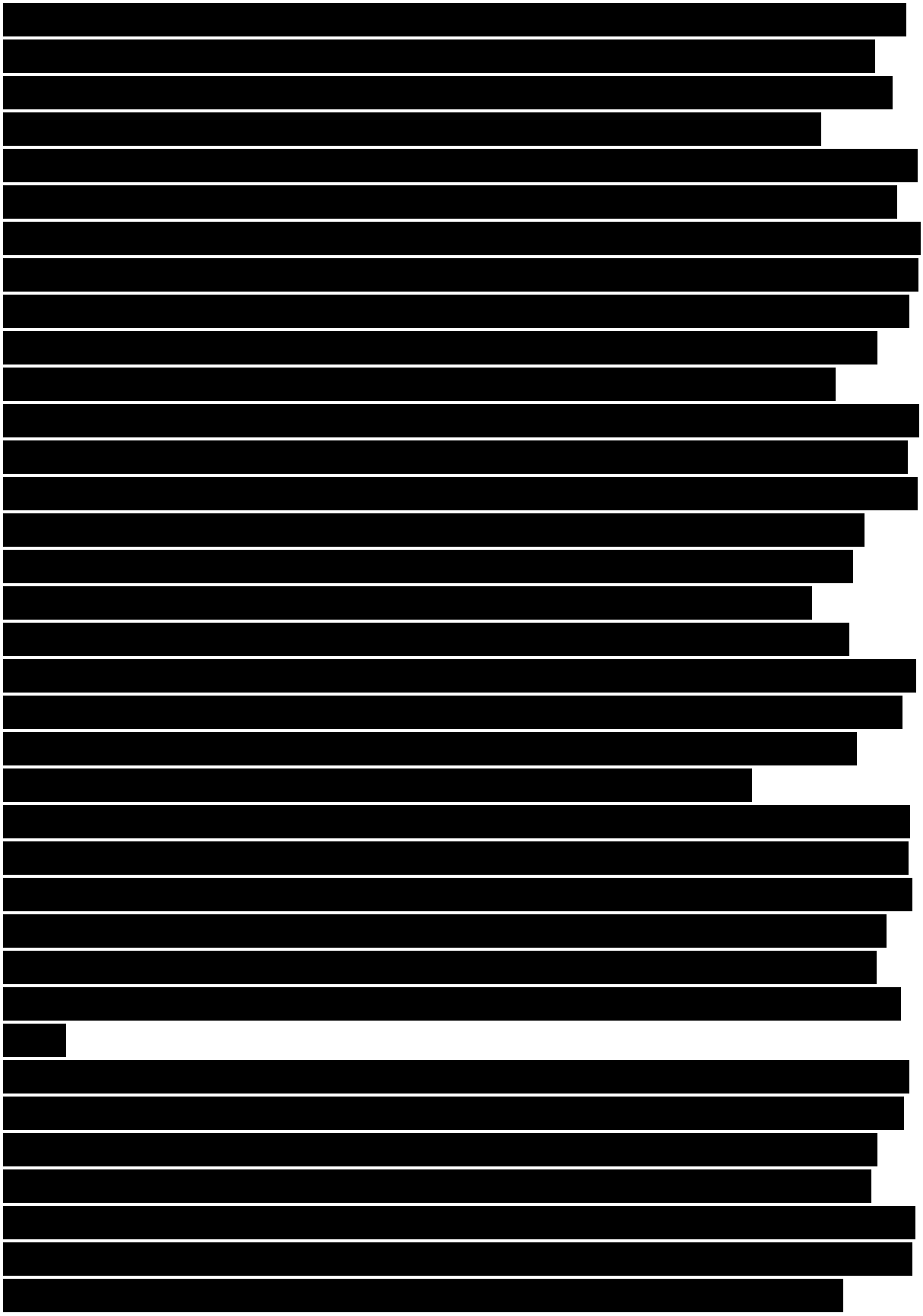
The lower urinary tract, which consists of the bladder and urethra, has a urine storage function, involving the storage of urine in the bladder, and a voiding function, involving the excretion of the stored urine. The general term for a condition where the urine storage function and urination function are impaired (storage disorder and urination disorder) is lower urinary tract dysfunction (LUTD). Symptoms caused by LUTD are called lower urinary tract symptoms (LUTS), which are classified into "storage symptoms," "voiding symptoms," and "post-micturition symptoms."[1)] Storage symptoms include increased daytime frequency, nocturia, urinary urgency, urinary incontinence, and bladder sensation. Voiding symptoms include slow stream, intermittent stream, hesitancy, straining, and terminal dribble. Post-micturition symptoms include feeling of residual urine and post-micturition dribble. Each of these symptoms is a problem that greatly affects the patients' activities of daily life and markedly impairs their quality of life (QOL).

In Japan, an epidemiological study on LUTS was conducted by the Japanese Continence Society in 10096 men and women aged 40 years or older (4570 included in the analysis) between November 2002 and March 2003.[2)] The incidence of any LUTS increased with age in both men and women, and some LUTS was present in approximately 78% of the elderly aged 60 years or older. The most frequent symptoms were nocturia and increased daytime frequency, followed by slow stream, feeling of residual urine, urinary urgency, and urgency urinary incontinence in this order. When the number of patients with symptoms was estimated based on their age and sex, the number of men and women with increased daytime frequency was 15.95 million and 17.22 million, respectively, the number of men and women with slow stream was 10.88 million and 6.57 million, respectively, the number of men and women with feeling of residual urine was 7.92 million and 3.75 million, respectively, and the number of men and women with urinary urgency was 4.49 million and 4.6 million, respectively. A recent epidemiological study has reported a relationship between metabolic syndrome and LUTS, indicating that the onset of LUTS including OAB is significantly more frequent in patients with 2 or more risk factors for arteriosclerosis, which causes blood flow disturbance.[3)]

One cause of impaired urination is DU, and this is considered to manifest as underactive bladder (UAB). UAB is a condition where bladder contraction is impaired during voiding, manifesting as voiding symptoms. The most important peripheral nerve controlling the bladder is the pelvic nerve (parasympathetic nerve), and the occurrence of UAB is due to disorder of the pelvic nerve. LUTD due to bladder outlet obstruction (BOO) such as prostatic hyperplasia is impaired urination resulting from urethral obstruction, and it is reported that voiding symptoms that recur after transurethral prostatectomy are often caused not by obstruction due to recurrence of prostatic adenoma but by failure of detrusor contraction.[4)] It has been reported that failure of detrusor contraction is found frequently (48%) in patients with LUTS aged 70 years or older, and that it is more common among those who have a history of urinary retention.[5)] In typical UAB where the patient has little desire to void despite

a large volume of urine in the bladder, and detrusor contraction is extremely weak or absent, the patient develops dysuria, and because voiding is also inefficient, there is a large amount of residual urine. Voiding symptoms of UAB include hesitancy, slow stream, and straining. UAB is treated firstly with intermittent urinary catheterization. The main drugs used to treat UAB are cholinergics, but drug therapy is positioned as adjuvant therapy in addition to intermittent urinary catheterization and is recommended to be administered after evaluation of the therapeutic effect of intermittent urinary catheterization for 4 weeks. Drugs include bethanechol chloride and distigmine bromide. Bethanechol chloride constricts the bladder by directly stimulating muscarinic receptors, and distigmine bromide constricts the bladder by increasing the amount of free bethanechol chloride via its inhibitory effect on cholinesterase. However, since these drugs may cause a serious adverse reaction that may be fatal, attention should be paid to the onset of cholinergic crisis (acute exacerbation of the condition of excessive acetylcholine that accompanies dyspnea and requires mechanical ventilation).
Among the main pathological conditions due to urine storage dysfunction is OAB. OAB involves urinary urgency as a necessary condition, and it is usually accompanied by pollakiuria and nocturia. LUTD due to BOO is urine storage dysfunction related to impaired bladder function occurring secondary to urethral obstruction, other than directly impaired urination due to urethral obstruction. In a bladder with BOO, it has been shown from animal experiments that in many cases, the volume of blood flow decreases, and in addition partial denervation occurs,[6] and partial denervation has also been observed in bladder biopsy specimens from OAB patients.[7,8] BOO causes the pressure inside the bladder to increase during voiding, increasing the tension in the bladder wall and leading to impaired blood flow in the bladder. As a result, the nerves inside the bladder wall (postganglionic fibers of the pelvic nerve) are susceptible to degeneration, and partial denervation develops. It is thought that this is accompanied by excessive reaction of the smooth muscle of the bladder to acetylcholine (denervation supersensitivity), leading to detrusor overactivity. OAB symptoms are storage symptoms such as urinary urgency, pollakiuria (daytime frequency and nocturia) and urgency urinary incontinence, and the filling phase is often accompanied by involuntary contraction of the bladder (detrusor overactivity).
It is known that elderly people may develop both voiding and storage symptoms. It has been reported that among elderly men with LUTS and without BOO such as prostatic hyperplasia, 40% had detrusor overactivity only, 31% had failure of detrusor contraction only, and 11% had both.[9] An epidemiological study has revealed that LUTS includes various symptoms and that both storage and voiding symptoms coexist.[10] Urinary urgency, nocturia, and urgency urinary incontinence are often present in patients with BOO such as prostatic hyperplasia and bladder neck sclerosis. Detrusor hyperactivity with impaired contractile function (DHIC) has been reported to be commonly present in elderly people, and inadvertent administration of anticholinergics to these patients may increase residual urine and cause urinary retention or overflow urinary incontinence.
As stated above, UAB symptoms are due to peripheral neuropathy, and since there are few therapeutics with satisfactory actions improving symptoms such as increased post void

residual, hesitancy and slow stream, efficacious therapeutics for impaired urination are to be hoped for. In addition, in some cases of OAB, impaired urine storage and impaired urination coexist and are interrelated, and it is thought to be necessary to consider the balance between both of these when administering treatment.[11] In this case, also, no efficacious therapeutic is available.



[redacted]

Based on these findings, we have planned to conduct an early phase 2 study to evaluate the efficacy of TAC-302 in DU patients with OAB.

1.2 TAC-302 [test product]

[redacted]

1.2.1 Mechanism of Action

[redacted]

1.3 Placebo [Comparator]

Placebo, the comparator, contains no active ingredient of the test product and is a capsule indistinguishable from the test product in appearance.

1.4 Benefit-Risk Overview

1.4.1 TAC-302

1.4.1.1 Potential Benefits

There are few drugs to treat UAB/DU, and the development of effective drugs for impaired urination is expected.[12)] In addition, in some cases of OAB, impaired urine storage and impaired urination coexist and are interrelated, and it is thought to be necessary to consider the balance between both of these when administering treatment.[11)] In this case, also, no efficacious therapeutic is available.

[redacted]

Since the clinical studies conducted to date enrolled healthy adults, no benefits to patients have been evaluated.

1.4.1.2 Potential Safety Risks

[redacted]

[redacted]

In conclusion, it cannot be ruled out that the findings and events observed in the non-clinical and clinical studies may also occur in this study.

1.4.2 Benefits and Risks Expected in This Study

The evaluation of PFS parameters, the IPSS, the OABSS, etc. in this study may provide the improvement of LUTS (storage, urination, and urination symptoms) in DU and OAB by treatment with TAC-302 for the study population. The pressure flow study is an invasive test to measure intravesical pressure by inserting a catheter into the bladder via the urethra and injecting water or physiological saline into the bladder to fill the bladder. Post-examination pain, hematuria, and urinary tract infection associated with catheter manipulation are most likely to occur. Usually, however, they can almost be managed by taking antibiotics and drinking water for the day to achieve diuresis.[13)]

1.5 Main Study Results

1.5.1 Nonclinical Studies

See the Investigator's Brochure.

1.5.2 Clinical Studies

1.5.2.1 Phase 1 Single-dose Study (Study 10054010)

[redacted]

1.5.2.1.1 Pharmacokinetics

[redacted]

[redacted]

1.5.2.1.2 Safety

[redacted]

1.5.2.2 Phase 1 Repeated-dose Study (Study 10054020)

[redacted]

1.5.2.2.1 Pharmacokinetics

[redacted]

[redacted]

1.5.2.2.2 Safety

[redacted]

[redacted]

1.6 Justification of Study Population and Study Design

1.6.1 Study Population

This study will target patients with OAB and voiding symptoms who have been confirmed to have DU based on the results of PFS and uroflowmetry. Patients with a strong placebo response under single-blind conditions in the observation period who do not meet the definition of OAB and voiding symptoms[14] at registration in the treatment period, and patients who do not meet the criteria for DU based on PFS and uroflowmetry selected with reference to past reports[15,16] will be deemed ineligible for registration in the treatment period, in order to select a study population which allows appropriate evaluation of the drug efficacy.

1.6.2 Study Design

[redacted]

[redacted]

1.6.3 TAC-302 Dose

[redacted]

1.6.4 Selection of Placebo

To objectively evaluate the efficacy and safety of TAC-302, a placebo group was established in the treatment period. PFS is currently essential for the diagnosis and evaluation of DU.[21] Although PFS is considered to have a smaller placebo effect than symptoms and QOL evaluations,[17] there is no evidence of variation associated with the natural course of DU or the PFS procedure in the study population of this study. Given this, as described in the objectives of the control group in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E10,[22] it was considered necessary to establish a placebo group because it is necessary to distinguish the results occurring in

patients after the test treatment (outcomes) from the results caused by factors such as natural progression of the disease and expectations of observers/patients.
The therapeutic effect on OAB is determined by evaluation of data including the number of urinations and questionnaires, but there is a large placebo effect involved in the evaluation of these. Accordingly, for studies verifying the clinical effect of OAB therapeutics, a placebo-controlled double-blind study is recommended.[17,18,19)] Evaluation of OAB symptoms in this study is a secondary endpoint, but it was considered to be necessary to establish a placebo group to evaluate OAB symptoms.

2. STUDY OBJECTIVES

2.1 Primary Objective

To investigate the efficacy of TAC-302 in DU patients with OAB, using evaluation of the BCI (males) or PIP 1 (females) at each time point as an indicator.

2.2 Secondary Objectives

(1) To investigate the efficacy of TAC-302 in DU patients with OAB, using the changes in values including PFS parameters, uroflowmetry parameters, BVE, the IPSS or the OABSS as indicators.
(2) To investigate the efficacy of TAC-302 in DU patients with OAB in comparison with placebo.
(3) To investigate the safety of TAC-302 in DU patients with OAB using data including the incidence of adverse events and adverse reactions as indicators.

2.3 Endpoints

2.3.1 Primary Endpoint

- BCI [maximum detrusor pressure at peak urine flow ($P_{det}Q_{max}$) + 5 × peak urine flow rate (Q_{max})] (males)
- PIP1 ($P_{det}Q_{max} + Q_{max}$) (females)

[Evaluation time points: week 0, week 12]

2.3.2 Secondary Endpoints

2.3.2.1 Efficacy

(1) PFS parameters (filling phase) [Evaluation time points: week 0, week 12]
- Volume at first desire to void
- Maximum bladder volume
- Bladder compliance
- Appearance of bladder involuntary contraction
- Bladder volume up to appearance of bladder involuntary contraction

(2) PFS parameters (voiding phase) [Evaluation time points: week 0, week 12]
- Detrusor pressure at start of voiding ($P_{det\ open}$)
- Maximum detrusor pressure ($P_{det\ max}$)
- Maximum flow rate (Q_{max})

- Average flow rate (Q_{ave})
- Detrusor pressure at maximum flow ($P_{det}Q_{max}$)
- Duration of bladder contraction
- Voided volume
- Post void residual

(3) Uroflowmetry parameters [Evaluation time points: weeks 0, 4, 8, 12]
- Maximum flow rate (free Q_{max})
- Average flow rate (free Q_{ave})
- Voided volume
- Voiding time

(4) Post void residual measured by ultrasonography [Evaluation time points: at registration in observation period, weeks 0, 4, 8, 12]

(5) BVE [Voided volume / (voided volume + post void residual)] [Evaluation time points: weeks 0, 4, 8, 12]
Calculated from the voided volume measured by uroflowmetry and the post void residual measured by ultrasonography

(6) Change in IPSS score at weeks 4, 8, and 12 of the treatment periods relative to baseline (week 0)
- IPSS total score
- IPSS storage symptoms score
- IPSS voiding symptoms score
- IPSS QOL score

(7) Change in IPSS score at weeks 4, 8, and 12 of the treatment periods relative to baseline (week 0)

(8) Change in KHQ score (by domain) at week 12 of the treatment period relative to baseline (week 0)

(9) Change in bladder diary record data at weeks 4, 8, and 12 of the treatment periods relative to baseline (week 0)
- Average number of micturition per 24 hours
- Average number of urgency urinary incontinence episodes per 24 hours
- Average number of urinary urgency episodes per 24 hours
- Average voided volume per urination
- Average number of nocturnal urinations

2.3.2.2 Safety

(1) Occurrence of adverse events and adverse reactions

(2) Blood pressure, pulse rate, body temperature, 12-lead electrocardiogram, and laboratory tests

3. STUDY DESIGN

This study is a central-registration, multi-center, double-blind, placebo-controlled, randomized parallel-group comparative study to investigate the efficacy and safety of TAC-302 in DU patients with OAB. The design of this study is shown in Figure 3-1. This study is composed of a single-blind observation period, a double-blind treatment period, and a follow-up period.

Patients considered eligible for the enrollment in the observation period after providing written informed consent will proceed to the observation period. The investigational drug for the observation period will be administered under single-blind conditions. In the observation period, the investigational drug (placebo) will be administered orally twice daily after breakfast and dinner for 2 to 4 weeks. Patients considered eligible for the enrollment in the treatment period after the end of the observation period will proceed to the treatment period. The investigational drug for the treatment period will be administered under double-blind conditions. The investigational drug in the treatment period will be randomly assigned, with patients allocated to the TAC-302 and placebo group in a 2:1 ratio. To maintain a balance between groups, dynamic assignment using assignment factors [sex (male and female), age at informed consent (< 65 years and ≥ 65 years)] will be performed. In the treatment period, the investigational drug (TAC-302 200 mg or placebo) will be administered orally twice daily after breakfast and dinner for 12 weeks. After the start of the treatment period (registration in the treatment period), patients will make visits in weeks 2, 4, 8, and 12, and the designated observations and tests will be performed. A follow-up examination will be performed 1 week after the end of week 12 of the treatment period. If any adverse event is considered to be an adverse reaction after the follow-up examination, the follow-up investigation should be performed until it is confirmed that the symptom (including abnormal laboratory values) has recovered to the state of before the onset as much as possible or is resolving.

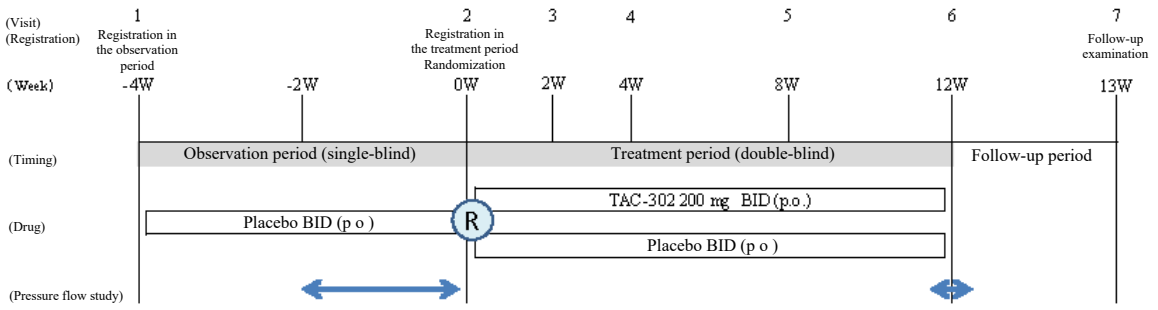


Figure 3-1 Study Design

3.1 Study Period

Study initiation date (planned): August 2017

Study completion date (planned): December 2019

[Region/Country]: Japan

3.1.1 Definition of Each Period for Each Patient

Each period described in this protocol is defined as follows.

Study period:	From the time of obtaining informed consent to the end of the follow-up examination
Observation period:	The period from registration in the observation period up to registration in the treatment period (registration in the treatment period will be performed between 2 to 4 weeks after registration in the observation period)
Treatment period:	From the time of registration in the treatment period to the end of week 12 of the treatment period
Follow-up period:	From the end of week 12 of the treatment period to the end of the follow-up examination (performed 1 week after the end of week 12 of the treatment period)

3.2 Patient Assignment and Blinding

3.2.1 Method of Assignment

This study is a randomized study conducted by central registration using an Interactive Web Response System (IWRS). Data will be entered according to the IWRS procedure.
The principal investigator or subinvestigator will provide each target patient with an explanation and then obtain written informed consent. A patient identification code will consist of a TAC302-site number (2 digits) - the order of consent obtainment at each site (3 digits). After it is confirmed that the patient meets the inclusion criteria and does not meet any exclusion criteria for registration in the observation period and has no problems with his/her eligibility, the patient will be enrolled in the observation period via the IWRS. After it is confirmed that the patient meets the inclusion criteria and does not meet any exclusion criteria for registration in the treatment period and has no problems with his/her eligibility, the patient will be enrolled in the treatment period via the IWRS.
When the registration in the treatment period is complete, patients will be randomly assigned to the TAC-302 group and the placebo group in a ratio of 2:1 via the IWRS based on a dynamic allocation method (minimization method) including the stochastic process.
Patients will be stratified according to the following assignment adjustment factors:

- Sex (male or female)
- Age at informed consent (< 65 years or ≥ 65 years)

The IWRS will assign an investigational drug to each patient, notify the study site of the drug number assigned to the patient, and give instructions for prescription of the investigational drug. Detailed information will be provided in the IWRS procedure.
If an investigational drug different from the drug number assigned by the IWRS should be dispensed in error to a patient, the site must notify the sponsor immediately. The site must also document the cause of investigational drug prescribing or dispensing errors. If a patient starts to receive an investigational drug in a group different from the group to which he/she has actually been assigned, administration of the investigational drug will be continued.

3.2.2 Blinding

This study is a double-blind study. During the conduct of the study, neither any of the patients, nor the principal investigator, subinvestigator, study coordinator, or sponsor will be informed about the treatment groups. Key codes will be prepared and unblinded according to the procedures for investigational drug assignment. The investigational drug assignment manager will store and manage the key codes until unblinding.

The following details will be shown in documents such as the procedures for investigational drug assignment, the emergency key code unblinding procedure or the key unblinding procedure.

- The method for assuring indistinguishability (the timing, person performing the procedures, the items carried out, etc.)
- Methods for storing, managing and handling key codes and emergency key codes and identification of the person storing the key codes
- Emergency key code unblinding procedure
- Timing and procedure for unblinding after data lock

4. SELECTION AND WITHDRAWAL OF PATIENTS

4.1 Inclusion Criteria

At each registration, patients meeting all of the following inclusion criteria will be eligible. The rationale is shown in Section 14.3.

4.1.1 Registration in the Observation Period

(1) Provided written informed consent in person

(2) Aged ≥ 20 years at the time of obtaining informed consent and able to receive treatment as an outpatient (irrespective of sex)

(3) Being able to use the toilet himself/herself and make accurate bladder diary records, in the opinion of the principal investigator or subinvestigator

(4) Having had lower urinary tract symptoms (storage symptoms, voiding symptoms, and post-micturition symptoms) for at least 12 weeks before registration in the observation period

(5) Scoring ≥ 2 points on any of the following questions for the IPSS voiding symptoms score at registration in the observation period

- Over the past month, how often have you found you stopped and started again several times when you urinated?
- Over the past month, how often have you had a weak urinary stream?
- Over the past month, how often have you had a push or strain to begin urination?

(6) Scoring ≥ 2 points for the urinary urgency score (Question 3), and having an OABSS total score of ≥ 3 points in OABSS evaluation at registration in the observation period

- Question 3: How often do you have a sudden desire to urinate, which is difficult to defer?

(7) Post void residual ≤ 300 mL measured at registration in the observation period

4.1.2 Registration in the Treatment Period

(1) Scoring ≥ 2 points on any of the following questions for the IPSS voiding symptoms score at registration in the observation period

- Over the past month, how often have you found you stopped and started again several times when you urinated?
- Over the past month, how often have you had a weak urinary stream?
- Over the past month, how often have you had a push or strain to begin urination?

(2) Meeting all of the following conditions based on information from bladder diary records in the 3 days directly before registration in the treatment period

1) Being able to use the toilet himself/herself and make accurate bladder diary records, in the opinion of the principal investigator or subinvestigator

2) An average of ≥ 8 urinations per 24 hours and meeting either of the following conditions

- An average of ≥ 1 urinary urgency episodes per 24 hours
- An average of ≥ 1 urgency urinary incontinence episode per 24 hours

(3) Post void residual ≤ 300 mL measured at registration in the treatment period

(4) Meeting the following criteria based on a urodynamic study (UDS) performed at registration in the treatment period

[a, b: Calculated from PFS parameters, c: Calculated from uroflowmetry parameters and the measurement of the post void residual according to ultrasound]

1) Criteria for males
   a) BCI ($P_{det}Q_{max}+5Q_{max}$) < 100
   b) Bladder outlet obstruction index (BOOI=$P_{det}Q_{max}-2Q_{max}$) < 40
   c) BVE [voided volume / (voided volume + post void residual)] < 90%

2) Criteria for females
   a) $P_{det}Q_{max}$ < 20
   b) Q_{max} < 15
   c) BVE [voided volume / (voided volume + post void residual)] < 90%

4.2 Exclusion Criteria

At each registration, patients meeting any of the following criteria will be ineligible.
The rationale is shown in Section 14.3.

4.2.1 Registration in the Observation Period

(1) Having the following concurrent or historical conditions, and having been diagnosed with neurogenic bladder accompanied by obvious neurological abnormality associated with the following diseases
   1) Cerebrovascular disorder (cerebral hemorrhage, cerebral infarction, etc.)
   2) Parkinson's disease
   3) Alzheimer's disease
   4) Multiple sclerosis
   5) Spina bifida
   6) Spinal cord disorder (spinal cord injury, etc.)

(2) Concurrent urinary tract infection (prostatitis, cystitis, etc.) or historical recurrent urinary tract infection [occurring ≥ 3 times within a period of 168 days (24 weeks) before registration in the observation period]. Concurrent urinary disease impairing determination of the effect of the investigational drug, such as cystitis interstitial, urinary tract stenosis, urinary tract obstruction, calculus urinary (calculus ureteric, calculus urethral, calculus bladder, etc.), benign tumor of the urethra (urethral polyp, cyst, papilloma, etc.) and urethral diverticulum.

(3) Concurrent bladder cancer or prostate cancer, or suspected bladder cancer or prostate cancer, or a history of these

(4) Cystocele classified as stage III or higher according to the POP-Q stage classification (females)

(5) Prostate gland volume ≥ 30 mL (males)

(6) Overflow urinary incontinence

(7) Clinically significant concurrent conditions (including symptoms and findings) such as severe liver disease (hepatitis viral, drug-induced liver injury, etc.), severe renal disease (acute renal failure, glomerulonephritis, nephritis interstitial, etc.), severe cardiovascular disease (cardiac failure congestive, symptomatic unstable angina pectoris, poorly controlled arrhythmia, myocardial infarction, etc.), severe blood dyscrasia (pancytopenia, leukopenia, etc.), severe respiratory disease (bronchial asthma, bronchitis chronic, etc.), severe digestive disease (peptic ulcer, reflux esophagitis, Crohn's disease, colitis ulcerative, etc.), severe neuropsychiatric disease (schizophrenia, dementia, etc.), severe immune disease (collagen disorder, etc.), severe metabolic or endocrine disease or malignant tumor

(8) Having received urethral catheter placement, or performing intermittent self-catheterization due to the inability to urinate spontaneously

(9) Meeting the following conditions at laboratory tests performed in the period of 14 days before registration in the observation period
   1) Aspartate aminotransferase (AST) > 3 × upper limit of normal (ULN)
   2) ALT > 3 × ULN
   3) T-Bil > 1.5 × ULN
   4) Serum creatinine > 1.5 × ULN

(10) The following have been performed in the period of 154 days (22 weeks) before registration in the observation period.
   1) Surgery of the pelvic organs (radical hysterectomy, radical surgery for rectal cancer, radical pelvic lymph node dissection, etc.) injuring the pelvic nerve or hypogastric nerve
   2) Prostatectomy
   3) Radiotherapy that may affect voiding function

(11) Having received another investigational drug in the period of 90 days before registration in the observation period

(12) Being pregnant, breastfeeding, or a female patient of childbearing potential with a positive (urine or serum) pregnancy test result in the period of 7 days before registration in the observation period
   Note) Women without childbearing potential are women who have undergone hysterectomy and postmenopausal women who have not experienced menstruation for at least 1 year with no associated medical reason such as administration of contraceptives

(13) In the case of women with reproductive potential, not consenting to use contraception during the study period and for a period of 30 days after the end of administration of the investigational drug*

(14) In the case of male patients, not consenting to use contraception during the study period and for a period of 90 days after the end of administration of the investigational drug*

(15) Being determined to be ineligible for this study in the opinion of the principal investigator or subinvestigator

* The principal investigator or subinvestigator will instruct patients to always perform contraception using a method such as the double-barrier method (a condom and pessary), an intrauterine device or oral contraceptives during the period of administration of the investigational drug and the period of contraception after the end of administration of the investigational drug.

4.2.2 Registration in the Treatment Period

(1) A rate of compliance with administration of the investigational drug of <80% in the observation period

(2) Having the following concurrent conditions, and having been diagnosed with neurogenic bladder accompanied by obvious neurological abnormality associated with the following diseases
   1) Cerebrovascular disorder (cerebral hemorrhage, cerebral infarction, etc.)
   2) Parkinson's disease
   3) Alzheimer's disease
   4) Multiple sclerosis
   5) Spina bifida
   6) Spinal cord disorder (spinal cord injury, etc.)

(3) Concurrent urinary disease impairing determination of the effect of the investigational drug, such as urinary tract infection (prostatitis, cystitis, etc.), cystitis interstitial, urinary tract stenosis, urinary tract obstruction, calculus urinary (calculus ureteric, calculus urethral, calculus bladder, etc.), benign tumor of the urethra (urethral polyp, cyst, papilloma, etc.) and urethral diverticulum.

(4) Concurrent bladder cancer or prostate cancer, or suspected bladder cancer or prostate cancer

(5) Cystocele classified as stage III or higher according to the POP-Q stage classification (females)

(6) Overflow urinary incontinence

(7) Clinically significant concurrent conditions (including symptoms and findings) such as severe liver disease (hepatitis viral, drug-induced liver injury, etc.), severe renal disease (acute renal failure, glomerulonephritis, nephritis interstitial, etc.), severe cardiovascular disease (cardiac failure congestive, symptomatic unstable angina pectoris, poorly controlled arrhythmia, myocardial infarction, etc.), severe blood dyscrasia (pancytopenia, leukopenia, etc.), severe respiratory disease (bronchial asthma, bronchitis chronic, etc.), severe digestive disease (peptic ulcer, reflux esophagitis, Crohn's disease, colitis ulcerative, etc.), severe neuropsychiatric disease (schizophrenia, dementia, etc.), severe immune disease (collagen disorder, etc.), severe metabolic or endocrine disease or malignant tumor

(8) Having received urethral catheter placement, or performing intermittent self-catheterization due to the inability to urinate spontaneously
(9) Being determined to be ineligible for this study in the opinion of the principal investigator or subinvestigator

4.3 Discontinuation Criteria for Individual Patients

Administration of the investigational drug will be discontinued in a patient meeting any of the following criteria. Discontinuation criteria for individual patients are shown below:

(1) It becomes unfeasible to continue administration due to the occurrence of an adverse event
(2) The patient requests withdrawal of his/her consent
(3) Major noncompliance with the study procedures is observed.
(4) The patient becomes unable to continue the study due to circumstances such as moving house, being transferred to another medical institution or being too busy
(5) It is discovered that the patient is not in the target population for this study (the patient does not meet the inclusion criteria, or meets any of the exclusion criteria).
(6) The patient becomes pregnant.
(7) Because the effect of the investigational drug is incomplete or symptoms have worsened, the principal investigator or subinvestigator determines that administration should be discontinued.
(8) It becomes necessary to discontinue the patient from the study for any other reason in the opinion of the principal investigator or subinvestigator.

5. STUDY ASSESSMENTS

The evaluations and examination items to be performed in this study are shown in Table 5-1 and the detailed schedule is shown in Table 5-2.

All information stipulated in the protocol should be recorded. If the designated observations or tests are performed in the period of 14 days before registration in the observation period, even if this is before informed consent is obtained, these can be used as data at registration in the observation period.

Table 5-1 Evaluations and Examination Items

Obtaining informed consent			
Date of obtaining informed consent			
Patient backgrounds			
Sex	Date of birth		Age[*1]
Race	Height		Weight
BMI[*2]	History of participation in clinical studies (within the past 90 days)		Medical history (within the past 180 days)[*3]
Onset time of lower urinary tract symptoms (LUTS) (storage symptoms, voiding symptoms, and post-micturition symptoms)			
Concurrent conditions	History of prior treatment		
Patient registration			
Patient identification code	Drug number		
Symptoms and findings			
Blood pressure (systolic and diastolic)	Pulse rate		Body temperature
Compliance with administration of the investigational drug			
Concomitant medication and concomitant therapy			
12-lead electrocardiography			
Heart rate	QT interval	RR interval	QTcF interval[*4]
Hematology tests			
Red blood cell count	Hemoglobin	Hematocrit	Platelet count
White blood cell count	Neutrophils	Eosinophils	Basophils
Lymphocytes	Monocytes		
Biochemistry tests			
Total protein	Albumin	A/G	T-Bil
Direct bilirubin	AST(GOT)	ALT(GPT)	ALP
LDH	γ-GTP	BUN	Creatinine
Creatine kinase	Blood glucose	Amylase	Triglycerides
Total cholesterol	CRP	Na	K
Cl	Ca[*5]		
Endocrinological tests			
Thyroid stimulating hormone (TSH)	free T_3	free T_4	Cortisol
Adrenocorticotropic hormone (ACTH)			
Urinalysis			
Protein	Glucose	Urobilinogen	Urine NAG
Urine β_2-microglobulin	Urine sediment[*6]		
Pregnancy test[*7]			
Serum or urine human chorionic gonadotropin			
Prostate gland volume measurement			
Pressure flow study (PFS) (filling phase)			
Volume at first desire to void	Maximum bladder volume	Bladder compliance	Appearance of bladder involuntary contraction
Bladder volume up to appearance of bladder involuntary contraction			
Pressure flow study (PFS) (voiding phase)			
BCI ($P_{det}Qmax + 5Q_{max}$): males		PIP1 ($P_{det}Q_{max} + Q_{max}$): females	
Detrusor pressure at maximum flow ($P_{det}Q_{max}$)		Detrusor pressure at start of voiding ($P_{det\ open}$)	
Maximum detrusor pressure ($P_{det\ max}$)		Maximum flow rate (Q_{max})	
Average flow rate (Q_{ave})		Duration of bladder contraction	
Voided volume		Post void residual	
Uroflowmetry			
Maximum flow rate (free Q_{max})	Average flow rate (free Q_{ave})	Voided volume	Voiding time
Post void residual measured by ultrasound			
be [voided volume/(voided volume + post void residual)] Post void residual measured by ultrasound and voided volume measured by uroflowmetry			
Symptom score evaluation			
IPSS	OABSS		
QOL score evaluation			
KHQ			
Bladder diary records			
Dates and times of voiding and urinary incontinence	Urinary urgency	Voided volume	
Evaluation of adverse events			

*1: Automatically calculated from the date of birth. *2: Automatically calculated from height and weight.

*3: This is a medical history determined by the principal investigator or subinvestigator to be important in the conduct of this study (such as diseases related to urinary organs).

*4: Automatically calculated from the QT interval and RR interval.

*5: In the evaluation of adverse events, if albumin is < 4.0 g/dL, determinations will be made using values corrected by the following formula.
[Corrected calcium (mg/dL)] = [Calcium (mg/dL)] – 0.8 × {[Albumin (g/dL)] – 4}

*6: Urine sediment will only be examined at registration in the observation period and registration in the treatment period.

*7: Required for female patients with childbearing potential. However, a pregnancy test will not be required for patients more than 1 year after menopause or patients in whom the possibility of pregnancy is medically ruled out.

Table 5-2 Observation and Testing Schedule

Timing	Observation period		Treatment period								Follow-up period	At discontinuation[8]
	At registration	3 days before registration in the treatment period	At registration[5]	Week 2[6]	3 days before the visit for week 4	Week 4[6]	3 days before the visit for week 8	Week 8[6]	3 days before the visit for week 12	Week 12[6]	Follow-up examination[7]	
Visit	1		2	3		4		5		6	7	
Week	-4 to -2		0	2		4		8		12	13	
Obtaining informed consent	X[1]											
Assigning of patient identification codes[2]	X											
Patient backgrounds	X		X									
Registration	X		X									
Investigational drug dispensing	X		X	X		X		X				
Retrieving leftover drugs			X	X		X		X		X		X
Checking of drug compliance			X	X		X		X		X		X
Physical examination	X		X	X		X		X		X	X	X
Blood pressure, pulse rate, and body temperature	X[9]		X	X		X		X		X	X	X
12-lead electrocardiography	X[9]		X							X	X	X
Laboratory tests[3]	X[9]		X	X		X		X		X	X	X
Pregnancy tests[4]	X											
Bladder diary records: Supplied	X			X		X		X				
Filled in		←	→		←	→	←	→	←	→		
Collected			X			X		X		X		X
Checked			X			X		X		X		X
Symptom score (IPSS, OABSS) evaluation	X		X			X		X		X		X
King's health questionnaire evaluation			X							X		X
Pressure Flow Study (PFS)[10]			X							X		X
Uroflowmetry			X[11]			X[11]		X[11]		X[11]		X[11]
Post void residual measured by ultrasound	X[9]		X[11]			X[11]		X[11]		X[11]		X[11]
Prostate gland volume measurement	X[9]											
Checking concomitant drugs/concomitant therapy[12]	←										→	X
Checking adverse events[12]	←										→	X

1) Obtaining informed consent: Obtained within the period of 28 days before registration in the observation period.
2) Assigning of patient identification codes: Assigned to patients providing informed consent.
3) Laboratory tests: Hematology tests, biochemistry tests, endocrinological tests and urinalysis will be performed. However, the urinalysis test urine sediment will only be performed at registration in the observation period and at registration in the treatment period.
4) Pregnancy tests: Required for female patients with childbearing potential. However, a pregnancy test will not be required for patients more than 1 year after menopause or patients in whom the possibility of pregnancy is medically ruled out. At tests before registration in the observation period, pregnancy tests (serum or urine) must be negative. The time window for performing the test is the period of 7 days before registration in the observation period.
5) Time window for registration in the treatment period: All observation and examination items at registration in the treatment period will be performed by registration in the treatment period, 2 to 4 weeks after registration in the observation period.
6) Time window for visits in the treatment period: Visits at weeks 2, 4, and 8 of the treatment periods will be allowed to be within the range of the standard date ±3 days. The visit at week 12 will be allowed to be within the range of the standard date −3 days to the standard date +7 days.
7) Time window for the follow-up examination: This will be performed 1 to 2 weeks after the end of week 12 of the treatment period. If the patient discontinued during the treatment period, it will be performed 1 to 2 weeks after the final dose of the investigational drug.
8) At discontinuation: The designated observations and examination items will be performed as far as possible. For patients providing informed consent but not enrolled in the treatment period, the observations and tests relating to safety evaluation will be performed as far as possible.
9) If the designated observations or tests are performed in the period of 14 days before registration in the observation period, even if this is before informed consent is obtained, these can be used as data at registration in the observation period.
10) PFS will be performed on the same date as uroflowmetry and measurement of the post void residual by ultrasound as far as possible.
11) For evaluating BVE, measurement of the post void residual by ultrasound will be performed after uroflowmetry.
12) Concomitant drugs/concomitant therapy and evaluation of adverse events: These will be investigated from informed consent to the end of follow-up.

5.1 Study Procedures

The following evaluations and examinations must be recorded in the patient's source documents.

5.1.1 Obtaining informed consent

Informed consent will be obtained within 28 days before enrollment in the observation period, and eligibility will be confirmed subsequently.

5.1.2 Assigning of Patient Identification Codes

Each patient will be assigned a unique patient identification code (Section 3.2) for screening at the study site.

5.1.3 Patient backgrounds

Patient background information shown in Table 5-1 will be collected.

5.1.4 Physical examination

Physical examination findings will be evaluated at the time points shown in Table 5-2. Adverse events will be evaluated as shown in Section 12.

5.1.5 Blood Pressure (Systolic and Diastolic), Pulse Rate, Body Temperature

Blood pressure (systolic and diastolic), pulse rate, and body temperature will be measured at the time points shown in Table 5-2. Measurement should be performed at the same site and by the same method for each patient at all measurement time points while the patient is at rest. The principal investigator or subinvestigator will be responsible for the assessment of changes in blood pressure (systolic and diastolic), pulse rate, and body temperature. Adverse events will be evaluated as shown in Section 12.

5.1.6 Compliance with administration of the investigational drug

From the start of administration of the investigational drug to the end of administration, at each visit, compliance with treatment with the investigational drug was checked, including checks using drug diaries, empty sheets of used investigational drug, and interview.

5.1.7 Concomitant medication and concomitant therapy

Information on all concomitant medications (prescription drugs and over-the-counter drugs) and therapies will be collected by interviews, etc. at least at each visit from the time of informed consent to the end of the study period, and the status of their use will be recorded in the source documents. Concomitant medications include drugs used to treat adverse events or serious adverse events. Concomitant medications and therapies used to treat adverse events or serious adverse events requiring follow-up at the follow-up examination will be collected until the end of the follow-up, and the status of their use will be recorded in the source documents. However, it is not necessary to enter test drugs, diagnostic drugs, and fluid replacement at the time of administration of injectable drugs in the electronic case report form (eCRF).

5.1.8 12-lead electrocardiography

12-lead ECG will be performed at the time points shown in Table 5-2. Measurement should be performed at rest using the same method for each patient.
The principal investigator or subinvestigator will be responsible for the assessment of the results of ECG. Adverse events will be evaluated as shown in Section 12.

5.1.9 Laboratory Values

Laboratory tests (hematology, biochemistry, endocrinology, and urinalysis) will be performed for the parameters listed in Table 5-1. Blood and urine samples for laboratory tests will be collected at the time points shown in Table 5-2.
The principal investigator or subinvestigator will assess whether all laboratory values are clinically significant changes or not. Any clinically significant change must be followed as specified in the protocol and recorded as an adverse event. Adverse events will be evaluated as shown in Section 12.

5.1.10 Pregnancy Test

For patients of childbearing potential, serum or urine human chorionic gonadotrophin will be tested at the time point shown in Table 5-2 to confirm that they are not pregnant. It is not necessary to perform the test in patients without childbearing potential.

Note) Women without childbearing potential are women who have undergone hysterectomy and postmenopausal women who have not experienced menstruation for at least 1 year with no associated medical reason such as administration of contraceptives

5.1.11 Symptom Score Evaluation (IPSS, OABSS)

As the evaluation of symptom scores, IPSS and OABSS will be evaluated by patients at the time points shown in Table 5-2.

5.1.12 King's Health Questionnaire (KHQ)

Patients will be asked to evaluate KHQ at the time points shown in Table 5-2.

5.1.13 Bladder diary records

The bladder diary will be supplied and collected from patients at the time points shown in Table 5-2 to check the contents of the diary.

5.1.14 Pressure Flow Study (PFS)

Pressure flow study will be performed at the time points shown in Table 5-2. For details, the procedure for pressure flow study will be followed.

5.1.15 Uroflowmetry

Pressure flow study will be performed at the time points shown in Table 5-2. For details, the procedure for uroflowmetry will be followed.

5.1.16 Post void residual measured by ultrasound

Post void residual will be measured by ultrasound at the time points shown in Table 5-2. For measurement after the registration in the treatment period, residual urine after uroflowmetry will be measured to evaluate the secondary endpoint of BVE.

5.1.17 Prostate gland volume measurement

For males only, prostate gland volume measurement will be performed at the time point shown in Table 5-2.

5.1.18 Evaluation of adverse events

Any untoward medical event (adverse event) will be checked at each visit from the time of informed consent to the end of the study period, as shown in Table 5-2. Adverse events will be evaluated as shown in Section 12.

5.2 Evaluations and Examination Items at Each Visit

The evaluations and examinations shown in Table 5-1 will be performed according to the schedule shown in Table 5-2.

6. INVESTIGATIONAL PRODUCTS

The sponsor will provide TAC-302 and placebo until the end of the study period.

6.1 Name, etc. of Investigational Products

The physical and chemical properties of the test product and the comparator are presented in Table 6.1-1 and Table 6.1-2.

Table 6.1-1 Overview of TAC-302 [Test Product]

Investigational drug code name	TAC-302
Generic name	Undetermined
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Dosage form	Capsule
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Expiry date	Shown in the investigational drug control and handling procedure

Table 6.1-2 Overview of Placebo [Comparator]

Composition	Capsule containing no active ingredient of the test product and indistinguishable from the test product in appearance.
[redacted]	[redacted]
Expiry date	Shown in the investigational drug control and handling procedure

6.2 Packaging and Labeling of Investigational Products

The following information is indicated on the outer box and aluminum bag of the investigational products. Details are shown in the investigational product control and handling procedure.

(1) Name of the sponsor
(2) Address
(3) Storage
(4) Quantity
(5) Manufacturing number

(6) Date of manufacture

6.3 Control of Investigational Products

The principal investigator and the investigational product manager will manage the investigational products in accordance with the provided investigational product control and handling procedure. The prescription history of the investigational products will be recorded in the investigational product accountability record.
The investigational products must not be used outside of this study.

6.4 Instructions on the Handling of Investigational Product for Patients

The principal investigator or subinvestigator will instruct patients to take the investigational product as specified during the study period. Detailed instructions are provided in the investigational product control and handling procedure and the medication diary. If a patient does not follow the specified method, the principal investigator or the sponsor may discontinue the study for the patient. Treatment compliance will be confirmed by checking the records in the investigational product accountability record and the consistency with the medication diary and source documents.

6.5 Implementation of Assignment Confirmation Test

This is a double-blind, controlled study, and the assignment confirmation test will be conducted to confirm that each treatment group (TAC-302 group and placebo group) has been allocated appropriately after assignment.

7. ADMINISTRATION METHOD

All administration status will be recorded in the source documents. Patients will be instructed on the administration method in accordance with the investigational drug control and handling procedure and the medication diary.

7.1 Administration Procedure

7.1.1 Method of Administration

7.1.1.1 Observation period

In the observation period, placebo will be administered orally twice daily after breakfast and dinner for 2 to 4 weeks under single-blind conditions. The number of investigational drug capsules per dose is shown in Table 7.1.1.1-1.

Table 7.1.1.1-1 Number of Investigational Drug Capsules Per Dose (Observation Period)

Group	Number of capsules per dose
Placebo	Placebo × 2 capsules

7.1.1.2 Treatment period

In the treatment period, under double-blind conditions, the investigational drug (TAC-302 or placebo) will be administered orally twice daily after breakfast and dinner for 12 weeks. The number of investigational drug capsules per dose is shown in Table 7.1.1.2-1.

Table 7.1.1.2-1 Number of Investigational Drug Capsules Per Dose (Treatment Period)

Group	Number of capsules per dose
TAC-302	TAC-302 100 mg × 2 capsules
Placebo	Placebo × 2 capsules

7.2 Restrictions

7.2.1 Contraception

The principal investigator or subinvestigator will instruct patients to ensure measures are taken to prevent pregnancy by using a double-barrier method (condom and diaphragm) or an intrauterine contraceptive device, etc. during the study period and the contraception period (for female patients with reproductive potential, 30 days after the completion of investigational product administration; for male patients, 90 days after the completion of investigational product administration).

7.3 Concomitant medication and concomitant therapy

7.3.1 Prohibited Concomitant Drugs

The following drugs will be prohibited from registration in the observation period to the visit at week 12 of the treatment period or the end of administration of the investigational drug. The rationale is shown in Section 14.4.

(1) Following drugs for OAB or impaired urination:
- Anticholinergics (oxybutynin hydrochloride, propiverine hydrochloride, tolterodine tartrate, solifenacin succinate, imidafenacin, fesoterodine fumarate, propantheline bromide, etc.)
- β_3 receptor agonists (mirabegron, etc)
- Flavoxate hydrochloride
- Tricyclic antidepressants (imipramine hydrochloride, amitriptyline hydrochloride, clomipramine hydrochloride, etc)
- Chinese herbal medicines (hachimijiogan, goshajinkigan, etc)
- Estrogen (estriol)
- Botulinum toxin
- Resiniferatoxin, capsaicin
- Anti-diuretic hormones (desmopressin, etc)
- Cholinergics (bethanechol chloride, etc)
- Cholinesterase inhibitors (distigmine bromide, etc)
- α_1 adrenaline receptor blockers (tamsulosin hydrochloride, naftopidil, silodosin, terazosin hydrochloride hydrate, urapidil, prazosin hydrochloride, alfuzosin hydrochloride, etc)
- 5α reductase inhibitors (dutasteride, finasteride)
- Phosphodiesterase (PDE) 5 inhibitors (tadalafil, sildenafil citrate, etc)
- Antiandrogens (chlormadinone acetate, allylestrenol)
- Other oral drugs (Paraprost, Eviprostat, Cernilton)

(2) Other drugs predicted to influence voiding function

(3) Other investigational drugs

7.3.2 Prohibited Concomitant Therapy

The following concomitant therapies will be prohibited from registration in the observation period to the visit at week 12 of the treatment period or the end of administration of the investigational drug. The rationale is shown in Section 14.5.

- Surgery of the pelvic organs (radical hysterectomy, radical surgery for rectal cancer, radical pelvic lymph node dissection, etc.) injuring the pelvic nerve or hypogastric nerve
- Prostatectomy
- Radiotherapy that may affect voiding function
- Physiotherapy (pelvic floor muscle training, feedback training, biofeedback training, bladder training, electric stimulation therapy, magnetic stimulation therapy, etc)

8. PHARMACOKINETICS/PHARMACODYNAMICS

Pharmacokinetics and pharmacodynamics will not be evaluated in this study.

9. PHARMACOGENOMICS

Pharmacogenomic research will not be conducted in this study.

10. DISCONTINUATION/TERMINATION OF STUDY

10.1 Criteria for Discontinuation of the Study at Study Sites

The sponsor or principal investigator may terminate the study at a study site where major or continuous non-compliance with GCP or the study protocol by the principal investigator or subinvestigator has interfered or may have interfered with the proper conduct of the study. In such a case, the institutional review board (IRB) should be notified immediately according to the applicable standard operating procedure (SOP) of the study site.

10.2 Criteria for Discontinuation of the Entire Study

The sponsor also reserves the right to discontinue this study for administrative reasons at any time. If becoming aware of circumstances that warrant termination of the study during the course of the study, the sponsor will terminate the study or part of the study appropriately. In such a case, the head of the study site should be notified immediately of the fact and the reason for discontinuation in writing. The head of the study site will promptly inform the IRB and the principal investigator in writing. The principal investigator or subinvestigator will promptly inform the patients and change the treatment to other therapies. The sponsor will promptly notify the regulatory authorities of the discontinuation of the study.

11. EFFICACY EVALUATIONS

11.1 Pressure Flow Study (PFS)

The principal investigator or subinvestigator will perform PFS. It has been reported to be advisable for PFS results to be found by central determination, for example by a central committee, in order to maintain objectivity and consistency in interpretation.[17)] To perform central determination in this study, test results will be provided to the sponsor as electronic data as far as possible. Details such as the procedures for performing PFS and method of providing PFS are shown in the procedures for performing pressure flow studies. Details of the organization and methods for central determination are shown in the procedures relating to central determination. To check inclusion criterion (4) for registration in the treatment period at registration in the treatment period, the principal investigator or subinvestigator will evaluate the PFS parameters, maximum flow rate (Q_{max}) and maximum detrusor pressure at peak urine flow ($P_{det}Q_{max}$). For male patients, BCI and BOOI will be calculated.

11.2 Uroflowmetry

The principal investigator or subinvestigator will perform uroflowmetry. Uroflowmetry test results will be provided to the sponsor on paper form so that they can be evaluated by central determination together with the PFS results. Details such as the procedures for performing uroflowmetry and the method of providing uroflowmetry are shown in the procedures for performing uroflowmetry. Details of the organization and methods for central determination are shown in the procedures relating to central determination. The principal investigator or subinvestigator will evaluate the voided volume to check BVE [voided volume/(voided volume + post void residual)] for inclusion criterion (4) for registration in the treatment period at registration in the treatment period.

11.3 Symptom score evaluation

11.3.1 IPSS and QOL Scores

Voiding symptoms and storage symptoms will be evaluated using the IPSS and QOL scores. The definition of IPSS is shown in Table 11.3.1-1 and details of the contents are shown in Appendix 1.

The principal investigator or subinvestigator will instruct the patients to write down the applicable scores for each question. While the patients are making evaluations, care should be taken not to bias this evaluation, for example by standing next to the patients or talking to them.

Table 11.3.1-1 IPSS Definition

Question 1 (feeling of residual urine)	Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?
Question 2 (increased daytime frequency)	Over the past month, how often have you had to urinate again less than two hours after you finished urinating?
Question 3 (intermittent stream)	Over the past month, how often have you found you stopped and started again several times when you urinated?
Question 4 (urinary urgency)	Over the past month, how often have you found it difficult to postpone urination?
Question 5 (slow stream)	Over the past month, how often have you had a weak urinary stream?
Question 6 (straining)	Over the past month, how often have you had a push or stain to begin urination?
Question 7 (nocturia)	Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?

Source: Adapted from Japanese Continence Society, Clinical Practice Guideline for Overactive Bladder Writing Committee Eds. Clinical Practice Guideline for Overactive Bladder (2nd Edition). Tokyo: RichHill Medical Inc.; 2015. p.105.

The IPSS total score will be the total score of questions 1 to 7, and a score of 0 to 7 points will be classified as mild, a score of 8 to 19 points, as moderate, and a score of 20 to 35 points, as severe.[23)] The total of the scores for question 1 on post-micturition symptoms and questions 3, 5, and 6 on voiding symptoms will be taken to be the IPSS voiding symptoms score, and the total of the scores for questions 2, 4, and 7 on storage symptoms will be taken to be the score for IPSS storage symptoms.[24)]

The score for the question “If you were to spend the rest of your life with your urinary condition as it is right now, how would you feel about that?” will be taken to be the IPSS QOL score, and a score of 0 to 1 points will be classified as mild, a score of 2 to 4 points, as moderate, and a score of 5 to 6 points, as severe.[23)]

11.3.2 Overactive Bladder Symptom Score (OABSS)

OAB symptoms will be evaluated using the OABSS. The contents of the OABSS are shown in Appendix 2.

The principal investigator or subinvestigator will instruct the patients to write down the applicable scores for each question. While the patients are making evaluations, care should be taken not to bias this evaluation, for example by standing next to the patients or talking to them.

The definition of the OABSS total score will be the total score for all questions, and a score ≤ 5 will be determined to be mild, a score of 6 to 11, to be moderate, and a score ≥ 12, to be severe.[23)]

11.4 King’s health questionnaire (KHQ)

The QOL in DU patients with OAB will be evaluated using the KHQ. The contents of KHQ are shown in Appendix 3.

The principal investigator or subinvestigator will instruct the patients to write down the applicable scores for each question. While the patients are making evaluations, care should be taken not to bias this evaluation, for example by standing next to the patients or talking to them.

The definition of each domain in the Japanese edition of the KHQ and the method for calculating the score are decided with reference to the Clinical Practice Guideline for Overactive Bladder.[23)]

11.5 Bladder diary records

The times of urination, times of urinary incontinence, whether urinary urgency is present and voided volume for each urination recorded by the patient will be evaluated using bladder diary records.

The principal investigator or subinvestigator will explain the method for writing bladder diary records. Details of the method for writing records are shown in the manual explaining bladder diary records and how to write them. Patients will be instructed to write the following in bladder diary records for the 3 days before the next visit: times of urination, times of urinary incontinence, whether urinary urgency was present and the voided volume for each urination. The decision on whether to select bladder diary records will not depend on whether or not data for voided volume are missing.

Bladder diary records will be supplied to patients at each visit, and patients were instructed to bring them to the next visit. In principle, bladder diary records will be collected at the next visit.

12. SAFETY EVALUATIONS

12.1 Adverse Events

12.1.1 Definitions of Adverse Events

An adverse event is any untoward medical occurrence in a patient participating in a clinical study which does not necessarily have to have a causal relationship with an investigational product.

For adverse event terms, diagnoses should be recorded as much as possible. If a diagnosis is not available, then signs and symptoms will be reported.

Any sign, symptom, or abnormal laboratory test or test finding due to an underlying disease (LUTS [urine storage, voiding and post-micturition symptoms] accompanying OAB or DU) or any concurrent condition that is present before the start of this study will not be regarded as an adverse event. However, any newly occurring symptom or worsening of a concurrent condition will be reported as an adverse event.

All clinically significant or medically important changes in laboratory values will be reported as adverse events. Any symptom reported by the principal investigator or subinvestigator as an adverse event derived from a diagnosis will not be regarded as an adverse event.

Cases where a laboratory test value will be regarded as an adverse event:

- Requires treatment
- Requires interruption or discontinuation of the investigational product
- Any other change considered to be medically significant in the opinion of the principal investigator or subinvestigator

Details on how to enter data are provided in the Manual for eCRF Completion/Change/Modification.

Pregnancy and medication error are described in Section 12.5.

12.1.2 Severity of Adverse Events

The severity of adverse events will be rated as one of the following (; [semicolon] means "or"):

(1) Mild

Mild; No symptom or mild symptom; Clinical or laboratory findings only; Requires no treatment

(2) Moderate

Moderate; Requires minimal/local/noninvasive treatment; Limiting age-appropriate instrumental activities of daily living*

(3) Severe

Severe or medically significant but not immediately life-threatening; Requires inpatient hospitalization or prolongation of existing hospitalization; Inactivity/Inactivity; Limiting self-care activities of daily living** In addition, life-threatening events or events requiring emergency intervention, or death due to an adverse event are also regarded as

severe.

*: Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc

**: Self-care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

12.1.3 Causal Relationship with Investigational Product

The causal relationship between an adverse event and the investigational product will be assessed using the following 2-point scale, taking into account various factors (eg, patient's condition, medical history, concomitant medications, temporal relationship between the investigational product administration and onset of the adverse event). When the causal relationship with the investigational product is evaluated as "no reasonable possibility," the reason will be entered in the eCRF.

(1) Reasonable possibility **(Related)**: The event follows a reasonable temporal sequence from administration of the investigational product, and any of the following conditions are met:
- A positive dechallenge: This means that the event improves or resolves after the investigational product is stopped (temporarily or permanently).
- A positive rechallenge: This means that the event reappears after the investigational product is restarted.
- The event cannot be reasonably explained by the patient's clinical state and/or therapies administered other than the investigational product.
- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (eg, angioedema, Stevens-Johnson syndrome).

(2) No reasonable possibility **(Not related)**: There is no evidence to suggest a reasonable possibility between the investigational product and the adverse event.
If considered as "no reasonable possibility":
- The adverse event occurred prior to investigational product administration.
- When the adverse event may have occurred due to the primary disease, complications, concomitant drugs, patient's predisposition, etc.

12.1.4 Outcome of Adverse Events

The outcome of an adverse event will be classified into the following:

(1) Recovered/resolved
The symptom or finding has disappeared or returned to the previous condition.

(2) Recovering/resolving
The symptom or finding has almost disappeared or almost returned to the previous condition.

(3) Not recovered/not resolved
When the symptom or finding has not improved and remains unchanged

(4) Recovered/resolved with sequelae
The symptom has resolved, but dysfunction that interferes with daily life is considered to have occurred due to the adverse event.

(5) Fatal
The patient died due to the adverse event.

12.1.5 Reporting of Adverse Events

Adverse events will be reported from the time of informed consent through the end of the follow-up examination. All adverse events will be documented in the source documents. The eCRF should include adverse events occurring in relation to this study from the time of informed consent to the start of investigational product administration and adverse events occurring after the start of investigational product administration. The evaluation in the observation period will be performed using the observations and tests at the registration in the observation period as a baseline, and the evaluation in the treatment period will be performed using the observations and tests at the registration in the treatment period as a baseline.
The principal investigator or subinvestigators will notify the sponsor of any adverse event or serious medical event including death which is reported or observed by a physician after the end of the follow-up examination and whose causal relationship with the investigational product cannot be ruled out.

12.1.6 Follow-up of Adverse Events

If an adverse event occurs, the principal investigator or subinvestigator will immediately take appropriate measures and follow up the event until it is confirmed to have resolved or to be resolving. However, if follow-up of the adverse event cannot be continued for any of the following reasons, the reason will be entered in the eCRF:

- The causal relationship with the investigational product cannot be evaluated because other treatment was performed.
- The follow-up becomes difficult due to transfer to another hospital, etc.
- The patient refuses to be followed.
- The patient dies.
- Although the adverse event has not resolved or is not resolving, the principal investigator or subinvestigator considers that the adverse event is stable or no further improvement is expected.

12.2 Serious Adverse Events

12.2.1 Definitions of Serious Adverse Events

An adverse event that results in one of the following at any dose is a serious adverse event:

(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 for treatment. The following are not considered hospitalizations for the purposes of assessing seriousness:
   - Emergency room visits < 24 hours;
   - Pre-planned hospitalization;
   - Hospitalization for study-related tests.

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

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

(f) Other medically important conditions.
Note: Any other important medical event that based upon appropriate medical judgment may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes (a) to (e) listed in the definitions above. (eg, may not result in death, be life-threatening, or require hospitalization).
Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, and blood dyscrasias, or convulsions that do not result in inpatient hospitalization, or development of drug dependency or drug abuse.

12.2.2 Reporting of Serious Adverse Events

A serious adverse event must be reported to the sponsor **within 24 hours** from the time the principal investigator or subinvestigator first becomes aware of the serious adverse event. Comprehensive information available at the time of initial reporting (including narrative description, medical history, and concomitant medications) needs to be provided with careful consideration regarding causality and serious criterion. The contact information for serious adverse events is shown below.

After the initial serious adverse event notification to the sponsor, all follow-up serious adverse event information will be submitted each time they become available (eg, diagnosis, outcome, causality assessment, results of specific investigations).

The principal investigator will submit further necessary information if it is requested by the sponsor, the head of the study site, or the IRB.

All serious adverse events occurring from the time of informed consent to the end of the follow-up examination will be reported to the sponsor. If any serious adverse event (including death) occurs outside the study period specified in the protocol, the principal investigator will report the serious adverse event to the sponsor only if he/she suspects it to be related to the investigational product.

Contact for serious adverse events

Clinical Development Department, Taiho Pharmaceutical Co., Ltd.

1-2-4 Uchikanda, Chiyoda-ku, Tokyo 101-047, Japan

[redacted]

(8:40 am to 5:30 pm, except for Saturdays, Sundays, holidays, and December 29 to January 4)

For hours other than the above, contact the product leader or clinical team leader.

For the contact information for the product leader and the clinical team leader, see the attachment to the protocol.

12.2.3 Follow-up of Serious Adverse Events

Serious adverse events should be followed up in the same manner as the follow-up of adverse events. The follow-up procedure for adverse events is described in Section 12.1.6. If the follow-up of a serious adverse event cannot be continued, the reason will be recorded in the serious adverse event report form as well.

12.2.4 Expectedness to Investigational Product

The expectedness (known, unknown) to the investigational product will be determined based on the description of the Investigator's Brochure. If the nature and severity are consistent with the description, the event will be regarded as "known." Even if the event is listed in the Investigator's Brochure but if its nature and severity are not consistent with the description (eg, interstitial nephritis for acute renal failure, fulminant hepatitis for hepatitis), the event is regarded as "unknown."

Since no serious adverse event for which a causal relationship cannot be ruled out has occurred so far with TAC-302, all serious adverse events occurring in this study will be handled as "unknown."

12.3 Adverse Events of Special Interest

12.3.1 Definition of Adverse Events of Special Interest

Adverse events of special interest are not defined in this study.

12.4 Adverse Reactions

12.4.1 Definition of Adverse Reactions

Adverse events (including abnormal laboratory values) occurring during or after the treatment period for which a causal relationship with the investigational product is assessed as "reasonably possibility" by the principal investigator or subinvestigator are considered to be adverse reactions.

12.5 Other Information

12.5.1 Pregnancy

In this study, female patients of reproductive potential are required to practice contraception during the study period and for 30 days after the completion of investigational product administration. Male patients are required to practice contraception during the study period and for 90 days after the end of investigational product administration.

If obtaining pregnancy information such as pregnancy of a patient or the patient's partner during the specified contraception period, the principal investigator or subinvestigator will report the pregnancy information of the patient **within 24 hours** after he or she initially learned the pregnancy or the outcome of pregnancy. Pregnancy information will be recorded on a Pregnancy Form and reported to the sponsor by e-mail or fax. New and/or corrected information must be entered into the Pregnancy Form and submitted to the sponsor via email or fax.

The principal investigator or subinvestigator will follow the pregnancy of the patient and report the outcome. If the outcome of the pregnancy is a stillbirth, congenital anomaly/birth defect, or a serious event in the mother, it should be reported as a serious adverse event to the sponsor. Live births will be followed up by the principal investigator or subinvestigator, and any information that may be associated with the investigational product should be reported to the sponsor even after study completion.

12.5.2 Medication Errors

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

The following procedures should be followed:

- Any medication error with the investigational product should be reported to the sponsor immediately regardless of the occurrence of an adverse event (even if it does not fulfill the definition of a serious adverse event).
- There is no known antidote available for an investigational product overdose. Patients should be carefully monitored, and aggressive treatment should be performed with prophylactic and symptomatic therapies to prevent or treat possible adverse reactions.

13. STATISTICAL CONSIDERATIONS

Statistical analyses will be performed according to the following plan. Details will be specified in a separately prepared statistical analysis plan. The first version of the statistical analysis plan will be prepared before unblinding.

13.1 Analysis Plan

13.1.1 Timing of Statistical Analysis

Statistical analysis will be performed after completion of the study in all patients in this study. Before unblinding, preliminary investigation (blind review) of the distribution of efficacy and safety measurements or endpoints and the relationships between items will be performed, and details such as the handling of patient data and the method of statistical analysis will be finalized.

13.1.2 Analysis Sets and Criteria for Handling Patient Data

13.1.2.1 Analysis set

The definitions of the analysis sets in this study are as follows.

Table 13.1.2.1-1 Definition of Analysis Sets

Analysis set	Definition
Screening patients	The set of all patients who provided informed consent
All enrolled patients in the observation period	The set of all patients who were enrolled in the observation period
All enrolled patients in the treatment period	The set of all patients who were enrolled in the treatment period
All treated patients in the observation period	The set of patients enrolled in the observation period who took the investigational drug at least once
All treated patients in the treatment period	The set of patients enrolled in the treatment period who took the investigational drug at least once
Full analysis set(FAS)	The set of patients enrolled in the treatment period who took the investigational drug for the treatment period at least once and who had at least 1 efficacy endpoint measurement before the start of the treatment period and in the treatment period
Per protocol set(PPS)	The set of patients in the full analysis set (FAS), excluding patients who met any of the following criteria: (1) Being discovered to have a violation of the inclusion criteria (2) Being discovered to meet any of the exclusion criteria (criteria affecting efficacy evaluation) (3) A compliance rate for the treatment period of < 80%

	(4) Being administered prohibited concomitant drugs or prohibited concomitant therapy considered likely to influence efficacy evaluation (5) No evaluation of the primary endpoint at week 12 of the treatment period

If there are patients in unforeseen situations with respect to whether they belong to analysis sets, the sponsor will decide how to handle these patients after discussion with personnel including the medical expert, before unblinding.

13.1.2.2 Criteria for Handling Patient Data

The criteria for handling patient data in this study are as follows.
If there are patients with problems associated with the handling of patient data in this study other than those below, the sponsor will decide how to handle these patients after discussion with personnel including the medical expert, before unblinding.

(1) Handling of missing values and abnormal values
- The handling of missing values for efficacy endpoints will be designated separately for each analysis.
- Missing values for safety endpoints will not be imputed, and when percentages such as the incidence of adverse events are calculated, in analysis of the observation period, the analysis set will be used as the denominator, and in analysis of the treatment period, the patients in the analysis set who take the investigational drug for the treatment period at least once will be used as the denominator.
- All measured data will be used in analysis except for abnormal values for which there is an obvious reason, such as laboratory values affected by hemolysis at the time of blood collection. If any abnormal values are excluded from analysis, these values will be identified and the reasons for excluding them will be shown.

(2) Handling of data from patients administered treatment for a group different from the group they are assigned to
- In analysis of all treated patients and the PPS, data from patients administered treatment for a group different from the group they are assigned to will be handled as data for the group with the regimen actually administered.
- For analyses using the FAS, data will be handled as data from the randomized assigned group.

13.1.3 Methods of Statistical Analysis

The methods of primary statistical analysis of the primary objective and secondary objectives in this study are as follows.

13.1.3.1 Patient Disposition and Patient Backgrounds

(1) Patient disposition

- The numbers of patients enrolled in each group (including a breakdown by sex) will be tabulated so that the patients belonging to each analysis set can be seen, and a list of patients excluded from analysis sets with the reasons for exclusion will also be displayed.

(2) Patient backgrounds

- In the PPS, information including distributions of the major patient background data and disease characteristics will be summarized.

13.1.3.2 Analysis of the Primary Endpoint

The primary endpoint, BCI (males) or PIP1 (females), will be analyzed as follows.

(1) Primary analysis

- Summary statistics and 95% confidence intervals at each evaluation time point will be calculated by group in the PPS.

(2) Sensitivity analysis of the primary analysis

- (1) will be evaluated in the FAS.

(3) Secondary analysis of the primary endpoint

The following analysis will be performed in the FAS and PPS.

- Time course plots at each evaluation time point will be prepared by group.
- Paired t-tests for the values at baseline (week 0) and week 12 of the treatment period will be performed by group.
- Summary statistics and 95% confidence intervals for the change and percentage change at week 12 of the treatment period relative to baseline (week 0) will be calculated by group.
- The treatment effect in the TAC-302 group relative to the placebo group will be estimated using model analysis of the change and percentage change at week 12 of the treatment period relative to baseline (week 0).

13.1.3.3 Analysis of Secondary Endpoints

13.1.3.3.1 Analysis of Efficacy

The following analysis will be performed by group in the FAS and PPS.

(1) PFS parameters (filling phase) [Evaluation time points: week 0, week 12]

1) Volume at first desire to void
2) Maximum bladder volume
3) Bladder compliance
4) Appearance of bladder involuntary contraction
5) Bladder volume up to appearance of bladder involuntary contraction

- For 1), 2), 3), and 5), summary statistics and 95% confidence intervals for the measured values at each evaluation time point, and for the change and percentage change at week 12 of the treatment period relative to baseline (week 0), will be calculated.

- For 4), the frequency of involuntary bladder contractions at each evaluation time point (weeks 0 and 12) will be tabulated.

(2) PFS parameters (voiding phase) [Evaluation time points: week 0, week 12]

1) Detrusor pressure at start of voiding ($P_{det\ open}$)
2) Maximum detrusor pressure ($P_{det\ max}$)
3) Maximum flow rate (Q_{max})
4) Average flow rate (Q_{ave})
5) Detrusor pressure at maximum flow ($P_{det}Q_{max}$)
6) Duration of bladder contraction
7) Voided volume
8) Post void residual

- Summary statistics and 95% confidence intervals for the measured values at each evaluation time point, and for the change and percentage change at week 12 of the treatment period relative to baseline (week 0), will be calculated.

(3) Uroflowmetry parameters [Evaluation time points: weeks 0, 4, 8, 12]

1) Maximum flow rate (free Q_{max})
2) Average flow rate (free Q_{ave})
3) Voided volume
4) Voiding time

- Summary statistics and 95% confidence intervals for the measured values at each evaluation time point, and for the change and percentage change at weeks 4, 8 and 12 of the treatment periods relative to baseline (week 0), will be calculated.

(4) Post void residual measured by ultrasonography [Evaluation time points: at registration in observation period, weeks 0, 4, 8, 12]

- Summary statistics and 95% confidence intervals for the measured values at each evaluation time point, and for the change and percentage change at weeks 4, 8 and 12 of the treatment periods relative to baseline (week 0), will be calculated.

(5) BVE [Voided volume / (voided volume + post void residual)] [Evaluation time points: weeks 0, 4, 8, 12]

Calculated from the voided volume measured by uroflowmetry and the post void residual measured by ultrasonography

- Summary statistics and 95% confidence intervals for the measured values at each evaluation time point, and for the change and percentage change at weeks 4, 8 and 12 of the treatment periods relative to baseline (week 0), will be calculated.

(6) Change in IPSS score at weeks 4, 8, and 12 of the treatment periods relative to baseline (week 0)

1) IPSS total score
2) IPSS storage symptoms score
3) IPSS voiding symptoms score
4) IPSS QOL score

- Summary statistics at each evaluation time point will be calculated by group.

(7) Change in IPSS score at weeks 4, 8, and 12 of the treatment periods relative to baseline (week 0)
- Summary statistics at each evaluation time point will be calculated by group.

(8) Change in the KHQ score (by domain) at week 12 of the treatment period relative to baseline (week 0)
- Summary statistics at each evaluation time point will be calculated by group.

(9) Change in bladder diary record data at weeks 4, 8, and 12 of the treatment periods relative to baseline (week 0)
1) Average number of micturition per 24 hours
2) Average number of urgency urinary incontinence episodes per 24 hours
3) Average number of urinary urgency episodes per 24 hours
4) Average voided volume per urination
5) Average number of nocturnal urinations
- Summary statistics at each evaluation time point will be calculated by group.

The relationships between each endpoint will be investigated exploratively for the primary endpoint and secondary endpoints (efficacy). The investigated endpoints are specified in the statistical analysis plan.

13.1.3.3.2 Treatment Status

The following analysis will be performed by group in patients treated in the observation period and patients treated in the treatment period.

(1) Treatment Status
- The treatment status (cumulative dose and total duration of treatment) for each patient will be summarized.

(2) Treatment completion status
- Summary statistics for treatment compliance will be calculated for each patient.
- Whether patients are discontinued from the study and the reasons for discontinuation will be tabulated.

13.1.3.3.3 Safety Analysis

The following analysis will be performed by group in the patients treated in the treatment period.

(1) Adverse events

The following analyses will be performed:
- The incidences of adverse events will be calculated.
- For each adverse event item, the numbers of patients who experience adverse events and the incidences of adverse events will be displayed by severity.
- Incidences will be calculated by time of onset of adverse events in the treatment period.
- A list of the adverse event term, severity, date of onset, action taken, outcome of the adverse event, causal relationship with the investigational drug and comment

about the adverse events will be prepared for each adverse event item by patient, for all adverse events occurring from the start of administration of the investigational drug to the date of the end of the follow-up examination.

(2) Adverse reactions

- Adverse reactions will be analyzed in a similar manner to adverse events (except the preparation of lists).

(3) Blood pressure, pulse rate, and body temperature

- Summary statistics for blood pressure, pulse rate and body temperature at each evaluation time point will be calculated.
- For blood pressure and pulse rate, summary statistics for the change in the measured value at each evaluation time point relative to directly before the start of administration of the investigational drug for the treatment period will be calculated.

(4) 12-lead electrocardiography

The QT interval corrected with the Fridericia method (QTcF), which is an examination item in 12-lead electrocardiography, will be used.

- For the QTcF interval and heart rate, summary statistics for measured values will be calculated for each evaluation time point.
- For the QTcF interval and heart rate, summary statistics for the change in the measured value at each evaluation time point relative to directly before the start of administration of the investigational drug for the treatment period will be calculated.
- For the QTcF interval, the measured values at each evaluation time point were divided into categories and their frequencies will be tabulated.
- For the QTcF interval, the change in the measured value at each evaluation time point relative to directly before the start of administration of the investigational drug for the treatment period were divided into categories and their frequencies will be tabulated.

(5) Laboratory Values

- Summary statistics at each evaluation time point will be calculated for each laboratory test.

13.1.4 Target Sample Size and Rationale for the Sample Size

[redacted]

14. RATIONALES

14.1 Rationale for the Endpoints

[redacted]

14.2 Rationale for the Method of Administration

[redacted]

14.3 Rationale for the Inclusion/Exclusion Criteria

14.3.1 Rationale for the Inclusion Criteria

14.3.1.1 Registration in the Observation Period

[redacted]

14.3.1.2 Registration in the Treatment Period

[redacted]

14.3.2 Rationale for the Exclusion Criteria

14.3.2.1 Registration in the Observation Period

[redacted]

14.3.2.2 Registration in the Treatment Period

[redacted]

14.4 Rationale for Prohibited Concomitant Medications

[redacted]

[redacted]

14.5 Rationale for Prohibited Concomitant Therapies

[redacted]

14.6 Rationale for the Contraception Period

[redacted]

15. CASE REPORT FORMS

In this study, the sponsor will provide electronic case report forms (eCRFs) and an electronic data capture (EDC) system. To protect eCRF data, data will be transmitted from study sites via an SSL system on the Internet. Access to the EDC system will be limited only to the principal investigator, subinvestigator, and authorized personnel authenticated by IDs and passwords assigned to each user. IDs and passwords shall be kept confidential and shall never be shared with others. Monitors will be given access to the EDC system for source data verification. The monitors, data manager, auditors, etc of the sponsor will be given access to the EDC system with authority according to their roles. The monitors, data manager, auditors, etc will not be authorized to enter, correct, or electronically sign eCRFs.

15.1 eCRF Documentation

An eCRF will be completed for each patient enrolled in the observation period. All contents, except for special notes, will be entered in English. The principal investigator, subinvestigator, and study coordinator will enter, change, correct, or add data in eCRFs according to the "Manual for eCRF Completion/Change/Modification." The principal investigator will confirm that there is no problem in the contents entered in each eCRF and electronically sign the eCRF.

The sponsor will check the contents of each eCRF and may issue queries for additional items to be checked. The principal investigator, subinvestigator, and study coordinator will check the contents of data that require verification, make modifications as necessary, and respond to the sponsor.

15.2 eCRF Completion Instructions

When completing eCRFs, the following points should be considered:

(1) The sponsor will distribute the "Manual for eCRF Completion/Change/Modification" to the principal investigator, subinvestigator, and study coordinator. The principal investigator or subinvestigator will enter, change, modify, or add data in eCRFs in accordance with the manual. The study coordinator can enter, change, modify, or add data in eCRFs based on source documents prepared by the principal investigator or subinvestigator according to the manual.

(2) Information used for personal authentication in the EDC system, such as IDs and passwords, should never be shared among the principal investigator, subinvestigator, and study coordinator from the viewpoint of preparing eCRFs based on appropriate personal authentication. To prevent unauthorized access to eCRFs by masquerading, information such as IDs and passwords used for personal authentication shall be stored so that it will not be leaked to others. The sponsor, principal investigator, subinvestigator, and study coordinator will check the audit trail of the EDC system as appropriate to confirm whether there is any unauthorized access or data manipulation by masquerading.

(3) When a modification or change is made to eCRF entries, the reason should also be entered. The reason for modification/change will be recorded as an audit trail together with the contents of modification/change.
(4) When a section to be filled out remains blank, if necessary, an expression to differentiate it from input omission should be entered as “MS (No Data).”
(5) The principal investigator will check eCRF entries against source data such as medical records (charts), confirm the contents, and electronically sign each eCRF.
(6) The electronic signature must be personally affixed by the principal investigator.

16. PROTOCOL COMPLIANCE, DEVIATIONS, AND AMENDMENTS

16.1 Protocol Compliance

The principal investigator will sign or seal and date the protocol or an alternative document to confirm agreement with the sponsor on the contents of the protocol and compliance with the protocol.

16.2 Protocol Deviations

Major protocol deviations include the following:

(1) Violation of the inclusion criteria, which may have a significant impact on the efficacy and safety evaluations of TAC-302
(2) Violation of the exclusion criteria, which may have a significant impact on the efficacy and safety evaluations of TAC-302
(3) Violation where a patient meets the discontinuation criteria but does not discontinue investigational product administration
(4) Deviation that leads to a serious GCP violation

If a change is made to the protocol, the principal investigator and the sponsor should agree on the change in writing in advance and obtain written approval of the IRB based on the preliminary review.
The principal investigator should promptly provide a written report on any change significantly affecting the conduct of the study or increasing the risk to patients to the sponsor, the head of the study site, and the IRB via the head of the study site.
If there is an inevitable medical reason such as avoidance of urgent risks to patients, the protocol may be deviated or modified without prior written agreement with the sponsor and prior approval of the IRB. In such a case, the principal investigator should promptly report the details and the reason for the deviation or change to the sponsor and the head of the study site and submit it to the IRB via the head of the study site to obtain written approval.
The principal investigator will record all protocol deviations, regardless of the reason.

16.3 Protocol Amendments

If considering it necessary to amend the protocol, the sponsor will submit a protocol amendment to the principal investigator. The principal investigator will thoroughly review the details of the amendment.
If the protocol is amended, the sponsor should obtain the agreement of the principal investigator. However, no new agreement is required for administrative amendments only (eg, change in the sponsor’s organization or system, change of the name of the study site or department, change of the address or telephone number of the study site or the sponsor, change of the principal investigator’s title, change of monitors).
The sponsor will submit the protocol amendment to the head of the study site and obtain approval from the IRB via the head of the study site.

17. Access to Source Data/Documents

The principal investigator and the head of the study site will provide all study-related records such as source documents for direct access during study-related monitoring, audits, and inspections by the IRB and regulatory authorities.

17.1 Source Data/Documents

Source documents are original documents, data, and records (eg, informed consent forms, medical records, test notes, memoranda, drug prescription records, data and test results recorded by various automatic instruments, patient files, patient enrollment sheets, list of screened patients, investigational product control records, medication diaries, pressure flow study [PFS] results, uroflowmetry test results, IPSS, OABSS, KHQ, bladder diary records, and records kept at the pharmacy, laboratories, and medical technology departments involved in this study).

The following items are “data to be directly entered in eCRFs and regarded as source data.” If there is a record in a medical record, etc, the medical record, etc will be the source document. If data are not recorded in a medical record and directly entered in eCRFs, the principal investigator or subinvestigator will enter the data.

- Past history and complications considered to significantly affect the study by the principal investigator or subinvestigator
- Purpose of concomitant medications and therapies
- Name, purpose, and duration of concomitant medications and therapies prescribed at other hospitals
- Presence or absence of adverse events, seriousness, severity, outcome, reason for completion of follow-up, causal relationship with the investigational product
- Presence or absence of discontinuation/dropout and the reason
- Comments, reason for completion of follow-up

17.2 Direct Access

The sponsor’s monitor will check the eCRFs against the source documents to confirm the following: If there is any inconsistency with a source document, a record explaining the reason shall be obtained from the principal investigator.

- Data required by the protocol are accurately recorded in the eCRFs and serious adverse event reports and are consistent with the source documents.
- All changes in the TAC-302 dosing regimen or dosing method, if any, have been entered in the eCRFs.
- Adverse events have been entered into the eCRFs as per protocol.
- All withdrawals and dropouts of enrolled patients have been entered in the eCRFs and the reasons are explained.

18. QUALITY CONTROL AND QUALITY ASSURANCE IN THE STUDY

The sponsor will implement the following quality control and quality assurance duties according to the sponsor's SOPs.

18.1 Quality Control in the Study

The sponsor will control the quality of the study according to the individual SOPs relating to the conduct of the study and the monitoring plan for this study. The main duties are as follows:

- Explaining matters such as the method of selecting patients and the method of investigating and evaluating efficacy and safety, through holding events such as meetings to explain the protocol to the principal investigator, subinvestigators or study coordinator.
- Performing periodic monitoring of study sites to check that the study is being conducted in compliance with the protocol and GCP.
- Viewing the source data to check that the contents entered into the electronic case report forms (eCRFs) are accurate. Preparing the "Manual for eCRF Completion/Change/Modification" and requesting the principal investigator/subinvestigator to modify it when a change or a modification becomes necessary.
- Inspecting the contents entered into the eCRFs.
- Checking that the required documents to be stored at study sites are stored appropriately.
- Making records and reports about the running of the study, the collection of data, data management, statistical analysis and analysis of data such as adverse events, according to the sponsor's SOPs, and inspecting and checking them.

18.2 Sponsor's Auditing and Regulatory Inspection

The principal investigator will permit auditing by the sponsor and inspection by regulatory authorities for the purpose of ensuring compliance with the protocol, GCP, and applicable regulatory requirements.

The principal investigator will agree to allow the auditors and inspectors direct access to study records. The personnel performing these activities will not disclose any personal identity or personal medical information assessed.

The principal 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 study. The principal investigator should contact the sponsor immediately when being notified of a planned inspection by the regulatory agency or the IRB. Any results arising from such an inspection will be immediately communicated by the principal investigator to the sponsor.

The principal investigator will take appropriate measures required by the sponsor and take corrective actions for all findings and observations found during audits and/or inspections.

19. DATA HANDLING AND RECORD KEEPING

19.1 Handling of Data

All information provided to the principal investigator by the sponsor, including the protocol, eCRFs, Investigator's Brochure, and results obtained during the course of the study, is confidential. Persons involved in the conduct of this study will agree not to mention such information in any way without prior written consent of the sponsor.

The patient's personal data and the principal investigator's and subinvestigator's personal data which may be included in the sponsor's database will be treated in compliance with all applicable laws and regulations.

When processing and retaining the patient's personal data and the principal investigator's and subinvestigator's personal data, the sponsor will take all appropriate measures to safeguard and prevent access to these data by any unauthorized third party.

19.2 Retention of Records

19.2.1 Principal Investigator and Study Site

The principal investigator and the study site will be responsible for the retention of all study documents according to applicable regulatory requirements and GCP.

The principal investigator and the study site will agree to inform the sponsor in writing of the intention to remove or destroy any study-related records. Prior to contacting the sponsor, the principal investigator and the study site will ensure that the applicable regulatory requirements have been satisfied. The sponsor will permit the principal investigator and the study site in writing to destroy such records.

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

19.2.2 Sponsor

The sponsor shall 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 discontinuing the clinical development of the investigational product, the sponsor shall maintain essential documents to be retained by the sponsor in conformance with the applicable regulatory requirements.

20. COMPENSATION FOR HEALTH INJURY

The sponsor is insured according to applicable regulatory requirements and provide a summary of compensation to the study site.

Except for claims that have arisen due to medical malpractice or negligence, in preparation for compensation claims arising out of cases which no legal responsibility is clearly identified, the sponsor will specify the compensation policy and payment procedure for summary of compensation in case of a health injury related to the study.

When patients receive compensation, summary of compensation should be complied with.

21. PUBLICATION AND SECONDARY USE OF DATA

21.1 Publication

The sponsor will retain the right to use the results of this study for submission to government and regulatory authorities of each country.
The results of this study will be reviewed by the sponsor in accordance with applicable publication guidelines and financial agreement guidelines and published in scientific journals. The timing of publication, presenter, etc will be determined in consultation between the coordinating investigator and the sponsor.

21.2 Secondary Use of Data

The sponsor will reserve the right to secondary use of the study data. Secondary use of data refers to the use (including external provision) of collected data for purposes other than this study.
Major examples of secondary use of data are as follows:

- Use in other clinical studies
- Integrated analysis with relevant clinical studies
- Independent analysis by regulatory authorities and information sharing between regulatory authorities
- Use for epidemiological studies

22. ETHICS

22.1 Ethical Conduct of the Study

It is mandatory that all considerations regarding the protection of patients by complying with the protocol, the ICH GCP Guidelines, the ethical principles that have their origin in the Declaration of Helsinki, and all applicable regulatory requirements and grasping the latest information.

22.2 Approval by the Institutional Review Board

The study must be approved by an appropriately constituted IRB, as required by ICH guidelines (E6 Part 3). The conduct of this study must be reviewed and approved by the IRB and then approved by the head of the study site.
During the course of the study, the principal investigator will be responsible for obtaining continued review of the study. The timeframe for renewal is based on IRB requirements, but at least annually is required by regulations. At the end of the study, the IRB will be notified of the study completion and its outcome.

22.3 Procedure for Obtaining Informed Consent

Informed consent must be obtained in compliance with the guidelines provided in the Declaration of Helsinki, ICH Guideline (E6), and applicable regulatory requirements.
The principal investigator or subinvestigator will fully inform each patient of all pertinent aspects of the study in simple text.
Prior to the participation in the study, the informed consent form must be signed and dated by the patient and by the person giving an explanation about informed consent. A copy of the signed informed consent form will be given to the patient. The informed consent form approved by the IRB will be used.
By signing and dating the informed consent form prior to any study procedure specified in this protocol, the patient will be deemed to have consented to participate in the study.
The principal investigator will prepare an informed consent form based on a draft informed consent form provided by the sponsor. When the revision is necessary, the principal investigator will discuss with the sponsor, prepare the revised version, and use the version approved by the IRB.

23. STUDY ADMINISTRATIVE STRUCTURE

Details are described in the attachment.

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25. APPENDICES

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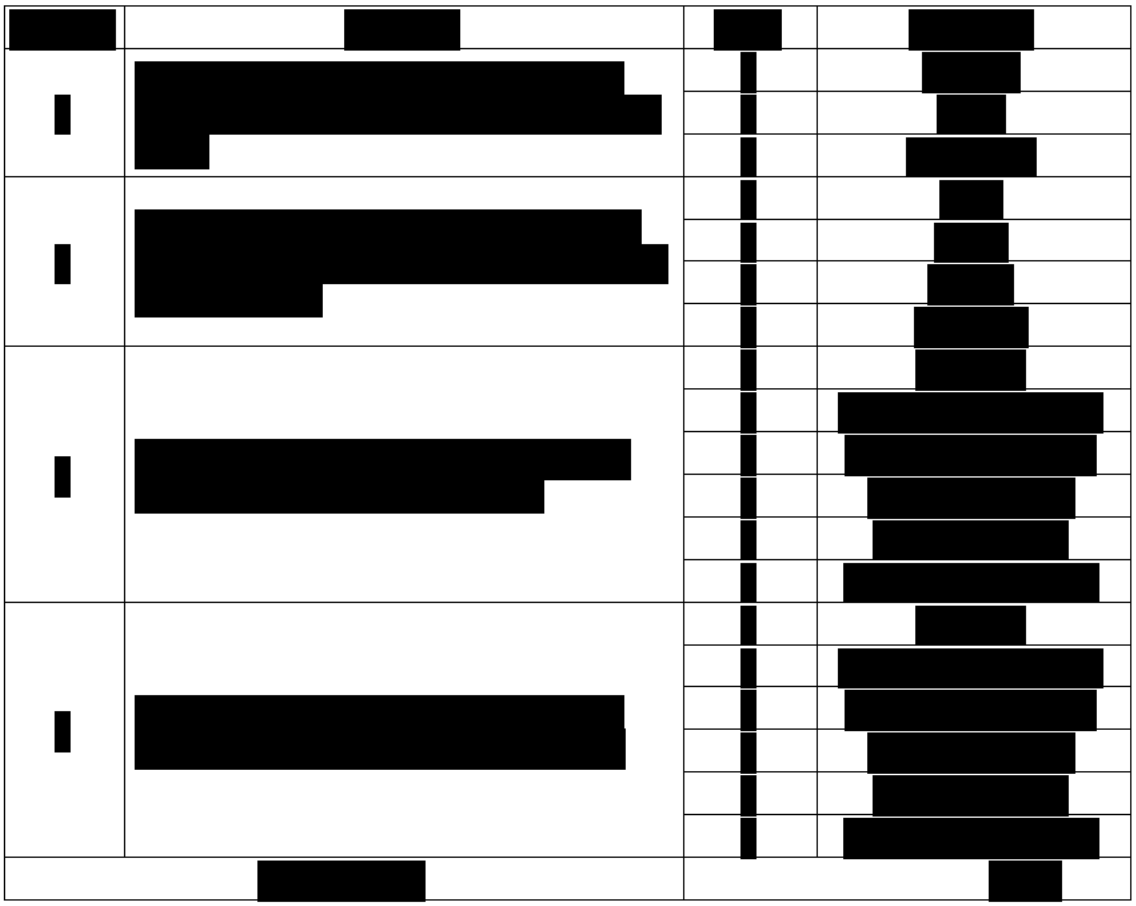

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