Statistical Analysis Plan

Version 2.0

Name of investigational product	TAC-302
Study title	A Phase 2a Study of TAC-302 in Detrusor Underactivity Patients with Overactive Bladder
Protocol number	10054040
Date of preparation or revision	08 January 2020
Author	[redacted]

History of preparation and revision

Date	Author	Reason for preparation or revision
29 November 2019	[redacted]	Preparation of the first version
08 January 2020	[redacted]	Before unblinding, the analyses were changed based on the results of the blind review.

Date and signature

[redacted] Person in charge of statistical analysis	DD Month YYYY	
[redacted] Person responsible for statistical analysis	DD Month YYYY	
Taiho Pharmaceutical Co., Ltd. Statistical team leader	DD Month YYYY	

Changes in Statistical Analysis Plan

Version 1.0 (29 November 2019) to Version 2.0 (08 January 2020)

Item	Before change	After change	Reason for change
6.2.1 Table 6-3	< 65 years, ≥ 65 years	< 60 years, ≥ 60 years < 65 years, ≥ 65 years < 70 years, ≥ 70 years < 75 years, ≥ 75 years	The other categories have been added based on the results of the blind review.
7.3	Analysis of covariance with age (< 65 years, ≥ 65 years) as a covariate	By age (< 60 years and ≥ 60 years in males and < 70 years and ≥ 70 years in females), the above analysis excluding time course plots and analysis of covariance will be performed.	Separate age categories for men and women were specified based on the results of the blind review. Text was moved from 8.1.11.
8.1.11	Analysis of the primary endpoint and secondary endpoints (7.3 and 8.1.1 to 8.1.9)	Analysis of secondary endpoints (8.1.1 to 8.1.9)	Text was moved to 7.3.
	Secondary endpoints will be analyzed by sex (8.1.1 to 8.1.9). In analysis of covariance and analysis using an MMRM, sex will be excluded from the covariates.	Analysis will be performed as for analysis of secondary endpoints by sex (8.1.1 to 8.1.9). In analysis of covariance and analysis using an MMRM, values at baseline and age (< 60 years and ≥ 60 years in males and < 70 years and ≥ 70 years in females) will be used as covariates.	Separate categories for men and women were specified based on the results of the blind review.
8.3.1	≥ 65 years, < 65 years	≥ 65 years, < 65 years	A typographical error was corrected.
	The numbers of patients who experienced adverse events and the incidences of adverse events will be displayed. Similar analysis will be performed for adverse reactions. Similar analysis will also be performed by age (≥ 65 years and < 65 years).	The numbers of patients who experienced adverse events and the incidences of adverse events will be displayed. Similar analysis will be performed for adverse reactions. Similar analysis will also be performed by age (≥ 65 years and < 65 years). In addition, similar analysis will be performed by age (≥ 75 years and < 75 years).	Tabulation by age was added based on the results of the blind review.
	-	For each adverse event item, the numbers of patients who experienced adverse events and the incidences of adverse events will be displayed. Similar analysis will be performed for adverse reactions. Similar analysis will also be performed by age (≥ 65 years and < 65 years). In addition, similar analysis will be performed by age (≥ 75 years and < 75 years).	This was added to make the description more detailed. Tabulation by age (≥ 75 years and < 75 years) was added based on the results of the blind review.

	For each adverse event item, the numbers of patients who experienced adverse events and the incidences of adverse events will be displayed by severity. Similar analysis will be performed for adverse reactions. Similar analysis will also be performed by age (≥ 65 years and < 65 years).	For each adverse event item, the numbers of patients who experienced adverse events and the incidences of adverse events will be displayed by severity. Similar analysis will be performed for adverse reactions.	This text was deleted because analysis by age will not be performed in analysis by severity.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations and terms used in the statistical analysis plan are defined below.

Abbreviation (term)	Description (definition)
BCI	Bladder Contractility Index
BMI	Body mass index
BOO	Bladder Outlet Obstruction
BVE	Bladder Voiding Efficiency
CIC	Clean Intermittent Catheterization
DU	Detrusor Underactivity
FAS	Full analysis set
ICH-E3 Guideline	"Guideline for Structure and Content of Clinical Study Reports"[1)]
IPSS	International Prostate Symptom Score
KHQ	King's Health Questionnaire
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect Models for Repeated Measures
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
free Q_{max}	Maximum flow rate
QOL	Quality of life
QTcF	QT corrected for heart rate by Fridericia’s formula

1. SCOPE AND OBJECTIVES

This plan specifies the details of the statistical analysis plan for "A Phase 2a Study of TAC-302 in Detrusor Underactivity Patients with Overactive Bladder" (Protocol No. 10054040).

1.1 Primary Objective

To investigate the efficacy of TAC-302 in DU patients with OAB, using evaluation of the BCI (males) or PIP1 (females) at each time point as an indicator.

1.2 Secondary Objectives

(1) To investigate the efficacy of TAC-302 in DU patients with OAB, using the changes in values including pressure flow study parameters, uroflowmetry parameters, BVE, IPSS or OABSS as indicators.
(2) To investigate the efficacy of TAC-302 in DU patients with OAB compared to 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. STUDY DESIGN AND TARGET SAMPLE SIZE

2.1 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 detrusor underactivity patients with overactive bladder. This study is composed of a single-blind observation period, a double-blind treatment period, and a follow-up period.

2.1.1 Primary Endpoint

BCI ($P_{det}Q_{max} + 5 \times Q_{max}$) at Weeks 0 and 12 (males)
PIP1 ($P_{det}Q_{max} + Q_{max}$) at Weeks 0 and 12 (females)

2.2 Target Sample Size

2.2.1 Target Sample Size

75 patients to be enrolled in the treatment period (48 males and 27 females)

2.2.2 Rationale for the Sample Size

[redacted]

3. Data and Analysis Sets to Be Used for Statistical Analysis

3.1 Documents and Data Other Than Case Report Forms

A list of documents and data necessary for statistical analysis other than case report forms is shown in Table 3-1.

Table 3-1: Documents or Data Necessary for Statistical Analysis Other Than Case Report Forms

Item	Documents or data	Remarks
Attribution of patients	Flag of attribution of each patient to each analysis set	To identify the attribution of each patient to each analysis set.
	List of patients excluded from analysis sets and reasons for exclusion	To list patients excluded from analysis sets.
	UDS data subset and CIC status	To analyze by UDS data subset and by CIC status. The definition of UDS data subset is shown in 8.1.15.
Assignment information	Key code and allocation adjustment factors at the time of enrollment	To identify treatment groups and analyze using allocation adjustment factors.
Deviation information	Description of deviation and deviation flag	To provide a list of patients with deviations.
Conversion to MedDRA terms	Correspondence table between verbatim terms of adverse events and MedDRA terms	To tabulate the incidence of adverse events using standardized terms.
	Correspondence table between medical history and complication terms and MedDRA terms	To list medical history and complications using MedDRA terms.
Institutional reference value	Institutional reference values of laboratory values	To assess normal/abnormal laboratory values.
Drug name	Correspondence table between verbatim terms of concomitant drugs and WHO Drug Dictionary	To tabulate concomitant drugs in groups and specify the order.
Centralized assessment results	Results of centralized assessment of pressure flow study and uroflowmetry	For analysis of pressure flow study (only in patients enrolled in the treatment period) and uroflowmetry. However, for the results of pressure flow study in patients who are enrolled in the observation period and do not proceed to the treatment period, eCRF data (evaluation by the study site) will be used because there are no results of centralized assessment.
Efficacy evaluation	Efficacy evaluation data handling table	To additionally specify the handling of efficacy evaluation data

3.2 Analysis Sets

The analysis sets and their definitions are shown in Table 3-2. If there are patients for whom attribution to analysis sets is problematic based on factors other than the criteria shown below, handling of such patients will be determined by discussion between the sponsor and medical expert, etc. The primary efficacy analysis set will be PPS, and the primary safety analysis set will be all treated patients in the treatment period.

Table 3-2 Definition of Analysis Sets

Analysis Sets	Definition
Screening Patients	All patients who gave 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 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

4. METHODS OF STATISTICAL ANALYSIS

The objective of the primary analysis is to evaluate the efficacy of TAC-302. As the primary analysis, summary statistics and the 95% confidence interval of BCI (males) or PIP1 (females) at Weeks 0 and 12 of the treatment period will be calculated at each evaluation time point by treatment group.

5. TIMING OF STATISTICAL ANALYSIS

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

6. ENDPOINTS AND COMMON ITEMS IN STATISTICAL ANALYSIS

6.1 Endpoints

The efficacy and safety endpoints are defined below.

6.1.1 Efficacy Endpoints

6.1.1.1 Pressure Flow Study (PFS)

The volume at first desire to void, maximum bladder volume, bladder compliance, appearance of bladder involuntary contraction, and bladder volume up to appearance of bladder involuntary contraction will be evaluated based on the pressure flow study (filling phase). The 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}), maximum detrusor pressure at peak urine flow ($P_{det}Q_{max}$), duration of bladder contraction, voided volume, and post void residual will be evaluated based on the pressure flow study (voiding phase).

For the duration of bladder contraction, the duration of bladder contraction for urination including Qmax is defined as the duration of bladder contraction-1 and the duration of bladder contraction for all evaluable urinations during the voiding phase is defined as the duration of bladder contraction-2.

In the summary of patient backgrounds and the analysis by appearance of bladder involuntary contraction, patients judged to have bladder involuntary contraction at any of the evaluation time points (Weeks 0 and 12/at discontinuation) will be handled as those with bladder involuntary contraction. For the results at each evaluation time point (Weeks 0 and 12/at discontinuation), patients judged to have no bladder involuntary contraction at all time points will be handled as those without bladder involuntary contraction. Patients without data on presence/absence will be excluded from the analysis.

6.1.1.2 Uroflowmetry

The maximum flow rate (free Q_{max}), average flow rate (free Q_{ave}), voided volume, and voiding time will be evaluated based on uroflowmetry.

DeltaQ is defined as follows[3)]:

DeltaQ=free Q_{max}-free Q_{ave}

6.1.1.3 Evaluation of Symptom Scores

The endpoints to be used for the evaluation of symptom scores are IPSS, QOL score, and OABSS.

6.1.1.3.1 IPSS and QOL Score

Voiding symptoms and storage symptoms will be evaluated using the IPSS and QOL score.

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 will be classified as moderate, and a score of 20 to 35 points will be classified as severe. 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.

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 will be classified as moderate, and a score of 5 to 6 points will be classified as severe.

6.1.1.3.2 Overactive Bladder Symptoms Score (OABSS)

The OAB symptoms will be evaluated using OABSS.

The total OABSS score is defined as the total score of all questions. A score of 5 points or less is considered mild, a score of 6 to 11 points is considered moderate, and a score of 12 points or more is considered severe.

6.1.1.4 King's Health Questionnaire (KHQ)

The QOL in DU patients with OAB will be evaluated using the KHQ. The scoring method for each domain based on the Japanese version of KHQ is shown below.

Table 6-1 Scoring Method for Each Domain Based on the Japanese Version of KHQ

Each domain	Scoring method
General health	(Q1 score − 1) / 4 x 100
Incontinence impact	(Q2 score − 1) / 3 x 100
Restrictions on job/housework	(Q3a + 3b − 2) / 6 × 100
Limitation of physical activities	(Q4a + 4b − 2) / 6 × 100
Limitation of social activities	If Q5c score is ≥ 1: (Q4c + 4d + 5c score − 3) / 9 x 100 *If Q5c score is 0: (Q4c + 4d + 5c score − 2) / 6 x 100
Personal relationships	If Q5a + 5b ≥ 2: (Q5a+5b-2)/6×100 If Q5a + 5b = 1: (Q5a+5b-1)/3×100 If Q5a + 5b = 0: Handle the score as a missing value (not applicable)
Emotions	(Q6a + 6b + 6c score − 3) / 9 × 100
Sleep/energy	(Q7a + 7b score − 2) / 6 × 100
Severity measures	(Q8a + 8b + 8c + 8b + 8e score − 5) / 15 × 100

6.1.1.5 Bladder Diary Records

The times of urination, times of urinary incontinence, whether urinary urgency is present, and voided volume for each urination will be evaluated using Bladder Diary records.

The average number of daytime urinations is defined as follows. Nocturnal urination is defined as urination after bedtime on the day and before wake-up on the next day.

Average number of daytime urinations = average number of micturitions per 24 hours – average number of nocturnal urinations

6.1.2 Safety Endpoints

6.1.2.1 Adverse Events and Adverse Reactions

An adverse event is any untoward medical occurrence in a patient participating in the study. Adverse events for which a causal relationship with the investigational product is assessed as “reasonably possible” are considered to be adverse reactions.

6.1.3 Endpoints for Treatment Compliance

6.1.3.1 Compliance Rate

The definition of compliance rate in the observation and treatment periods is shown below.

[1] Observation period

Compliance rate during the observation period (%) = (number of doses with no dose modification/interruption during the observation period) / (prescribed number of doses from the first dose of investigational product during the observation period to the last dose of investigational product during the observation period) × 100

[2] Treatment period

Compliance rate during the treatment period (%) = (number of doses with no dose modification/interruption during the treatment period) / (prescribed number of doses from the first dose of investigational product during the treatment period to the last dose of investigational product during the treatment period) × 100

6.2 Common Items in Statistical Analysis

6.2.1 Patient Backgrounds

A list of patient backgrounds to be measured at enrollment is shown in Table 6-2. The details of categories when the background factors of continuous values among the background factors shown in Table 6-2 are divided by category are shown in Table 6-3.

Table 6-2 Background Factors

Item	Factor
Patient backgrounds	Sex, age, height, body weight, presence or absence of medical history, presence or absence of complications, race, ethnicity, and BMI
Disease characteristics	Timing of onset of lower urinary tract symptoms, presence or absence of pelvic visceral surgery, presence or absence of radiotherapy, presence or absence of drug therapy for the primary disease, bladder outlet obstruction index (males) ($P_{det}Q_{max} - 2Q_{max}$), prostate volume measurement (males), free Q_{max}, voiding time, voided volume (uroflowmetry), post void residual measured by ultrasonography, BVE (voided volume / [voided volume + post void residual] × 100), $P_{det}Q_{max}$, Q_{max}, BCI (males), PIP1 (females), IPSS total score, IPSS storage symptoms score, IPSS voiding symptoms score, IPSS (Q1, Q3, Q5, and Q6), presence or absence of CIC, presence or absence of bladder involuntary contraction, severity based on IPSS total score, severity based on IPSS QOLS score, and severity based on OABSS score

Table 6-3 Details of Categories

Category	Definition
Age category	< 60 years, ≥ 60 years < 65 years, ≥ 65 years < 70 years, ≥ 70 years < 75 years, ≥ 75 years
Race	Asian/Oriental, Other
Ethnicity	Japanese, .Other

6.2.2 Statistical Methods

6.2.2.1 Summary Statistics of Continuous Variables

Summary statistics of continuous variables will be presented together with the sample size, minimum, maximum, first quartile, median, third quartile, mean, and standard deviation.

6.2.2.2 Estimation Method

(1) Confidence interval of proportion

The confidence interval of proportion will be determined by an exact method based on F distribution.[2)]

The upper confidence limit P_U and the lower confidence limit P_L will be estimated using the following formula. P is the proportion, X is the number of patients with events, N is the number of patients in the analysis set, and α is the two-sided significance level.

$$P = X / N$$

$$P_U = \frac{\nu_1 F_{\nu_1,\nu_2}(\alpha/2)}{\nu_2 + \nu_1 F_{\nu_1,\nu_2}(\alpha/2)}, \quad \begin{matrix} \nu_1 = 2(X+1) \\ \nu_2 = 2(N-X) \end{matrix}$$

$$P_L = \frac{\nu_2}{\nu_2 + \nu_1 F_{\nu_1,\nu_2}(\alpha/2)}, \quad \begin{matrix} \nu_1 = 2(N-X+1) \\ \nu_2 = 2X \end{matrix}$$

6.2.3 Allocation Adjustment Factors to Be Used for Analysis

In the analysis using allocation adjustment factors, the data of allocation adjustment factors at the time of enrollment will be used.

Allocation adjustment factors are shown below.

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

6.2.4 Statistical Analysis Software

In this study, all statistical processing will be performed using SAS Version 9.4 (SAS/STAT 14.2).

7. Primary Endpoint Analyses

The items to be analyzed for the primary endpoint are summarized below.

7.1 Primary Analysis Corresponding to the Primary Objective

For BCI (males) and PIP1 (females), summary statistics and 95% confidence intervals for each evaluation time point (Weeks 0 and 12) were calculated by group in the PPS.

7.2 Sensitivity Analysis of Primary Analysis

The primary analysis will be performed in the FAS.

7.3 Secondary Analyses of the Primary Endpoint

For BCI (males) and PIP1 (females), the following analyses will be performed in the FAS and PPS.

- Time course plots at each evaluation time point (Weeks 0 and 12) will be prepared by group.
- Paired t-tests for the measured 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.

- For the measured values at each evaluation time point (Weeks 0 and 12) and the change and percentage change from baseline (Week 0) to Week 12 of the treatment period, the 95% confidence interval for the difference between the placebo group and the TAC-302 group will be calculated.
- For the change and percentage change from baseline (Week 0) to Week 12 of the treatment period, student's t test will be performed using the placebo group as the control.
- Analysis of covariance of the change and percentage change from baseline (Week 0) to Week 12 of the treatment period will be performed using treatment group, baseline value, and age (< 60 years or ≥ 60 years in males, < 70 years or ≥ 70 years in females) as covariates, and the least squares means in each treatment group, and the difference in least squares mean between the placebo group and the TAC-302 group and its two-sided 95% confidence interval will be estimated.
- By age (< 60 years and ≥ 60 years in males and < 70 years and ≥ 70 years in females), the above analysis excluding time course plots and analysis of covariance will be performed.

8. Secondary Endpoint Analyses

The analyses of the secondary endpoints are outlined below.

8.1 Analysis of Efficacy

In principle, the following analyses will be performed by treatment group in the FAS and PPS.

8.1.1 Pressure Flow Study (PFS) Parameters (Filling Phase)

For the volume at first desire to void, maximum bladder volume, bladder compliance, and bladder volume up to appearance of bladder involuntary contraction, the following analyses 1) to 5) will be performed. In addition, the analysis in 6) will be performed.

1) Summary statistics and 95% confidence intervals for the measured values at each evaluation time point (Weeks 0 and 12), and for the change and percentage change at Week 12 of the treatment period relative to baseline (Week 0), will be calculated.
2) Paired t-test for the measured values at baseline (Week 0) and Week 12 of the treatment period will be performed.
3) For the measured values at each evaluation time point (Weeks 0 and 12) and the change and percentage change from baseline (Week 0) to Week 12 of the treatment period, the 95% confidence interval for the difference between the placebo group and the TAC-302 group will be calculated.
4) For the change and percentage change from baseline (Week 0) to Week 12 of the treatment period, student's t test will be performed using the placebo group as the control.
5) Analysis of covariance of the change and percentage change from baseline (Week 0) to Week 12 of the treatment period will be performed using treatment group, baseline value, and age (< 65 years or ≥ 65 years) as covariates, and the least squares means in each treatment group, and the difference in least squares mean between the placebo group and the TAC-302 group and its two-sided 95% confidence interval will be estimated.
6) The frequency of involuntary bladder contractions at each evaluation time point (Weeks 0 and 12) will be tabulated.

8.1.2 Pressure Flow Study (PFS) Parameters (Voiding Phase)

The following analyses will be performed for the 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 rate ($P_{det}Q_{max}$), duration of bladder contraction, voided volume, and post void residual.

1) Summary statistics and 95% confidence intervals for the measured values at each evaluation time point (Weeks 0 and 12), and for the change and percentage change at Week 12 of the treatment period relative to baseline (Week 0), will be calculated.
2) Paired t-test for the measured values at baseline (Week 0) and Week 12 of the treatment period will be performed.
3) For the measured values at each evaluation time point (Weeks 0 and 12) and the change and percentage change from baseline (Week 0) to Week 12 of the treatment period, the 95% confidence interval for the difference between the placebo group and the TAC-302 group will be calculated.
4) For the change and percentage change from baseline (Week 0) to Week 12 of the treatment period, student's t test will be performed using the placebo group as the control.
5) Analysis of covariance of the change and percentage change from baseline (Week 0) to Week 12 of the treatment period will be performed using treatment group, baseline value, and age (< 65 years or ≥ 65 years) as covariates, and the least squares means in each treatment group, and the difference in least

squares mean between the placebo group and the TAC-302 group and its two-sided 95% confidence interval will be estimated.

6) A scatter plot with Q_{max} on the vertical axis and $P_{det}Q_{max}$ on the horizontal axis will be prepared for each sex.

8.1.3 Uroflowmetry Parameters

The following analyses will be performed for the maximum flow rate (free Q_{max}), average flow rate (free Q_{ave}), voided volume, and voiding time.

1) Summary statistics and 95% confidence intervals for the measured values at each evaluation time point (Weeks 0, 4, 8, and 12), and for the changes and percentage changes at Weeks 0, 4, 8, and 12 of the treatment period relative to baseline (Week 0), will be calculated.
2) Paired t-test for the measured values at baseline (Week 0) and Week 12 of the treatment period will be performed.
3) For the measured values at each evaluation time point (Weeks 0, 4, 8, and 12) and the changes and percentage changes from baseline (Week 0) to Weeks 4, 8, and 12 of the treatment period, the 95% confidence interval for the difference between the placebo group and the TAC-302 group will be calculated.
4) For the changes and percentage changes from baseline (Week 0) to each evaluation time point (Weeks 4, 8, and 12), student's t test will be performed using the placebo group as the control.
5) The same analyses as 1) to 4) will be performed for the case where missing data at Week 12 of the treatment period are imputed with the last observation carried forward (LOCF).

8.1.4 Post Void Residual Measured by Ultrasonography

The following analyses will be performed for post void residual measured by ultrasonography.

1) Summary statistics and 95% confidence intervals for the measured values at each evaluation time point (Weeks 0, 4, 8, and 12), and for the changes and percentage changes at Weeks 0, 4, 8, and 12 of the treatment period relative to baseline (Week 0), will be calculated.
2) Paired t-tests for the measured values at baseline (Week 0) and Weeks 4, 8, and 12 of the treatment period will be performed.
3) For the measured values at each evaluation time point (Weeks 0, 4, 8, and 12) and the changes and percentage changes from baseline (Week 0) to Weeks 4, 8, and 12 of the treatment period, the 95% confidence interval for the difference between the placebo group and the TAC-302 group will be calculated.
4) For the changes and percentage changes from baseline (Week 0) to each evaluation time point (Weeks 4, 8, and 12), student's t test will be performed using the placebo group as the control.
5) The same analyses as 1) to 4) will be performed for the case where missing data at Week 12 of the treatment period are imputed with LOCF.
6) The change and percentage change from baseline (Week 0) will be analyzed by MMRM using treatment group, evaluation time point (Weeks 4, 8, and 12 of the treatment period), and interaction between treatment group and evaluation time point as fixed effects and baseline value, sex, and age (< 65 years or ≥ 65 years) as covariates. The least squares means in each treatment group, and the difference in the least squares mean between the placebo group and the TAC-302 group and its two-sided 95% confidence interval at each evaluation time point will be estimated. Unstructured covariance structure will be assumed, and toeplitz type will be used if convergence is not achieved. If convergence is still not achieved, the first-order autoregressive, compound symmetry, and variance component will be used in this order. The Kenward-Roger method (2009)[4)] will be used to calculate degrees of freedom.

8.1.5 BVE [Voided Volume / (Voided Volume + Post Void Residual)]

The following analyses will be performed for BVE calculated from the voided volume measured by uroflowmetry and the post void residual measured by ultrasonography.

1) Summary statistics and 95% confidence intervals for the measured values at each evaluation time point (Weeks 0, 4, 8, and 12), and for the changes and percentage changes at Weeks 0, 4, 8, and 12 of the treatment period relative to baseline (Week 0), will be calculated.
2) Paired t-tests for the measured values at baseline (Week 0) and Weeks 4, 8, and 12 of the treatment period will be performed.
3) For the measured values at each evaluation time point (Weeks 0, 4, 8, and 12) and the changes and percentage changes from baseline (Week 0) to Weeks 4, 8, and 12 of the treatment period, the 95% confidence interval for the difference between the placebo group and the TAC-302 group will be calculated.
4) For the changes and percentage changes from baseline (Week 0) to each evaluation time point (Weeks 4, 8, and 12), student's t test will be performed using the placebo group as the control.
5) The same analyses as 1) to 4) will be performed for the case where missing data at Week 12 of the treatment period are imputed with LOCF.
6) The change and percentage change from baseline (Week 0) will be analyzed by MMRM using treatment group, evaluation time point (Weeks 4, 8, and 12 of the treatment period), and interaction between treatment group and evaluation time point as fixed effects and baseline value, sex, and age (< 65 years or ≥ 65 years) as covariates. The least squares means in each treatment group, and the difference in the least squares mean between the placebo group and the TAC-302 group and its two-sided 95% confidence interval at each evaluation time point will be estimated. Unstructured covariance structure will be assumed, and toeplitz type will be used if convergence is not achieved. If convergence is still not achieved, the first-order autoregressive, compound symmetry, and variance component will be used in this order. The Kenward-Roger method (2009) will be used to calculate degrees of freedom.

8.1.6 IPSS Score

The following analyses will be performed for the IPSS total score, IPSS storage symptoms score, IPSS voiding symptoms score, IPSS QOL score, Q1, Q3, Q5, and Q6.

1) Summary statistics and 95% confidence intervals for the measured values at each evaluation time point (Weeks 0, 4, 8, and 12), and for the changes and percentage changes at Weeks 0, 4, 8, and 12 of the treatment period relative to baseline (Week 0), will be calculated.
2) Paired t-tests for the measured values at baseline (Week 0) and Weeks 4, 8, and 12 of the treatment period will be performed.
3) For the measured values at each evaluation time point (Weeks 0, 4, 8, and 12) and the changes and percentage changes from baseline (Week 0) to Weeks 4, 8, and 12 of the treatment period, the 95% confidence interval for the difference between the placebo group and the TAC-302 group will be calculated.
4) For the changes and percentage changes from baseline (Week 0) to each evaluation time point (Weeks 4, 8, and 12), student's t test will be performed using the placebo group as the control.
5) The same analyses as 1) to 4) will be performed for the case where missing data at Week 12 of the treatment period are imputed with LOCF.
6) The change and percentage change from baseline (Week 0) will be analyzed by MMRM using treatment group, evaluation time point (Weeks 4, 8, and 12 of the treatment period), and interaction between treatment group and evaluation time point as fixed effects and baseline value, sex, and age (< 65 years or ≥ 65 years) as covariates. The least squares means in each treatment group, and the difference in the

least squares mean between the placebo group and the TAC-302 group and its two-sided 95% confidence interval at each evaluation time point will be estimated. Unstructured covariance structure will be assumed, and toeplitz type will be used if convergence is not achieved. If convergence is still not achieved, the first-order autoregressive, compound symmetry, and variance component will be used in this order. The Kenward-Roger method (2009) will be used to calculate degrees of freedom.

8.1.7 OABSS Score

The following analyses will be performed for the OABSS score.

1) Summary statistics and 95% confidence intervals for the measured values at each evaluation time point (Weeks 0, 4, 8, and 12), and for the changes and percentage changes at Weeks 0, 4, 8, and 12 of the treatment period relative to baseline (Week 0), will be calculated. The same analysis will be performed by presence or absence of CIC.
2) Paired t-tests for the measured values at baseline (Week 0) and Weeks 4, 8, and 12 of the treatment period will be performed.
3) For the measured values at each evaluation time point (Weeks 0, 4, 8, and 12) and the changes and percentage changes from baseline (Week 0) to Weeks 4, 8, and 12 of the treatment period, the 95% confidence interval for the difference between the placebo group and the TAC-302 group will be calculated. The same analysis will be performed by presence or absence of CIC.
4) For the changes and percentage changes from baseline (Week 0) to each evaluation time point (Weeks 4, 8, and 12), student's t test will be performed using the placebo group as the control.
5) The same analyses as 1) to 4) will be performed for the case where missing data at Week 12 of the treatment period are imputed with LOCF.
6) The change and percentage change from baseline (Week 0) will be analyzed by MMRM using treatment group, evaluation time point (Weeks 4, 8, and 12 of the treatment period), and interaction between treatment group and evaluation time point as fixed effects and baseline value, sex, and age (< 65 years or ≥ 65 years) as covariates. The least squares means in each treatment group, and the difference in the least squares mean between the placebo group and the TAC-302 group and its two-sided 95% confidence interval at each evaluation time point will be estimated. Unstructured covariance structure will be assumed, and toeplitz type will be used if convergence is not achieved. If convergence is still not achieved, the first-order autoregressive, compound symmetry, and variance component will be used in this order. The Kenward-Roger method (2009) will be used to calculate degrees of freedom.

8.1.8 KHQ Score (by Domain)

The following analyses will be performed for the score of each domain based on the Japanese version of KHQ.

1) Summary statistics and 95% confidence intervals for the measured values at each evaluation time point (Weeks 0 and 12), and for the change and percentage change at Week 12 of the treatment period relative to baseline (Week 0), will be calculated.
2) Paired t-test for the measured values at baseline (Week 0) and Week 12 of the treatment period will be performed.
3) For the measured values at each evaluation time point (Weeks 0 and 12) and the change and percentage change from baseline (Week 0) to Week 12 of the treatment period, the 95% confidence interval for the difference between the placebo group and the TAC-302 group will be calculated.
4) For the change and percentage change from baseline (Week 0) to Week 12, student's t-test will be performed using the placebo group as the control.

8.1.9 Bladder Diary Records

The following analyses will be performed for the average number of micturitions 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 daytime urinations, and average number of nocturnal urinations.

1) Summary statistics will be calculated for the measured values at each evaluation time point (Weeks 0, 4, 8, and 12) and the changes and percentage changes from baseline (Week 0) to Week 4, 8, and 12 of the treatment period. The same analysis will be performed by presence or absence of CIC.
2) Paired t-tests for the measured values at baseline (Week 0) and Weeks 4, 8, and 12 of the treatment period will be performed.
3) For the measured values at each evaluation time point (Weeks 0, 4, 8, and 12) and the changes and percentage changes from baseline (Week 0) to Weeks 4, 8, and 12 of the treatment period, the 95% confidence interval for the difference between the placebo group and the TAC-302 group will be calculated. The same analysis will be performed by presence or absence of CIC.
4) For the changes and percentage changes from baseline (Week 0) to each evaluation time point (Weeks 4, 8, and 12), student's t test, Wilcoxon rank sum test, and van Elteren test using the allocation adjustment factors as strata[5)] will be performed using the placebo group as the control.
5) The proportion of patients with a $\leq -50\%$ change in the average number of urgency urinary incontinence episodes per 24 hours will be calculated, and Fisher's exact test will be performed to compare the between-group difference.
6) The same analyses as 1) to 4) will be performed for the case where missing data at Week 12 of the treatment period are imputed with LOCF.
7) The change and percentage change from baseline (Week 0) will be analyzed by MMRM using treatment group, evaluation time point (Weeks 4, 8, and 12 of the treatment period), and interaction between treatment group and evaluation time point as fixed effects and baseline value, sex, and age (< 65 years or ≥ 65 years) as covariates. The least squares means in each treatment group, and the difference in the least squares mean between the placebo group and the TAC-302 group and its two-sided 95% confidence interval at each evaluation time point will be estimated. Unstructured covariance structure will be assumed, and toeplitz type will be used if convergence is not achieved. If convergence is still not achieved, the first-order autoregressive, compound symmetry, and variance component will be used in this order. The Kenward-Roger method (2009) will be used to calculate degrees of freedom.

8.1.10 Relationship Between Efficacy Endpoints

For the relationship of the change and percentage change from baseline (Week 0) to Week 12 of the treatment period between the efficacy endpoints, Pearson and Spearman correlation coefficients will be calculated, and scatter plots will be prepared. The combinations of endpoints to be evaluated are those for which a combination of diseases considered to be related (DU or DU-OAB) is specified in Figure 8-1.

Figure 8-1 Combinations of Efficacy Endpoints for Which the Relationship of Change and Percentage Change from Baseline (Week 0) to Week 12 of the Treatment Period Will Be Evaluated

		Pressure Flow Study						Uroflowmetry			
		BCI (males)	PIP1 (females)	Q_{max} (analyzed separately for males and females)	$P_{det}Q_{max}$ (analyzed separately for males and females)	Duration of bladder contraction -1 (analyzed overall and separately for males and females)	Duration of bladder contraction -2 (analyzed overall and separately for males and females)	free Q_{max} (analyzed separately for males and females)	free Q_{ave} (analyzed separately for males and females)	Voided volume (analyzed overall and separately for males and females)	Voiding time (analyzed overall and separately for males and females)
Pressure Flow Study	BCI										
	PIP1										
	Q_{max}										
	$P_{det}Q_{max}$										
	Duration of bladder contraction-1	DU	DU								
	Duration of bladder contraction-2	DU	DU								
Uroflow-metry (uroflow metry)	free Q_{max}	DU	DU	DU	DU						
	free Q_{ave}	DU	DU								
	Voided volume	DU	DU	DU	DU	DU	DU				
	Voiding time	DU	DU	DU	DU	DU	DU				
	Post void residual measured by ultrasonography	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
	BVE	DU	DU	DU	DU	DU	DU	DU	DU		DU
	IPSS total score	DU	DU	DU	DU	DU	DU	DU	DU		DU
	IPSS voiding symptoms score	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
	IPSS (Question 1)	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
	IPSS (Question 3)	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
	IPSS (Question 5)	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
	IPSS (Question 6)	DU	DU	DU	DU	DU	DU	DU	DU	DU	DU
	IPSS storage symptoms score	DU-OAB	DU-OAB					DU-OAB			
	OABSS	DU-OAB	DU-OAB					DU-OAB			
Bladder Diary records	Average number of micturitions per 24 hours	DU-OAB	DU-OAB					DU-OAB			DU-OAB
	Average number of urinary urgency episodes per 24 hours	DU-OAB	DU-OAB					DU-OAB			
	Average voided volume per urination	DU-OAB	DU-OAB					DU-OAB			DU-OAB

DU, relationship between endpoints for DU; DU-OAB, relationship between endpoints for DU improvement and OAB improvement

8.1.11 Analysis by Allocation Factor

- Analyses of secondary endpoints excluding analysis of covariance/analysis using an MMRM and scatter plots (8.1.1 to 8.1.9) will be performed by age group (< 65 years and ≥ 65 years).
- Analysis will be performed as for analysis of secondary endpoints by sex (8.1.1 to 8.1.9). In analysis of covariance and analysis using an MMRM, values at baseline and age (< 60 years and ≥ 60 years in males and < 70 years and ≥ 70 years in females) will be used as covariates.

8.1.12 Analysis by Severity Score

The following analyses will be performed. The same analyses will be performed by sex.

- Analyses of the primary and secondary endpoints excluding analysis of covariance/analysis using an MMRM and scatter plots (7.3 and 8.1.1 to 8.1.9) will be performed by IPSS total score at baseline (Week 0).
- Analyses of the primary and secondary endpoints excluding analysis of covariance/analysis using an MMRM and scatter plots (7.3 and 8.1.1 to 8.1.9) will be performed by IPSS QOL score at baseline (Week 0).
- Analyses of the secondary endpoints excluding analysis of covariance/analysis using an MMRM and scatter plots (7.3 and 8.1.1 to 8.1.9) will be performed by OABSS score at baseline (Week 0).

8.1.13 Analysis by Post Void Residual

The following analyses will be performed. The same analyses will be performed by sex.

- Analyses of the primary and secondary endpoints excluding analysis of covariance/analysis using an MMRM and scatter plots (7.3 and 8.1.1 to 8.1.9) will be performed by post void residual measured by ultrasonography (< 50 mL, ≥ 50 mL, < 100 mL, and ≥ 100 mL) at baseline (Week 0).

8.1.14 Analysis by Appearance of Bladder Involuntary Contraction

The following analyses will be performed in the PPS. The same analyses will be performed by sex.

- Analyses of the primary and secondary endpoints (7.3 and 8.1.1 to 8.1.5) will be performed by appearance of bladder involuntary contraction. However, frequency tabulation of the appearance of bladder involuntary contraction and analysis of covariance/analysis using an MMRM in 8.1.1, 8.1.4, and 8.1.5 will not be performed.

8.1.15 Analysis of UDS Data Subset

The following analyses will be performed in the PPS. The same analyses will be performed by sex. Cases raising queries were pointed out at the urodynamic study data review meeting, and as a result of consideration by the case review committee, the appropriate urodynamic study evaluation set, with cases raising queries excluded, was taken to be the UDS data subset.

- Analyses of the primary and secondary endpoints (7.3 and 8.1.1 to 8.1.5) will be performed in the UDS data subset. However, frequency tabulation of the appearance of bladder involuntary contraction and analysis of covariance/analysis using an MMRM in 8.1.1, 8.1.4, and 8.1.5 will not be performed.

8.2 Analysis of Administration Status

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

8.2.1 Study Drug Administration

Summary statistics for administration status (total dose and total duration of administration) will be presented for each patient.

8.2.2 Status of Administration Completion

- 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.

8.3 Safety Analysis

The following analyses will be performed for each treatment group in patients treated in the treatment period.

8.3.1 Adverse Events and Adverse Reactions

The following analyses will be performed at each time point.

- The numbers of patients who experienced adverse events and the incidences of adverse events will be displayed. Similar analysis will be performed for adverse reactions. Similar analysis will also be performed by age (≥ 65 years and < 65 years). In addition, similar analysis will be performed by age (≥ 75 years and < 75 years).
- For each adverse event item, the numbers of patients who experienced adverse events and the incidences of adverse events will be displayed. Similar analysis will be performed for adverse reactions. Similar analysis will also be performed by age (≥ 65 years and < 65 years). In addition, similar analysis will be performed by age (≥ 75 years and < 75 years).
- For each adverse event item, the numbers of patients who experienced adverse events and the incidences of adverse events will be displayed by severity. Similar analysis will be performed for adverse reactions.
- The incidence of adverse events in the treatment period will be presented by time of onset (at or before Week 2 of the treatment period; after Week 2 of the treatment period and at or before Week 4 of the treatment period; after Week 4 of the treatment period and at or before Week 8 of the treatment period; after Week 8 of the treatment period and at or before Week 12 of the treatment period; after Week 12 of the treatment period; and follow-up observation). Similar analysis will be performed for adverse reactions.
- All adverse events that occurred from the start of study treatment to the end date of the follow-up observation will be listed by the adverse event variable of each patient, together with the adverse event term, severity, date of onset, action, outcome, causal relationship with the study drug, and comments.
- The incidence of serious adverse events will be calculated. Similar analysis will be performed for adverse reactions.
- The incidence of adverse events leading to discontinuation/dose interruption will be calculated. Similar analysis will be performed for adverse reactions.

8.3.2 Laboratory Test Values

If the measured values of each laboratory test parameter (quantitative parameter) include "≤," the analysis will be performed using the numerical values excluding inequality.

- For each laboratory test parameter (quantitative parameter), the time course of measured values will be shown in graphs.
- Summary statistics for the laboratory test parameters (quantitative parameters) at each time point will be calculated.
- The frequency of each laboratory test parameter (urinalysis parameter) at each evaluation time point will be tabulated.

8.3.3 12-lead Electrocardiogram

- For QTcF interval and heart rate, summary statistics for measured values will be calculated for each evaluation time point.
- For 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.
- The measured value of QTcF interval at each evaluation time point will be divided into categories (≤ 450 msec, > 450 msec and ≤ 480 msec, > 480 msec and ≤ 500 msec, and > 500 msec), and the frequency of each category will be tabulated.
- For 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 will be divided into categories (≤ 30 msec, > 30 msec and ≤ 60 msec, and > 60 msec) and their frequencies were tabulated.
- A list of patients with abnormal 12-lead electrocardiogram changes will be prepared.

8.3.4 Blood Pressure, Pulse Rate, and Body Temperature

- Summary statistics for blood pressure, pulse rate, and body temperature at each 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.

9. Other Analyses

9.1 Analysis Sets

The proportion of patients in each analysis set and the reasons for exclusion will be tabulated by treatment group. A list of patients excluded from the analysis sets will be provided with the reasons.

9.2 Deviations

The presence or absence of deviations and items of deviations will be tabulated by treatment group. The details of patients with deviations will be listed.

9.3 Patient Backgrounds

For each treatment group, summary statistics will be calculated or frequency tabulations will be performed to present appropriate summaries, depending on the data of each item of patient background. The same analysis will be performed by sex. Furthermore, for patients treated in the observation period and dropped out during the observation period, the same analysis will be performed in the subgroups of patients who did not meet the inclusion criterion (4) at enrollment in the treatment period and those who dropped out for other reasons.

10. REVIEW AND REVISION OF THE STATISTICAL ANALYSIS PLAN

The statistical analysis plan will be finalized prior to unblinding.

When the statistical analysis plan is revised, a record of changes in the statistical analysis plan/report analysis plan will be prepared, and the changes and reasons for the changes will be described. Analyses newly planned after unblinding will be distinguished from the analyses planned in advance and described in the change record.

11. STATISTICAL ISSUES

Explanations about the ICH-E3 guideline[1)] and other statistical issues are summarized below.

11.1 Adjustment for Covariates

Adjustment for covariates will be performed using analysis of covariance. Details of specific covariates will be provided separately.

11.2 Handling of Dropouts or Missing Data

Handling of missing values in efficacy endpoints is specified for each analysis.

Missing data for safety endpoints will not be imputed.

Other than abnormal values for which there is an obvious rationale, such as the effect of hemolysis due to blood collection on laboratory test values, all measured data will be used for analysis. If abnormal values are excluded from the analysis, they will be specified and the reasons for exclusion will be stated.

In addition, in post-hoc exploratory analysis, for each analyzed item, the handling of missing values will be decided appropriately depending on the method of analysis and the characteristics of the endpoints being analyzed.

11.3 Interim Analysis and Data Monitoring

No interim analysis will be performed in this study.

11.4 Multicenter Studies

This is a multicenter study.

11.5 Multiple Comparison/Multiplicity

Not applicable in this study.

11.6 Use of an "Efficacy Subset" of Patients

This is not planned in this study, but it will be performed as necessary as additional analysis.

11.7 Active-Control Studies Intended to Show Equivalence

Not applicable in this study.

11.8 Examination of Subgroups

In this study, subgroup analyses by allocation adjustment factors, severity score, and post void residual are planned in some analyses. Additional analyses will be performed as necessary.

12. PREPARATION OF REPORT ANALYSIS PLAN

Only the major analysis items are shown in the statistical analysis plan. All analysis items to be performed are shown in the separately prepared report analysis plan.

13. REFERENCES

(1) “Structure and Content of Clinical Study Reports” (PAB/ED Notification No. 335 dated 01 May 1996)
(2) Akira Sakuma, Medical Statistics Q & A, Tokyo, Kanehara & Co., Ltd.; 1987: p.75
(3) Kwon Soo Lee, Phil Hyun Song, Young Hwii Ko. "Does uroflowmetry parameter facilitate discrimination between detrusor underactivity and bladder outlet obstruction?" Investig Clin Urol 2016;57:437-441.
(4) Kenward, M. G., and Roger, J. H. (2009). "An Improved Approximation to the Precision of Fixed Effects from Restricted Maximum Likelihood." Computational Statistics and Data Analysis 53:2583–2595.
(5) van Elteren, P. H. (1960). "On the combination of independent two-sample tests of Wilcoxon," Bulletin of the International Statistical Institute, 37, 351-361.