Statistical Analysis Plan

Version 4.0

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ABBREVIATIONS AND DEFINITION OF TERMS

As a rule, the definitions in the protocol will be followed for abbreviations and terms. However, the abbreviation used only in this document is defined below.

Abbreviation (Term)	Full expression (Definition)
ICH Guideline	"Structure and Content of Clinical Study Reports"[1)]

1. Synopsis

This document shows the details of the statistical analysis plan regarding "Early Phase II Randomized Study of TAS-205 in Patients with Duchenne Muscular Dystrophy (Protocol Number 10053040)."

2. Target Sample Size and Rationale for the Sample Size

Target sample size: a total of 33 subjects (11 subjects for each group)

Given that DMD is a rare disease that allows only limited recruitment of subjects and that this study is primarily intended to evaluate the efficacy of TAS-205 in an exploratory manner, the sample size was determined not statistically, but based on feasibility.

3. Statistical Analysis Methods and Statistical and Analytical Issues

3.1 Study Objectives

The primary objective of this study is to evaluate the efficacy of TAS-205 administered orally twice daily for 24 consecutive weeks compared with placebo in patients with DMD in an exploratory manner.

The secondary objective is to evaluate the safety and dose relationship of TAS-205 administered orally twice daily for 24 consecutive weeks compared with placebo in patients with DMD.

The exploratory objectives are to evaluate the effect of TAS-205 on the urinary excretion of tetranor-PGDM and tetranor-PGEM in pooled urine samples after twice-daily oral administration for 24 consecutive weeks, as well as the relationship between the urinary excretions and efficacy of TAS-205 in patients with DMD, and also to evaluate the change in the urinary excretion of creatinine and creatine in pooled urine samples after twice-daily oral administration of TAS-205 for 24 consecutive weeks in patients with DMD in an exploratory manner.

3.2 Timing of Statistical Analysis

Statistical analyses will be performed after all subjects have completed this study.

3.3 Documents or Data Necessary for Statistical Analysis Other than Case Report Forms

The documents and data necessary for statistical analysis other than the information recorded in case report forms are as follows.

Table 3.1 Documents or Data Necessary for Statistical Analysis Other than Case Report Forms

Item	Document or data	Remarks
Information regarding attribution and deviation of patients	Flag showing attribution of each patient in each analysis set and reasons for exclusion from analysis sets	To identify the following information regarding handling of patients from the records of discussion between the sponsor and the medical expert. (Flag showing attribution of patients, reasons for exclusion from analysis set, reasons why the investigational product is not administered, deviation flag, and details of deviation)
	Patients who have not received the investigational product, and the reasons why the patients concerned have not received the investigational product	
	Copy of deviation report, and list of patients with deviation (including deviation flag and reasons for deviation)	
Key code	Key code for each patient	To identify key code for each patient in key code breaking.
Date of enrollment and randomization adjustment factors	IWRS data	Because it is entered only in IWRS data.
Conversion to MedDRA terms	Table showing correspondence of adverse event terms recorded by the investigator with MedDRA terms	Because the adverse events recorded by the investigator in case report forms need to be converted to MedDRA terms for the purpose of summarization of adverse events.
	Table showing correspondence of the terms of previous medical history and complication with MedDRA terms	To list previous medical history and complication.
Normal reference range of study site	Normal reference range of laboratory test values	Because information regarding the normal reference range of laboratory test values is necessary.
Drug name	Table showing correspondence of the terms of concomitant drugs recorded by the investigator with WHO-DD terms	To designate alignment sequence and grouped analysis.
Evaluation of muscle volume	Skeletal muscle CT	Because it is not recorded in the case report forms.
Pharmacodynamic and exploratory endpoints	Urinary tetranor-PGDM concentration, urinary tetranor-PGEM concentration, urinary creatinine concentration, and urinary creatine concentration	Because it is not recorded in the case report forms.

3.4 Statistical and Analytical Issues

The points to consider for statistical issues in ICH-E3 Guideline are as follows.

3.4.1 ADJUSTMENTS FOR COVARIATES

Adjustments for covariates are conducted using the MMRM. Details about specific covariates are described individually.

3.4.2 HANDLING OF MISSING VALUES AND ABNORMAL VALUES

For missing values, no imputation will be applied. Data employed at each time point will be used in analysis. For primary and secondary efficacy endpoints, LOCF or MMRM imputation will be applied as needed. The incidence of adverse events, etc. will be analyzed using the analysis set as the denominator.

All measurement data will be used in analysis, except for abnormal values that can be clearly explained, including laboratory values affected by hemolysis at blood collection. Any abnormal value excluded from analysis will be identified, and the rationale for exclusion will be provided.

3.4.3 INTERIM ANALYSES AND DATA MONITORING

Interim analyses will not be conducted in this study.

3.4.4 MULTICENTER STUDIES

Although this study is a multicenter joint study, no related special analysis has been planned. Additional analyses will be planned after this study if necessary from the exploratory stand point.

3.4.5 MULTIPLE COMPARISONS AND MULTIPLICITY

Adjustments for multiplicity will not be conducted in this study.

3.4.6 USE OF AN "EFFICACY SUBSET" OF PATIENTS

In this study, the analysis for efficacy evaluation will be conducted in the per protocol set (PPS). The analysis will also be conducted in the full analysis set (FAS) as supplementary analysis.

3.4.7 ACTIVE-CONTROL STUDIES INTENDED TO SHOW EQUIVALENCE

Not applicable in this study.

3.4.8 EXAMINATION OF SUBGROUPS

In this study, the analysis of subgroups is planned. Details about specific analytical methods are described individually.

4. Definition of Analysis Sets and Criteria for Handling in Analysis

4.1 Definition of Analysis Sets

The analysis sets in this study are defined as below.

Table 4.1 Definition of Analysis Sets

Analysis set	Definition
All enrolled patients	All subjects enrolled in this study
Treated patients	All enrolled patients who received at least 1 dose of the investigational product
Full Analysis Set (FAS)	All treated patients who were evaluated for at least 1 efficacy endpoint (regardless of whether primary or secondary endpoint) after initiation of investigational product administration
Per Protocol Set (PPS)	All subjects in the FAS, excluding those who met any of the following conditions: ・Subjects who were found to fail to meet any of the inclusion criteria after enrollment ・Subjects who were found to meet any of the exclusion criteria after enrollment ・Subjects who did not receive sufficient doses of the investigational product (dosing rate at Week 24 < 70%) ・Subjects who used prohibited concomitant medications/therapies ・Subjects who failed to comply with the dosage regimen of restricted concomitant medications ・Subjects who were not evaluated for the primary endpoint

If there is any subject for whom there are problems in determination of attribution in the analysis sets, the handling of such subject will be determined through discussion between the sponsor and the medical expert before database lock.

4.2 Criteria for Handling in Analysis

- If it is questionable as to how some subject data are to be handled, the sponsor will discuss the case(s) with the medical expert to make a decision before key code breaking.
- Data from subjects who have been administered the investigational product different from their randomized investigational product will be handled as data for the actually administered investigational product in the analysis of treated patients or PPS.
- In the analysis of FAS, the data will be handled as data for the randomized investigational product.
- Evaluation made in the period other than the period of clinical assessments stipulated in the protocol will be excluded as a rule (Table 4.2). If the evaluation is included in the analysis, the fact should be stated clearly. If examination is conducted twice or more during the period, the examination closest to the stipulated date will be adopted.

Table 4.2 Permissible Range for Clinical Assessments

Stipulated days	Permissible range
Baseline period	Within 2 weeks after enrollment
Day4	±1 day
Day6	Day 6 only
Day15	+5 days*
Day29	±5 days
Day57, Day127	±7 days
Day85, Day169	±7 days
Follow-up period (21 days after the end of investigational product administration)	±7 days

* If all the days in the permissible range are holidays/national holidays and clinical assessments cannot be performed, the first working day after the holidays/national holidays is permitted.

5. Primary Analysis

The following analyses will be performed for the primary endpoint, defined as the change from baseline in 6-minute walk distance (6MWD) at Week 24:

(1) To evaluate the efficacy of TAS-205 appropriately, summary statistics will be calculated for each treatment group in the PPS.

(2) As sensitivity analysis, the analysis described in (1) will be performed in the FAS.

6. Secondary Analysis

Major items of secondary analysis in this study are shown below. Other items of standard analysis are shown in the list of the items of analysis.

6.1 Analysis of the Primary Endpoint

The following analyses will be performed in the PPS and FAS:

The following analyses will be performed for the primary endpoint, defined as the change from baseline in 6MWD at Week 24: Analysis will also be conducted in the group combining the low-dose group and the high-dose group excluding the analysis of MMRM.

- A 2-sample t-test will be performed between each treatment group and placebo group. This analysis will be performed with and without the LOCF imputation. Analyses will also be conducted with the following baseline definitions.
  (1) Analysis excluding the subjects for whom the value of (6MWD on Day 1 - 6MWD at screening)/6MWD at screening is 0.2 or higher or -0.2 or lower
  (2) Analysis using the mean value of 6MWD on Day 1 and 6MWD at screening as the baseline value
- With respect to the above analysis, subgroup analysis will be conducted for the following items.

  Subgroup analysis: Presence or absence of the history of steroid use, age category (≥5 years and <7 years, and ≥7 years), and baseline 6MWD (<350 m, and ≥350 m)
- The treatment effect will be estimated using the MMRM. The changes from baseline in 6MWD measured at other time points will also be included in this analysis. Covariates will be the assigned group, baseline value, time point, and the interaction term of the assigned group and time point.
- Using the MMRM, the dose relationship will be analyzed with treatment contrasts of (placebo group, low-dose group, high-dose group) = (-2 1 1), (-1 0 1), and (-1 -1 2). The changes from baseline in 6MWD measured at other time points will also be included in this analysis. Covariates will be the assigned group, baseline value, time point, and the interaction term of the assigned group and time point.
- For the above 2 analyses, analyses will be conducted in the PPS by adding age and the presence or absence of the history of steroid use to explanatory variables. In addition, subgroup analysis will be conducted for the following items.

  Subgroup analysis: Baseline 6MWD (<350 m, and ≥350 m)

6.2 Analysis of Secondary Endpoints

6.2.1 EFFICACY ANALYSIS

The following analyses will be performed in the PPS and FAS: Analysis will also be conducted in the group combining the low-dose group and the high-dose group excluding the analysis of MMRM and charts.

(1) 6MWD

Analyses will also be conducted with the following baseline definitions when analyses are conducted using the baseline summary and changes of 6MWD excluding the analysis of MMRM.

(1) Analysis excluding the subjects for whom the value of (6MWD on Day 1 - 6MWD at screening)/6MWD at screening is 0.2 or higher or -0.2 or lower
(2) Analysis using the mean value of 6MWD on Day 1 and 6MWD at screening as the baseline value

- Summary statistics will be calculated at each time point for each treatment group. The data at Week 24 will be analyzed with and without the LOCF imputation.
- Summary statistics for the change from baseline to Week 12 will be calculated, followed by a 2-sample t-test between each treatment group and placebo group.
- With respect to the above 2 analyses, subgroup analysis will be conducted for the following items.

Subgroup analysis: Presence or absence of the history of steroid use, age category (≥5 years and <7 years, and ≥7 years), and baseline 6MWD (<350 m, and ≥350 m)

- The time course by each time point will be plotted for each treatment group. Similarly, changes from baseline in the PPS will be plotted.
- For 6MWD at baseline in each group and the group combining all groups in the PPS, the correlation coefficient (Pearson) of the %MVI (%) in both legs of muscle volume measurement (skeletal muscle CT) at each time point will be calculated. See Table 10.1 Method to Derive %MVI (%) for derivation of %MVI (%) of the muscle volume measurement (skeletal muscle CT).
- For the changes in 6MWD from baseline to each time point in each group and the group combining all groups in the PPS, the correlation coefficient (Pearson) of the %MVI (%) in both legs of muscle volume measurement (skeletal muscle CT) will be calculated.

(2) The following analyses will be performed for each value measured in each motor function test (time to rise from the floor test, Timed 10-m walk/run test, Timed Up & Go test), measurement of muscle volume (skeletal muscle CT, BIA), lean body mass, quantitative muscle strength assessments (hip flexion/extension, knee flexion/extension, ankle extension/flexion), serum CK concentration (only the serum CK concentration during the hospitalization period will be used for the efficacy evaluation), and pulmonary function test (VC, FVC, FEV1.0, FEV1.0%): In the analysis of the muscle volume measurement (skeletal muscle CT) in the PPS, the subjects of the reference values will be excluded. See Table 10.1 Method to Derive %MVI (%) for derivation of %MVI (%) of the muscle volume measurement (skeletal muscle CT). In quantitative muscle strength assessments, the maximum values in the measurement without compensation will be used.

- Summary statistics will be calculated at each time point for each treatment group.
- Summary statistics for the change from baseline will be calculated, followed by a 2-sample t-test between each treatment group and placebo group at each time point. The data at Week 24 will be analyzed with and without the LOCF imputation.
- With respect to the above 2 analyses, subgroup analysis will be conducted for the following items.

Subgroup analysis: Presence or absence of the history of steroid use, age category (≥5 years and <7 years, and ≥7 years), and baseline 6MWD (<350 m, and ≥350 m)

- The treatment effect will be estimated at each time point using the MMRM. The changes from baseline in the values measured at other time points will also be included in this analysis. Covariates will be the assigned group, baseline value, time point, and the interaction term of the assigned group and time point.
- Using the MMRM, the dose relationship will be analyzed at each time point with treatment contrasts of (placebo group, low-dose group, high-dose group) = (-2 1 1), (-1 0 1), and (-1 -1 2). Covariates will be the assigned group, baseline value, time point, and the interaction term of the assigned group and time point.
- For the above 2 analyses, %MVI (%) of muscular amount measurement (skeletal muscle CT) will be analyzed in the PPS by adding age and the presence or absence of the history of steroid use to explanatory variables. In addition, subgroup analysis will be conducted for the following items.

Subgroup analysis: Baseline 6MWD (<350 m, and ≥350 m)

- The time course by each time point will be plotted for each treatment group. Similarly, changes in the muscle volume measurement (skeletal muscle CT) from baseline in the PPS will be plotted.

6.2.2 SAFETY ANALYSIS

The analyses described below will be performed in treated patients for each treatment group. In tabulation of adverse events (adverse drug reactions), System Organ Class (SOC) and Preferred terms (PT) of MedDRA will be used. An exact method based on F distribution will be used for estimation of the confidence interval of incidences.[2)]

The adverse events which have occurred or become exacerbated after administration of the investigational product will be tabulated.

(1) Adverse events
- The incidence of adverse events will be calculated.
- The incidence for each of the following conditions will be calculated.
  Adverse events, severe adverse events, serious adverse events, adverse events leading to suspension of administration, adverse events leading to dose reduction, adverse events leading to discontinuation of this study, and adverse events leading to death
- The incidence of adverse events for each adverse event type according to PT of MedDRA will be calculated. When a same event has occurred several times in a same patient, the event will be regarded as 1 event in tabulation.
- For each adverse event type, the number and proportion of subjects with adverse events will be calculated by severity. When a same event has occurred several times in a same patient, the event will be regarded as 1 event in tabulation. Tabulation of severity will be conducted by extracting 1 event in the priority order of severe, moderate, and then mild.
- For each adverse event type, all adverse events reported from the start of investigational product administration to the end day of the follow-up period will be listed for each subject with the adverse event term, severity, onset date, treatment provided, outcome, date of theoutcome confirmed, causal relationship to the investigational product, and comments on the event.

(2) Adverse drug reactions
- For adverse drug reactions, analyses will be performed in the same way as for adverse events.

(3) Laboratory values

Concerning Mg, the data collected by using the unit of mEq/L will be converted to the unit of mg/dL by the following formula before analysis.

Mg concentration after conversion (mg/dL) = 1.2 × Mg concentration before conversion (mEq/L)
- For each laboratory parameter, summary statistics at each evaluation time point will be calculated.
- For each laboratory parameter, the time course of each measured value will be plotted for each subject.

(4) 12-lead ECG

For QTc interval, a test parameter of 12-lead ECG, Fridericia's formula will be used.
- For QTcF interval and heart rate, summary statistics of measured values at each evaluation time point will be calculated.
- For QTcF interval and heart rate, summary statistics of the change from immediately before Day 1 dose in measured values at each evaluation time point after start of the dose will be calculated.
- The QTcF interval at each evaluation time point will be categorized into "≤450 msec, > 450 msec and ≤480 msec, > 480 msec and ≤500 msec, and > 500 msec" before frequency tabulation.
- The change in QTcF interval from the value immediately before Day 1 dose to each time point of evaluation will be categorized into "≤30 msec, > 30 msec and ≤60 msec, and > 60 msec" before frequency tabulation.

- The proportion of subjects with abnormal change in 12-lead ECG (patients for whom the result is judged to be "Abnormal with clinical significance") and the 2-sided 95% confidence interval will be calculated. A list of subjects with abnormal change in 12-lead ECG will also be created.

(5) Body weight, blood pressure, pulse rate, and body temperature
- For body weight, systolic blood pressure, diastolic blood pressure, pulse rate, and body temperature (axilla), summary statistics at each evaluation time point will be calculated.
- For body weight, blood pressure and pulse rate, summary statistics of the change from immediately before Day 1 dose at each evaluation time point will be calculated.

(6) Cardiac ultrasonography (echocardiography)
- For left ventricular EF and left ventricular FS, summary statistics at each evaluation time point will be calculated.
- For left ventricular EF and left ventricular FS, summary statistics of the change from the baseline value measured in the screening period at each evaluation time point will be calculated.
- The incidence of the cases with abnormalities on echocardiography (patients for whom Clinical Significance was judged to be "Yes") and 2-sided 95% confidence interval will be calculated.

6.3 Analyses of Pharmacodynamic and Exploratory Endpoints

The following analyses will be performed for urinary excretion of tetranor-PGDM/-PGEM, urine tetranor-PGDM/Cre concentration ratio, urine tetranor-PGEM/Cre concentration ratio, urinary creatinine excretion, urinary creatine excretion, and creatine in urine (%) in the PPS and FAS: Analysis will also be conducted in the group combining the low-dose group and the high-dose group excluding the analysis of MMRM and charts.

For the method to derive each endpoint, refer to Table 10.2. Method to Derive Pharmacodynamic Endpoints and Exploratory Endpoints.

- Summary statistics at each time point will be calculated for each treatment group.
- Summary statistics of the change rate from baseline at each time point will be calculated, followed by a 2-sample t-test between each treatment group and placebo group at each time point. If the data at Week 24 are missing, conduct analyses with and without the LOCF imputation.
- With respect to the above 2 analyses, subgroup analysis of the following items will be conducted for urinary tetranor-PGDM/creatinine concentration ratio in the PPS.
  Subgroup analysis: Baseline 6MWD (<350 m, and ≥350 m)
- The treatment effect will be estimated using the MMRM. The changes from baseline in the values measured at other time points will also be included in this analysis. Covariates will be the assigned group, baseline value, time point, and the interaction term of the assigned group and time point.
- Using the MMRM, the dose relationship will be analyzed with treatment contrasts of (placebo group, low-dose group, high-dose group) = (-2 1 1), (-1 0 1), and (-1 -1 2). Covariates will be the assigned group, baseline value, time point, and the interaction term of the assigned group and time point.
- With respect to the above 2 analyses, subgroup analysis of the following items will be conducted for urinary tetranor-PGDM/creatinine concentration ratio in the PPS.
  Subgroup analysis: Baseline 6MWD (<350 m, and ≥350 m)
- The correlation coefficients (Pearson and Spearman) with the change from baseline in each item specified in (1) and (2) of Section 6.2.1 will be calculated for the change rate from

baseline at each time point in each treatment group and the group combining all groups. In addition, scatter plots of pharmacodynamic endpoints will be generated for each group by plotting the change rates of urinary tetranor-PGDM excretion, urinary tetranor-PGEM excretion, urinary tetranor-PGDM/creatinine concentration ratio, and urinary tetranor-PGEM/creatinine concentration ratio from baseline to Week 24 along the horizontal axis, and the changes at Week 24 along the vertical axis. Moreover, scatter plots of exploratory endpoints will be generated by plotting the change rates of urinary creatinine excretion, urinary creatine excretion, and % creatine urine from baseline to Week 24 along the horizontal axis, and the changes in 6MWD and muscle volume (skeletal muscle CT) from baseline to Week 24 along the vertical axis.

- The time course by each time point will be plotted for each treatment group. Similarly, charts showing the time course of the change rates from baseline for urinary tetranor-PGDM excretion, urinary tetranor-PGEM excretion, urinary tetranor-PGDM/creatinine concentration ratio, and urinary tetranor-PGEM/creatinine concentration ratio in the PPS will be generated.

6.4 Subject Disposition and Characteristics

(1) Subject disposition

- The number of subjects randomized to each group will be tabulated in a manner so as to clarify attribution of subjects in each analysis set, and a summary and a list of subjects excluded from each analysis set will be provided with the reason for exclusion.
- The presence or absence of important protocol deviations will be tabulated among the all enrolled patients. The types of deviations will be displayed together with the number of subjects.
- The presence or absence of and the reasons for study discontinuation will be summarized among the all enrolled patients.

(2) Subject characteristics

- For each analysis set, excluding all enrolled patients, distribution of the following subject and disease characteristics will be summarized.
  1) Demographic variables: Gender, race, age, age category (≥5 years and <7 years, and ≥7 years), height, body weight, presence or absence of previous medical history, and presence or absence of complication.
  2) Subject characteristics variables: Previous medical history, complication, presence or absence of diagnosis of DMD, diagnosis of DMD, presence or absence of the history of steroid use, history of steroid use, presence or absence of history of surgery, history of surgery, rehabilitation status, presence or absence of fitting of splint/insole, presence or absence of the use of wheel chair, 6MWD test, time to rise from the floor test, timed 10-m walk/run test, Timed Up & Go test

6.5 Dosing Information

The following analyses by treatment group will be performed in treated patients:

(1) Dosing Information

- Summary of the total dose and total duration of administration for each subject will be shown. Analyses will also be conducted for the PPS.

(2) Completed administration

- Summary statistics of the dosing rate of TAS-205 will be calculated. The dosing rate will be calculated by the following formula.

$$\text{Dosing Rate} = \frac{\text{Actual number of tablets}}{(\text{Criteria number of tablets (Administration number of days}^{*1} \times \text{Tablets/dose} \times \text{n Dose/day}))^{*2}}$$

*1 To be induced from Day of last administration - Day of first administration + 1, because there is an allowable period for the day of last administration. The number of days will be calculated by subtracting 0.5 from the number of days of administration if administration is started in the evening on the day of first administration, and also by subtracting 0.5 from the number of days of administration if administration is terminated in the morning of the day of last administration.

*2 If the dose is reduced during the study, the denominator for the dosing rate will be the sum of the number of days of administration before dose reduction × tablets/dose before dose reduction × twice/day and the number of days of administration after dose reduction × tablets/dose after dose reduction × twice/day.

- The Dosing Completed Rate of TAS-205 (proportion of subjects who were administered TAS-205 as in a specified schedule) will be calculated. The subjects will be the patients for whom the dosing rate is lower than 100%.
  - The presence or absence of concomitant medication and concomitant therapy (other than steroids) will be tabulated.
  - The presence or absence of the use of steroids will be tabulated.

6.6 Exploratory Analysis

The following analyses will be performed in the PPS. The analysis of %MVI of muscle volume measurement (skeletal muscle CT) will be performed in the lower leg, thigh, and thigh + lower leg.

(1) 6MWD

- For the group combining all groups, the correlation coefficients (Pearson and Spearman) of 6MWD at Week 24 and %MVI (%) of muscle volume measurement (skeletal muscle CT) will be calculated.
- For each group and the group combining all groups, the correlation coefficients (Pearson and Spearman) of the changes in 6MWD at Week 24 and the changes in MVI (%) of the muscle volume measurement (skeletal muscle CT) in both legs and P values for the correlation coefficients will be calculated. In addition, subgroup analysis will be conducted for the following items.

  Subgroup analysis: Baseline 6MWD (<350 m, and ≥350 m)
- Analysis of covariance will be performed using the following variables as conditions.

  Objective variable: Change in 6MWD at Week 24

  Explanatory variables: Baseline 6MWD, age, presence or absence of the history of steroid use, baseline %MVI (%) in both legs, and changes in %MVI (%) in both legs at Week 24

  In addition, subgroup analysis will be conducted for the following items.

  Subgroup analysis: Baseline 6MWD (<350 m, and ≥350 m)
- For each group and the group combining all groups, the correlation coefficients (Pearson and Spearman) of the changes in 6MWD at Week 24 and the change rates of urinary tetranor-PGDM/creatinine concentration ratio and urinary tetranor-PGDM on Day 168 and P values for the correlation coefficients will be calculated. In addition, subgroup analysis will be conducted for the following items.

  Subgroup analysis: Baseline 6MWD (<350 m, and ≥350 m)
- Analysis of covariance will be performed using the following variables as conditions.

Objective variable: Change in 6MWD at Week 24

Explanatory variable: Baseline 6MWD, age, presence or absence of the history of steroid use, baseline urinary tetranor-PGDM/creatinine concentration ratio, and the change rate of urinary tetranor-PGDM/creatinine concentration ratio on Day 168

In addition, subgroup analysis will be conducted for the following items.

Subgroup analysis: Baseline 6MWD (<350 m, and ≥350 m)

(2) %MVI (%) of muscle volume measurement (skeletal muscle CT)

- For each group and the group combining all groups, summary statistics of baseline %MVI (%) in both legs will be calculated.
- For each group, summary statistics of baseline %MVI (%) will be calculated, and 2-sample t-test between groups will be performed. In addition, subgroup analysis will be conducted for the following items.

  Subgroup analysis: Baseline 6MWD (<350 m, and ≥350 m)
- For the group combining all groups, the correlation coefficients (Pearson and Spearman) of each %MVI (%) at baseline will be calculated.
- For each group and the group combining all groups, the correlation coefficients (Pearson and Spearman) of the changes in the %MVI (%) in both legs at Week 24 and the change rates of urinary tetranor-PGDM/creatinine concentration ratio and urinary tetranor-PGDM on Day 168, and P values for the correlation coefficients will be calculated. In addition, subgroup analysis will be conducted for the following items.

  Subgroup analysis: Baseline 6MWD (<350 m, and ≥350 m)
- Analysis of covariance will be performed using the following variables as conditions.

  Objective variables: Changes in %MVI (%) in both legs at Week 24

  Explanatory variables: Baseline %MVI (%) in both legs, age, presence or absence of the history of steroid use, baseline urinary tetranor-PGDM/creatinine concentration ratio, and the change rate of urinary tetranor-PGDM/creatinine concentration ratio on Day 168

  In addition, subgroup analysis will be conducted for the following items.

  Subgroup analysis: Baseline 6MWD (<350 m, and ≥350 m)

(3) Pharmacodynamic Endpoints

- For each group and the group combining the low-dose group and the high-dose group, summary statistics of the change rates of urinary tetranor-PGDM excretion, urinary tetranor-PGEM excretion, urinary tetranor-PGDM/creatinine concentration ratio, and urinary tetranor-PGEM/creatinine concentration ratio will be calculated at each time point, and 1-sample t-test using the change rate = 0% as null hypothesis will be conducted at each time point. In addition, subgroup analysis will be conducted for the following items.

  Subgroup analysis: Baseline 6MWD (<350 m, and ≥350 m)

7. List of Items Analyzed

A list and summary of the items analyzed, including the above-mentioned items of primary analysis and secondary analysis, as well as the standard items of analysis considering ICH-E3 Guideline are shown in Appendix.

8. General Matters in Data Analysis

8.1 Statistical Analytical Software

Generation of the figures, tables and tabulated lists planned in this document will be performed using SAS Version 9.4. The format of output of the results will be RTF.

When any statistical analytical software other than those mentioned above or any self-made software is used, it should be clearly stated in the statistical analysis plan.

8.2 General Matters related to Format of Figures, Tables and Tabulated Lists

Details about the form of output of individual figures and tables will be stipulated in the report analysis plan.

The paper size will be A4. Portrait will be used as the standard for figures and summary tables, and landscape will be used as the standard for tabulated lists and data lists. However, it will be decided according to the characteristics of individual figures and tables.

The name of the investigational product and the protocol number will be shown at the left top of each page; the date and time of output and page number will be shown at the right top; the output program name will be shown at the left bottom; and the user ID of the person executing the analytical program will be shown at the right bottom.

8.3 Common Rules for Data Processing

○ Rules regarding number of days and period

1. The number of days will be calculated by subtracting the day of start from the day of completion and adding 1.
   (Example)
   Number of days of administration: if administration is terminated on the day of the start of administration, the administration period will be 1 day.
   Duration to the onset of adverse events: If any adverse event occurs on the day after the day of the start of administration, the duration to the first occurrence of adverse event will be 2 days.
2. When the number of days is converted to the number of years, number of months, and number of weeks, 1 year will be counted as 365.25 days, 1 month will be counted as 30.4375 days, and 1 week will be counted as 7 days.

○ Rules for number of decimal places and rounding

1. Mean values, standard deviations, and median values will be displayed (rounded) to the place (or decimal place) next to the lowest place of source data.
2. Percentage will be displayed to 1 decimal place (example, 12.3%). Values are rounded to 1 decimal place.
3. In calculation of statistic values such as mean values, standard deviations, and median values, rounding is not performed during the process of calculation. Only the final values obtained as a result of calculation will be rounded.
4. P values will be displayed to 3 decimal places (example, 0.001). The values will be rounded to 3 decimal places.

○ Summary statistics

When summary statistics are displayed, the “number of subjects,” “median values,” “mean values,” “standard deviations,” “minimum values,” and “maximum values” will be displayed as a set unless otherwise there are any particular reasons.

○ LOCF

If the data at the last time point of observation are missing, the data which are not missing and have been obtained immediately before that time point will be used for interpolation, irrespective of whether or not the data are within the acceptable range.

○ Confidence interval of incidences

The confidence interval of incidences (or incidence rates) will be obtained by an exact method based on F distribution.

The number of subjects in the analysis set is put as N and the number of subjects exhibiting adverse events is put as X. Thus, the incidence (P) and the upper limit (P_U) and lower limit (P_L) of the exact 2-sided 100(1-α)% confidence interval of the incidence will be estimated by the following formulas.[2)] In the case of 95% confidence interval, α=0.05.

$$P = X / N$$

$$P_U = \frac{\upsilon_1 \cdot F_{\alpha/2}(\upsilon_1, \upsilon_2)}{\upsilon_2 + \upsilon_1 \cdot F_{\alpha/2}(\upsilon_1, \upsilon_2)}, \qquad \begin{aligned} \upsilon_1 &= 2 \cdot (X + 1) \\ \upsilon_2 &= 2 \cdot (N - X) \end{aligned}$$

$$P_L = \frac{\upsilon_2}{\upsilon_2 + \upsilon_1 \cdot F_{\alpha/2}(\upsilon_1, \upsilon_2)}, \qquad \begin{aligned} \upsilon_1 &= 2 \cdot (N - X + 1) \\ \upsilon_2 &= 2 \cdot X \end{aligned}$$

○ Adverse events

Adverse events will be coded according to MedDRA/J, and Preferred Terms (PT) will be used for tabulation unless otherwise specified. The version of MedDRA to be used will be the newest version available as of the time of data fixation as a rule, but it will be decided by the MedDRA manager.

○ MMRM

The confidence coefficient for estimation of confidence interval will be 2-sided 95%.

In the analysis of MMRM, SAS MIXED procedure will be used as shown in the following SAS code.

```
proc mixed data = INDATA ;
    class       ATRTN† (ref='1'[Placebo]) AVISITN† SUBJID† ;
    model       AVAL† = BASE† ATRTN AVISITN ATRTN*AVISITN / ddfm = KR ;
    lsmeans     ATRTN*AVISITN / diff cl alpha = 0.05 ;
    repeated    AVISITN / subject = SUBJID type = UN# ;
    estimate    "Low Dose TAS-205 Saturation - Week 12"   ATRTN   -2 1 1‡
                    ATRTN*AVISITN   -2 0 1 0 1 0 / cl alpha = 0.05 ;
    estimate    "Low Dose TAS-205 Saturation - Week 24"   ATRTN   -2 1 1‡
                    ATRTN*AVISITN   0 -2 0 1 0 1 / cl alpha = 0.05 ;
    estimate    "Placebo vs High Dose TAS-205 - Week 12"   ATRTN   -1 0 1‡
                    ATRTN*AVISITN   -1 0 0 0 1 0 / cl alpha = 0.05 ;
    estimate    "Placebo vs High Dose TAS-205 - Week 24"   ATRTN   -1 0 1‡
                    ATRTN*AVISITN   0 -1 0 0 0 1 / cl alpha = 0.05 ;
    estimate    "High Dose TAS-205 Saturation - Week 12 "   ATRTN   -1 -1 2‡
                    ATRTN*AVISITN   -1 0 -1 0 2 0 / cl alpha = 0.05 ;
    estimate    "High Dose TAS-205 Saturation - Week 24 "   ATRTN   -1 -1 2‡
                    ATRTN*AVISITN   0 -1 0 -1 0 2 / cl alpha = 0.05 ;
run ;
```

† ATRTN: Treatment group (placebo group [reference group], low-dose group, high-dose group)
AVISITN: Time point (Week 12, Week24)
SUBJID: Patient ID
AVAL: Response variable
BASE: Baseline value

‡ Contrast coefficient (-2 1 1): Paired comparison of low-dose group saturation
Contrast coefficient (-1 0 1): Paired comparison of linear trend
Contrast coefficient (-1 -1 2): Paired comparison of high-dose group saturation

If convergence is not achieved with UN, TOEP will be used. If convergence is not achieved yet, the following will be used in this order: AR(1)→CS→VC.

9. References

1. "Structure and Content of Clinical Study Reports" (May 1, 1996, PAB/ED Notification No. 335)
2. Sakuma, A., *Igaku Tokei* (Medical Statistics) Q&A, p75, Kanehara Shuppan, 1987

10. Appendix

Table 10.1 Method to Derive %MVI (%)

Evaluation of muscle volume	Method of derivation
%MVI (%) in right leg	Muscle in middle part (right surface area) / (muscle in middle part (right surface area) + fat in middle part (right surface area) - subcutaneous fat in middle part (right surface area)) × 100
%MVI (%) in left leg	Muscle in middle part (left surface area) / (muscle in middle part (left surface area) + fat in middle part (left surface area) - subcutaneous fat in middle part (left surface area)) × 100
%MVI (%) in both legs	Muscle in middle part (bilateral surface area) / (muscle in middle part (bilateral surface area) + fat in middle part (bilateral surface area) - subcutaneous fat in middle part (bilateral surface area)) × 100

Table 10.2 Method to Derive Pharmacodynamic Endpoints and Exploratory Endpoints

Pharmacodynamic and exploratory endpoints	Method of derivation
Urine tetranor-PGDM/Cre concentration ratio (ng/mg creatinine)	PGDM† / Cre†
Total urinary tetranor-PGDM excretion (ng)	PGDM† × urine volume (mL)
Urinary tetranor-PGEM/creatinine concentration ratio (ng/mg creatinine)	PGEM† / Cre†
Total urinary tetranor-PGEM excretion (ng)	PGEM† × urine volume (mL)
Urinary creatinine excretion (g)	Cre† × urine volume (mL)
Urinary creatine excretion (g)	Cr† × urine volume (mL)
% creatine in urine (%)	Urinary creatine excretion (g) / [Urinary creatine excretion (g) + Urinary creatinine excretion (g)] × 100

†PGDM: Urinary tetranor-PGDM concentration (ng/mL)
PGEM: Urinary tetranor-PGEM concentration (ng/mL)
Cre: Urinary creatinine concentration (g/mL)
Cr: Urinary creatine concentration (g/mL)