Early Phase II Randomized Study of TAS-205 in Patients with Duchenne Muscular Dystrophy

TAS-205
Protocol No.: 10053040 Ver.P02
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This study will be conducted in accordance with the Guideline for Good Clinical Practice (GCP) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), as well as applicable regulatory requirements in Japan.

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List of Abbreviations

Abbreviation	Full expression
ACTH	adrenocorticotropic hormone
AE	adverse event
Ae	cumulative amount of drug excreted in urine
A/G	albumin/globulin ratio
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC0-t	area under the concentration-time curve from 0 to t hours ($AUC_{0-\infty}$ or AUC_{0-inf}: area under the concentration-time curve extrapolated to infinity)
BIA	bioelectrical impedance analysis
BUN	blood urea nitrogen
Cmax	maximum plasma concentration
CK	creatine kinase
Cre	creatinine
CRP	C-reactive protein
CT	computed tomography
CYP	cytochrome P450
DMD	duchenne muscular dystrophy
DP	D-type prostanoid
EF	ejection fraction
FAS	full analysis set
FEV 1.0	forced expiratory volume 1.0
FS	fractional shortening
FVC	forced vital capacity
GCP	good clinical practice
γ-GTP	γ-glutamyl transpeptidase
HBs	hepatitis B surface
HCV	hepatitis C virus
HDL-C	high density lipoprotein cholesterol
HIV	human immuno deficiency virus
HPGDS	hematopoietic-type prostaglandin D synthase
IRB	institutional review board
IWRS	interactive Web Response System
LC/MS/MS	liquid chromatography / tandem mass spectrometry
LDH	lactate dehydrogenase
LOCF	last observation carried forward
MedDRA	medical dictionary for regulatory activities
MMRM	mixed-effect models for repeated measures

Abbreviation	Full expression
PGD_2	prostaglandin D_2
PGDM	prostaglandin D_2 metabolite
PGE_2	prostaglandin E_2
PGEM	prostaglandin E_2 metabolite
P-gp	p-glycoprotein
POC	Proof of Concept
PPS	per protocol set
QTc	corrected QT
SOP	standard operating procedure
$t_{1/2}$	half life of elimination
VC	vital capacity
6MWD	6-minute walk distance

Synopsis

Sponsor:	Taiho Pharmaceutical Co., Ltd.
Investigational product:	TAS-205
Generic name:	Not yet confirmed.

Study title:

Early Phase II Randomized Study of TAS-205 in Patients with Duchenne Muscular Dystrophy

Protocol No.:	10053040
Development phase:	Early Phase II
Indication:	Duchenne muscular dystrophy (DMD)
Background/Rationale:	DMD affects approximately 1 in 3500 male births worldwide, and the number of patients with DMD in Japan is estimated to be approximately 5000. DMD is caused by a mutation in the dystrophin gene resulting in the absence of dystrophin protein, while involvement of immunity and inflammatory responses in the development of the disease is also suggested. Prostaglandin D_2 (PGD_2) is one of the major prostaglandins involved in inflammation. It is produced from arachidonic acid, a cell membrane constituent, via phospholipase A_2, cyclooxygenase, and then prostaglandin D synthase. There are 2 types of prostaglandin D synthase: lipocalin-type, primarily located in the central nervous system,[1, 2)] and hematopoietic type, primarily expressed in mast cells, type 2 T helper cells, and microglial calls.[3)] [redacted] In the Phase I single- and repeated-dose study of TAS-205 in patients with DMD (hereinafter referred to as Study 10053030), TAS-205 was demonstrated to be highly safe and tolerable at doses of 1.67 to 13.33 mg/kg. Given these results, the present early Phase II study was planned to evaluate the efficacy of TAS-205 in patients with DMD.

Study objectives/endpoints:	Primary objective: 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 **Primary endpoint:** Efficacy: • Evaluation of motor function: Change from baseline in the measured 6-minute walk distance (6MWD) at Week 24 **Secondary endpoints:** Efficacy: • Evaluation of motor function: (1) Measured 6MWD and the change from baseline in the measured 6MWD at Week 12, (2) Time measured in the time to rise from the floor test, Timed 10-m walk/run test, and Timed Up & Go test, as well as the change from baseline in each measured value • Evaluation of muscle volume: Measured values in skeletal muscle computed tomography (CT) and bioelectrical impedance analysis (BIA), as well as the change from baseline in each measured value • Measured lean body mass and the change from baseline in each measured value • Evaluation of muscle strength: Quantitative muscle strength assessments with a hand-held dynamometer (hip flexion/extension, knee flexion/extension, ankle extension/flexion) and the change from baseline in each measured value • Measured serum creatine kinase (CK) concentration and the change from baseline in the measured value • Pulmonary function test (non-invasive vital capacity measurement using a spirometer): Measured vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in 1.0 second (FEV1.0), and the percent ratio of FEV1.0 to forced vital capacity (FEV1.0%), as well as the change from baseline in each measured value Safety: • Safety evaluation by cardiac ultrasonography (echocardiography), 12-lead ECG, blood pressure, pulse rate, body temperature, and laboratory tests (incidences of adverse events and adverse drug reactions, etc.) **Pharmacodynamic endpoints:** • Urinary tetranor-PGDM/creatinine concentration ratio • Total urinary tetranor-PGDM excretion • Urinary tetranor-PGEM/creatinine concentration ratio • Total urinary tetranor-PGEM excretion **Exploratory endpoints:** • Urinary creatinine excretion • Urinary creatine excretion • Creatine in urine (%)[*1] *1 Creatine in urine (%) = urinary creatine excretion (g/day) / [urinary creatine excretion (g/day) + urinary creatinine excretion (g/day)] × 100 (the value shall be rounded to 2 decimal places)[5)]

Study design:	This study is a double-blind randomized study to evaluate the efficacy of TAS-205 for deterioration of physical function (e.g., motor function, muscle volume, muscle strength) compared with placebo in patients with DMD; that is, the study is designed as an exploratory efficacy study. The target total sample size of 33 patients will be obtained through central registration. Patients enrolled as subjects will be randomized to one of 3 groups (low-dose group: 6.67 to 13.33 mg/kg/dose, high-dose group: 13.33 to 26.67 mg/kg/dose, and placebo group) (randomization ratio: 1:1:1), and receive the investigational product orally twice daily, once after breakfast and once after dinner, for 24 consecutive weeks starting after dinner on Day 1 (subjects will be hospitalized on Day -2 within 12 days after enrollment and start Day 1 within 14 days after enrollment) to evaluate the efficacy in a double-blind manner. Subjects will be administered the number of tablets per dose specified based on their body weights measured within 14 days before enrollment.
Study status:	Study start day (planned): February, 2016 Study completion day (planned): August, 2017 Patient enrollment period (planned): May, 2016 to October, 2016 Implementing countries: Japan only
Number of patients planned:	In this study, a total of 33 patients will be enrolled through central registration.
Patient eligibility:	**Inclusion criteria:** Patients who meet all of the following criteria at the enrollment are eligible to participate in this study: (1) A legal guardian (legal representative) of a male pediatric patient with the ability to give consent provides written informed consent to participate in the study (whenever possible, informed voluntary assent should also be obtained personally from the patient after all information has been given in a way that suits the patient's level of understanding). (2) Patients with a diagnosis of dystrophinopathy as determined by a dystrophin genetic test or muscle pathology findings, symptoms or signs characteristic to DMD (e.g., proximal muscular weakness, waddling gait, Gowers sign), and progressive walking difficulty at the time of informed consent. (3) Patients aged 5 years or more at the time of informed consent (4) Patients weighing ≥ 7.5 kg and < 60 kg within 14 days before enrollment (5) Patients who can rise from the floor or a chair and walk by themselves at the screening test (confirmed by medical interview, actual performance, etc.), with 6MWD of more than 75 m (use of wheelchair in daily activities is permissible) (6) Patients who can stay in the hospital for the time period specified in the

	study (7) Patients who can continue with administration of the specified number of tablets (8) If the patient is receiving oral steroids for DMD treatment, he had begun the treatment more than 6 months before informed consent, and his symptoms remain stable with no change in the prescription-based dosage regimen of steroids within 3 months **Exclusion criteria:** Patients who meet any of the following criteria at the enrollment will be excluded from the study: Patients who meet any of the following criteria (except for criterion (2)) during the baseline period after enrollment cannot receive the administration of the investigational product during the period: (1) Patients who have serious concomitant drug hypersensitivity (2) Patients with FVC of < 50% of the predicted value[*1] based on the spirometric reference value in Japanese children (developed by the Lung Function Review Committee of the Japanese Society of Pediatric Pulmonology in 2008)[6)] within 14 days before enrollment *1 FVC will be predicted using the following formula: FVC prediction: $2.108+(-0.1262) \times \text{age (years)}+0.00819 \times \text{age (years)}^2+(-3.118) \times \text{height (m)}+2.553 \times \text{height (m)}^2$ (3) Patients who continuously use mechanical ventilation (except for use while sleeping) (4) Patients with a left ventricular ejection fraction (EF) of < 40% or left ventricular fractional shortening (FS) of < 25% on the cardiac ultrasonography (echocardiography) performed within 14 days before enrollment (5) Patients who have been confirmed to have clinically significant symptoms of cardiac failure or respiratory failure (6) Patients receiving immunosuppressive medications (other than corticosteroids for DMD treatment) (7) Patients who have used cyclooxygenase (COX)-1 or COX-2 inhibitors, or nonsteroidal anti-inflammatory drugs (NSAIDs) during 7 days before the 6MWD test in the screening period (8) Patients who have a history of surgery that may affect muscle strength or motor function within 6 months before enrollment or who will undergo surgery during the study (9) Patients who have incurred an injury (trauma/damage) that may affect muscle strength or motor function within 3 months before enrollment or who have an uncured injury (trauma/damage) that may affect muscle strength or motor function at the enrollment (10) Patients with systemic allergic disease, chronic inflammatory disease, or

	other diseases that may prevent correct interpretation of efficacy or safety data (excluding allergic rhinitis, localized or mild atopic dermatitis, eczema, etc.) (11) Patients who have received gene-/cell-based therapy or stop-codon readthrough therapy with antisense oligonucleotides, or who have participated in another clinical trial and received an investigational product within 90 days before investigational product administration in the present study (12) Participants of another clinical trial or participants of other clinical research or another study in which they may undergo a motor function test during 7 days before a motor function test scheduled in the present study (13) Patients who have been confirmed to be hepatitis B surface (HBs) antigen-, hepatitis C virus (HCV) antibody-, or human immunodeficiency virus (HIV) antigen- or antibody-positive before enrollment (14) The patient's legal representative is unwilling to agree that the patient will use appropriate contraception throughout the study period and for 180 days after the end of the study. 1) The investigator or subinvestigator will discuss appropriate contraception with the patient and his legal representative, and instruct the patient to avoid pregnancy of a partner without fail using a double barrier method (condom plus diaphragm) or intrauterine contraceptive device throughout the study participation or contraception period if applicable. (15) Patients who are judged by the investigator or subinvestigator to have brain dysfunction, including intellectual disability, tendency of autism, and attention deficit hyperactivity disorder, that may affect the evaluation of motor function (16) Patients with a corrected QT interval (QTc) of 450 msec or more on the 12-lead ECG performed within 14 days before enrollment (corrected by Fridericia's formula) (17) Patients who are deemed not eligible for the study by the investigator or subinvestigator for any other reason
Study participation period:	From the day of written informed consent by the patient's legal representative to the end day of the follow-up period.
Efficacy evaluation criteria:	For the evaluation of motor function, muscle volume, and muscle strength, a separately prepared written evaluation procedure will be followed. There are no standard evaluation criteria established for DMD.

Safety evaluation criteria:	**Definition of adverse event**: An adverse event is defined as any unfavorable medical event that occurs in a subject participating in the study, regardless of whether it is considered related to the investigational product. A diagnosis will be recorded as an adverse event wherever possible. If no definite diagnosis can be established, signs or symptoms will be recorded. Symptoms associated with DMD or concurrent illness and abnormal laboratory or other test findings that have been present since before the study initiation will not be assessed as adverse events. However, any new symptoms or worsening of concurrent illness will be assessed as adverse events. All clinically or medically significant abnormal test values will be reported as adverse events. Symptoms derived from a diagnosis already reported as an adverse event by the investigator or subinvestigator will not be assessed as adverse events. Abnormal laboratory test values assessed as adverse events are: • those requiring medical treatment • those requiring prolonged administration, discontinuation, or dose reduction of the investigational product • those deemed medically significant by the investigator or subinvestigator for any other reason **Severity of adverse events:** One of the following severities will be selected and evaluated: Mild: Mild; no symptom or mild symptom; only clinical or test finding; requiring no treatment Moderate: Moderate; requiring minimum/local/non-invasive treatment; limiting age-appropriate activities of daily living except for self-care* Severe: Severe or medically significant, but not immediately life-threatening; requiring hospitalization or prolongation of existing hospitalization; disability; limiting self-care activities.** An event leading to life-threatening consequences or requiring emergency intervention, or death due to adverse event (AE) is also assessed as severe. * "Activities of daily living except for self-care" refers to meal preparation, shopping for daily goods and clothing, use of a telephone, financial management, etc. ** "Self-care activities" refers to bathing, dressing/undressing, food intake, use of a bathroom, and oral drug intake without being bedridden.

Analytical methods:

Analysis sets:

The analysis sets in this study are defined as below.

Analysis set	Definition
Enrolled subjects	All subjects enrolled in the study
Subjects administered the investigational product	All enrolled subjects who received at least 1 dose of the investigational product
Full Analysis Set (FAS)	All subjects administered the investigational product 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 (administration 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

Primary endpoint:

The following analyses will be performed for the primary endpoint, defined as the change from baseline in 6MWD at Week 24:

(1) Primary analysis

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

(2) Sensitivity analysis for the primary analysis

- The analysis described in (1) will be performed in the FAS.

(3) Secondary analyses of the primary endpoint

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

- A 2-sample t-test will be performed between each treatment group and

	placebo group. This analysis will be performed with and without the Last Observation Carried Forward (LOCF) imputation. - The treatment effect will be estimated using the Mixed effect Models for Repeated Measures (MMRM). The changes from baseline in 6MWD measured at other time points will also be included in this analysis. - 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. For the analytical methods of the secondary, pharmacodynamic, and exploratory endpoints, refer to Sections 13.1.3.3 and 13.1.3.4.
Rationale for sample size:	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.

Table 1 Clinical Assessment Schedule

Clinical assessment item	Screening period[*12]	Enrollment	Baseline period		Administration period											Follow-up period[*16, 18] Follow-up, discontinuation
Visit (n)	1	–	2					3	4	5	6		7	8		9
Week	Within 2 weeks before enrollment	–	Within 2 weeks after enrollment		0	0.57	0.86	2	4	8	11	12	18	23	24	27
Day[*1] (standard day)	Within 14 days before enrollment	–	-2 [*13]	-1	1 [*14]	4	6	15	29	57	83	85	127	167	169 [*16]	190
Informed consent/assent	X															
Subject ID code entry[*2]	X															
Investigation of subject characteristics	X	X														
Enrollment		X														
Body weight[*3]	X				X [*15]		X	X	X	X		X	X		X	X
Height	X															
Hospitalization[*4]			X								X			X		
Investigational product (TAS-205/placebo) administration[*5]			Prescription		X [*5]	→	→	→	→	→	→	→	→	→	X [*5]	
Medical examination	X				X [*15]	X	X	X	X	X		X	X		X	X
Blood pressure, pulse rate, body temperature[*6]	X				X [*15]	X	X	X	X	X		X	X		X	X
Hematology/biochemistry[*6]	X				X [*15]		X	X	X	X		X	X		X	X
Endocrinology[*6]					X [*15]		X					X			X	(X) [*19]
Urinalysis[*6]	X				X [*15]		X	X	X	X		X	X		X	X
12-lead ECG[*7]	X				X [*15]	X	X	X	X	X		X	X		X	X
Cardiac ultrasonography (echocardiography)[*7]	X											X			X	X
Pulmonary function test	X				X [*15]		X		X			X			X [*17]	
Motor function: 6MWD	X				X [*15]							X			X [*17]	
Motor function: time to rise from the floor, Timed 10-m walk/run test, Timed Up & Go test					X [*15]							X			X [*17]	
Measurement of muscle volume: skeletal muscle CT					X [*15]										X [*17]	
Measurement of muscle volume: BIA[*8]					X [*15]		X	X	X	X		X	X		X [*17]	
Lean body mass[*8]					X [*15]		X	X	X	X		X	X		X [*17]	
Quantitative muscle strength assessments					X [*15]							X			X [*17]	
Urinary tetranor-PGDM/PGEM concentrations, urinary creatinine and creatine concentrations, urine weight, and urine specific gravity (pooled urine)[*9]				X		X					X			X		
Subject medication diary (investigation of treatment compliance, etc.)[*10]				Supply	X	→	→	→	→	→	→	→	→	→	X	(X)
Concomitant medication/therapy[*11]	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X
Evaluation of adverse events[*11]	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	X

1. Permissible range for clinical assessments: After Day 1 (except for the follow-up and discontinuation tests), clinical assessments will be performed as specified in Section 5.1.10. The permissible range for the 2nd (Week 12) and 3rd hospitalization (Week 24) will be the standard hospitalization day ± 7 days. For hospitalization on any day other than the standard hospitalization day, pooled urine will also be started on the day after hospitalization, and the efficacy evaluation including that of motor function (hereinafter referred to as the efficacy evaluation), will be performed on the end day of pooled urine. However, if the efficacy evaluation cannot be performed on the end day of pooled urine due to an adverse event or any other reason, the efficacy evaluation may be performed within the end day of pooled urine + 2 days (this permissible range for the efficacy evaluation will also apply to the baseline evaluation). The increase in the number of hospitalization days due to the delay of the efficacy evaluation (excluding prolonged hospitalization due to inpatient treatment) will not be assessed as a serious adverse event.
   For hospitalization within the permissible range of standard hospitalization day at Week 24 (Day 167) ± 7 days (Day 160 to Day 174), the investigational product will not be administered after the efficacy evaluation.
2. Subject ID code entry: A unique subject ID code will be provided to each patient whose legal representative has received an explanation of informed consent (the patient should also receive an explanation of informed consent/assent whenever possible).
3. Body weight: No dose increase/decrease will be considered according to body weight increase/decrease during the study.
4. Hospitalization: In principle, the duration of the initial hospitalization (Day -2 to Day 6) will be 8 days and 7 nights. In principle, the discharge day for the 2nd hospitalization (hospitalized on Day 83 and discharged on Day 85) and the 3rd hospitalization (hospitalized on Day 167 and discharged on Day 169) will be the day of the efficacy evaluation; however, subjects who visit the site from afar may be discharged on the day after the efficacy evaluation. Subjects will be appropriately instructed before hospitalization to bring all the prescribed investigational products (managed by their legal representatives) and subject medication diary at each hospitalization.
5. Investigational product administration: The first dose will be administered after dinner on Day 1, and the last dose will be administered after breakfast on the efficacy evaluation day at Week 24. Any suspended or missed dose during the administration period will not be administered later than administration after breakfast on the efficacy evaluation day at Week 24. The investigational product will be additionally prescribed in accordance withTable 3.2-1.
6. Blood pressure, pulse rate, body temperature, hematology/biochemistry/endocrinology, and urinalysis: The subject will be kept at rest and fasted wherever possible for 3 to 4 hours (standard) before blood collection for laboratory tests. The measurement on the efficacy evaluation day will be performed before the evaluation. Blood pressure and pulse rate will be measured after the subject is confirmed to be at rest in a supine or sitting position for several minutes, and the measurement will be immediately repeated if any abnormality is observed. Since cortisol is subject to diurnal variation, the endocrinological parameters, including adrenocorticotropic hormone (ACTH), will be measured at 8:00 to 10:00 am (standard) only during the hospitalization period.
7. 12-lead ECG, cardiac ultrasonography (echocardiography): The measurement will be performed after the subject is confirmed to be at rest for several minutes. The measurement on the efficacy evaluation day will be performed before the evaluation.
8. BIA, lean body mass: The measurement will be performed using a body composition monitor (TANITA BC-622).
9. Urinary tetranor-PGDM and tetranor-PGEM concentrations, urinary creatinine and creatine concentrations, urine weight, and urine specific gravity: During the baseline and administration periods, urine will be pooled (under refrigeration) for approximately 24 hours from immediately after waking on the day after hospitalization. Urine will also be pooled for approximately 24 hours from immediately after waking on Day 4 to immediately after waking on Day 5 (initiation of pooled urine within Day 4 ±1 day is permissible as shown in Section 5.1.10). For urinary tetranor-PGDM and tetranor-PGEM concentrations, frozen samples will be collected by an external contractor and analyzed at the Pharmacokinetics Research Laboratories of Taiho Pharmaceutical Co., Ltd. Urinary creatinine and creatine concentrations, urine weight, and urine specific gravity will be measured at the study site. Urine volume (mL) will be calculated from the measured urine weight (g) and urine specific gravity (g/mL) at the study site.
10. Subject medication diary: The subject and his legal representative will bring the subject medication diary at each visit and submit it during the medical examination. The subject medication diary will be collected at each visit for ongoing drug accountability check and appropriate instruction. If the subject medication diary is left behind at home, it may be collected at the subsequent visit. Drug accountability to facilitate additional prescription of the investigational product is described in Note 5, above.
11. Assessments of concomitant medication/therapy and adverse events: Investigated from the time of informed consent to the end of the follow-up period (follow-up or discontinuation test)
12. Data from any evaluation/test performed as specified within 14 days before enrollment can be used as screening data, even if obtained before informed consent.
13. Initial hospitalization: The subject will be hospitalized (on Day -2) within 12 days after enrollment.
14. Administration start day (Day 1): The administration of the investigational product will be started after dinner on the end day of pooled urine (within 14 days after enrollment); however, if it is not possible to perform the efficacy evaluation (corresponding to Note 1) due to an adverse event or any other reason, or to start the investigational product administration on the end day of pooled urine, the administration may be started after dinner within the end day of pooled urine + 2 days (within up to 16 days after enrollment) (the actual administration start day will be designated as Day 1). The increase in the number of hospitalization days due to the delay of the administration start day (excluding prolonged hospitalization due to inpatient treatment) will not be assessed as a serious adverse event.
15. Clinical assessments in the baseline period: Performed no later than administration on the investigational product administration start day (administration after dinner on Day 1), in principle
16. Discontinuation test: Performed at the first visit after discontinuation whenever possible (safety endpoints will be evaluated)
17. Efficacy endpoints on the end day of administration: Evaluated after the last dose of the investigational product (standard: administration after breakfast on Day 169)
18. Follow-up test: Performed 21 days after the last day of the investigational product administration (standard day ± 7 days is permissible).
19. Endocrinology at the follow-up test: Performed only if an abnormal change (adverse event) is observed in the test on the discharge day for the 3rd hospitalization (standard: Day 169). Such an endocrinological test will be performed around 8:00 to 10:00 am on the follow-up test day. For subjects who visit the study site from afar, a stay at night before the follow-up test day (stay at or outside the study site; planned hospitalization or stay at a nearby facility) will be considered to collect blood within the specified time window whenever possible.

1. Background Information

1.1 Introduction

Duchenne Muscular Dystrophy (DMD) affects approximately 1 in 3500 male births worldwide, and the number of patients with DMD in Japan is estimated to be approximately 5000. DMD is caused by a mutation in the dystrophin gene resulting in the absence of dystrophin protein, which is normally located immediately beneath the muscle sarcolemma. The clinical course of DMD is characterized by maximal motor function between the ages of 4 and 5 years, followed by progressive muscle weakness and then loss of the ability to walk at approximately 10 years of age. The gene mutations include exon deletions, duplications, and micro mutations such as point mutations, which account for approximately 60%, 10%, and 30%, respectively.

While the cause of DMD is the lack of dystrophin protein due to a mutation in the dystrophin gene, the mechanism for development of DMD is not fully understood. It is suggested that immunity and inflammatory responses may be involved in the development of the disease. Prostaglandin D_2 (PGD_2) is one of the major prostaglandins involved in inflammation, and is produced from arachidonic acid, a cell membrane constituent, by phospholipase A_2, cyclooxygenase, and then prostaglandin D synthase. There are 2 types of prostaglandin D synthase: one is known as lipocalin-type and primarily located in the central nervous system[1, 2] and produces PGD_2, which centrally acts via the prostaglandin D_2 receptor 1 (DP1) to induce sleep, regulate pain response, etc.[6]; and the other is hematopoietic prostaglandin D synthase, which is known to be primarily expressed in mast cells, type 2 T helper cells, and microglial calls.[3]

[redacted]

For patients with DMD, no effective treatments are available except for oral steroids, but oral steroids require dose reduction, change in regimen, and even dose suspension in order to manage associated adverse reactions; therefore, a new treatment is highly needed. While no clinical studies to evaluate the efficacy of TAS-205 have been conducted in patients with allergic rhinitis, development of a new treatment for DMD is considered to be highly valuable, and thus a Phase I single- and repeated-dose study in patients with DMD was conducted. In this study, TAS-205 was demonstrated to be highly safe and tolerable in patients with DMD when given at 1.67 to 13.33 mg/kg as a single dose and at repeated doses twice daily for 7 days. TAS-205 also decreased urinary excretion of tetranor-PGDM (total excretion of tetranor-PGDM and tetranor-PGDM/Cre concentration ratio), a marker of PGD_2 production, with increasing dose. Significantly increased urinary excretion of tetranor-PGDM in nonambulatory subjects compared with ambulatory subjects when analyzed by ambulatory function as the subject characteristic, as well as higher urinary excretion in patients with DMD aged 8 years or older compared with healthy subjects of the same age and reportedly increased urinary excretion with age[10] suggest involvement of PGD_2 production in the development of DMD. In conclusion, it was considered of great significance to evaluate the efficacy of TAS-205 in patients with DMD, and an early Phase II study in these patients was therefore planned.

1.2 TAS-205

1.2.1 Mechanism of Action

TAS-205 inhibits HPGDS selectively and competitively.

1.3 Overview of Risks and Benefits

1.3.1 TAS-205

Since only Phase I studies have been conducted with TAS-205 to investigate the tolerability, pharmacokinetics, and pharmacodynamics in healthy adult male subjects and patients with DMD, and only

limited information is available on the efficacy, benefits of TAS-205 has not been confirmed yet at the initiation of the present study.

1.3.2 Risks and Benefits Expected in the Study

This study is expected to provide information on the efficacy of TAS-205 (high and low doses) for deterioration of physical function (motor function, muscle volume, and muscle strength) and the dose relationship of TAS-205 in patients with DMD. In addition, the study is expected to provide information on the long-term safety of TAS-205 administered twice daily for 24 consecutive weeks. Since no significant or potentially significant risks have been identified with TAS-205, no risks are expected in the present study; however, the high dose of TAS-205 has never been administered in clinical studies, and thus the tolerability of TAS-205 at the high dose has not been demonstrated yet at the initiation of the present study.

1.4 Major Study Results

1.4.1 Nonclinical Studies

Refer to the Investigator's Brochure DMD Ver. 3 (revised on March 24, 2016).

1.4.2 Clinical Studies

1.4.2.1 Study 10053010 (Phase I Study in Healthy Adult Subjects)

[redacted]

1.4.2.2 Study 10053030 (Phase I Study in Patients with DMD)

A Phase I single- and repeated-dose clinical study of TAS-205 was conducted in patients with DMD (hereinafter referred to as Study 10053030) to evaluate the safety and pharmacokinetics of TAS-205, as well as the effects of TAS-205 on urinary excretion of tetranor-PGDM and tetranor-PGEM in an exploratory manner after a single oral dose and repeated oral doses twice daily for 7 days (Steps 1 and A: 1.67 - 3.33 mg/kg/dose, Steps 2 and B: 3.33 - 6.67 mg/kg/dose, Steps 3 and C: 6.67 - 13.33 mg/kg/dose).

In the single dose period, a total of 15 subjects in the TAS-205 group, with 5 subjects per step, and a total of 6 subjects in the placebo group were treated with the investigational product. Pharmacokinetics was evaluated only in 15 subjects in the TAS-205 group. Pharmacodynamics was evaluated in 15 subjects in the TAS-205 group and 6 subjects in the placebo group.

In the repeated dose period, a total of 14 subjects in the TAS-205 group (in Steps A to C) and a total of 5 subjects in the placebo group were treated with the investigational product. Pharmacokinetics was evaluated only in the 14 subjects in the TAS-205 group administered the investigational product, and all subjects in the placebo group were excluded from the pharmacokinetic evaluation. Pharmacodynamics was evaluated in the 14 subjects in the TAS-205 group and 5 subjects in the placebo group were treated with the investigational product.

The pharmacokinetics of TAS-205 was linear in the dose range studied and reached steady state after repeated doses for 4 days. In addition, it was suggested that TAS-205 decreased urinary excretion of tetranor-PGDM (total excretion of tetranor-PGDM and tetranor-PGDM/Cre concentration ratio) with increasing dose at each measurement time point, without affecting urinary excretion of tetranor-PGEM.

In the safety evaluation in this study, no deaths or other serious adverse events were reported in any subjects. No subjects were withdrawn from the study due to adverse events in any dosing period. In the TAS-205 group as compared with the placebo group, adverse events occurred, and adverse drug reactions also occurred in the single dose period, but not in the repeated dose period. None of the adverse events reported in the TAS-205 group were common to all steps or tended to increase dose-dependently in any dosing period; all adverse events were mild in severity and resolving or resolved. In addition, no clinically significant abnormal changes were observed in laboratory values, 12-lead ECG, blood pressure, or pulse rate. In the repeated dose period, an abnormal change in body temperature was observed in 1 subject in Step B in the TAS-205 group; however, this was associated with nasopharyngitis. Other measured values were comparable to those in the placebo group, with no clinically significant changes post-/pre-dose .

In conclusion, TAS-205 was demonstrated to be highly safe and tolerable in patients with DMD when given at 1.67 to 13.33 mg/kg/dose as a single oral dose and repeated oral doses twice daily for 7 days.

1.5 Rationale for the Study and Study Population

1.5.1 Study Population

This study is an early Phase II study to evaluate the efficacy of TAS-205 (low dose and high dose) administered orally twice daily for 24 consecutive weeks in patients with DMD. The study will also be conducted to evaluate the safety of TAS-205 as well as the relationship between the pharmacodynamic or exploratory endpoints and the efficacy in an exploratory manner. Since the efficacy for deterioration of physical function will be primarily evaluated, this study will include ambulatory patients with DMD aged 5 years or older who meet all of the inclusion criteria and none of the exclusion criteria.

1.5.2 Study Design

[redacted]

[redacted]

1.5.3 Dosage of TAS-205

[redacted]

[redacted]

Since a marked increase in body weight during the 24-week evaluation period is unlikely and dose increase/decrease according to body weight increase/decrease during the study may be unnecessary based on the dose setting in 7.5-kg or 15-kg increments of body weight in the present study, the dose for each subject during the evaluation period will be fixed based on the body weight data in the screening period (within 14 days before enrollment). In summary, the subjects assigned to the active drug groups will receive the number of TAS-205 tablets per dose specified by the body weight measured within 14 days before enrollment, as shown in Table 7.1.1-1, orally twice daily, within 30 minutes after breakfast and dinner, for 24 consecutive weeks.

1.5.4 Selection of TAS-205 Placebo

In this study, a placebo group will be included to evaluate the efficacy of TAS-205 for deterioration of physical function (e.g., motor function, muscle volume, muscle strength) after oral administration twice daily for 24 consecutive weeks as well as the safety after repeated administration for 24 weeks, in an appropriate and objective manner. In order to maintain blindness of the low-dose and high-dose groups, in which different numbers of TAS-205 50 mg tablets (active drug) will be administered, the subjects assigned to the low-dose group will receive the active drug tablets with the same number of placebo tablets. In summary, the subjects assigned to the placebo and the low-dose groups will receive the number of tablets per dose specified based on the body weight measured within 14 days before enrollment, as shown in Table 7.1.1-1, orally twice daily, within 30 minutes after breakfast and dinner, for 24 consecutive weeks. Since this study is designed to permit subjects who had been using steroid before informed consent to continue their steroid therapy as far as no changes are made to their dosage regimen after informed consent, inclusion of a placebo group is considered ethically acceptable.

2. Study Objectives

2.1 Primary Objective

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.

2.2 Secondary Objective

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.

2.3 Exploratory Objectives

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.

2.4 Endpoints

2.4.1 Primary Endpoint

Efficacy:

Evaluation of motor function: Change from baseline in the measured 6MWD at Week 24

2.4.2 Secondary Endpoints

Efficacy:

- Evaluation of motor function: (1) Measured 6MWD and the change from baseline in the measured 6MWD at Week 12, (2) Time measured in the time to rise from the floor test, Timed 10-m walk/run test, and Timed Up & Go test, as well as the change from baseline in the time measured in each test
- Evaluation of muscle volume: Measured values in skeletal muscle CT and BIA as well as the change from baseline in each the measured value
- Measured lean body mass and the change from baseline in each measured value
- Evaluation of muscle strength: Quantitative muscle strength assessments with a hand-held dynamometer (hip flexion/extension, knee flexion/extension, ankle extension/flexion) and the change from baseline in each measured value
- Measured CK concentration and the change from baseline in the measured value
- Pulmonary function test (non-invasive vital capacity measurement using a spirometer): Measured VC, FVC, FEV1.0, and FEV1.0%, as well as the change from baseline in each measured value

Safety:

- Safety evaluation by cardiac ultrasonography (echocardiography), 12-lead ECG, blood pressure, pulse rate, body temperature, and laboratory tests (incidence of adverse events and adverse drug reactions, etc.)

2.4.3 Pharmacodynamic Endpoints

- Urine tetranor-PGDM/Cre concentration ratio
- Total urinary tetranor-PGDM excretion
- Urine tetranor-PGEM/Cre concentration ratio
- Total urinary tetranor-PGEM excretion

2.4.4 Exploratory Endpoints

- Urinary creatinine excretion
- Urinary creatine excretion
- Creatine in urine (%)[*1]

*1 Creatine in urine (%) = urinary creatine excretion (g/day) / [urinary creatine excretion (g/day) + urinary creatinine excretion (g/day)] × 100 (the value shall be rounded to 2 decimal places)[5)]

3. Study Design

This study is a double-blind, randomized study to evaluate the efficacy of TAS-205 for deterioration of physical function (e.g., motor function, muscle volume, muscle strength) compared with placebo in patients with DMD; that is, the study is designed as an exploratory efficacy study.

The target total sample size of 33 patients will be obtained through central registration.

Subjects will be enrolled and randomized to low-dose group (6.67 to 13.33 mg/kg/dose), high-dose group (13.33 to 26.67 mg/kg/dose), or placebo group (randomization ratio: 1:1:1), and receive the investigational product orally twice daily, once after breakfast and once after dinner, for 24 consecutive weeks starting after dinner on Day 1 (subjects will be hospitalized on Day -2 within 12 days after enrollment and start Day 1 within 14 days after enrollment) to evaluate the efficacy in a double-blind manner. Subjects will receive the number of tablets per dose specified based on their body weights measured within 14 days before enrollment, as shown in Table 7.1.1-1.

The study design is shown in Figure 3-1 below.

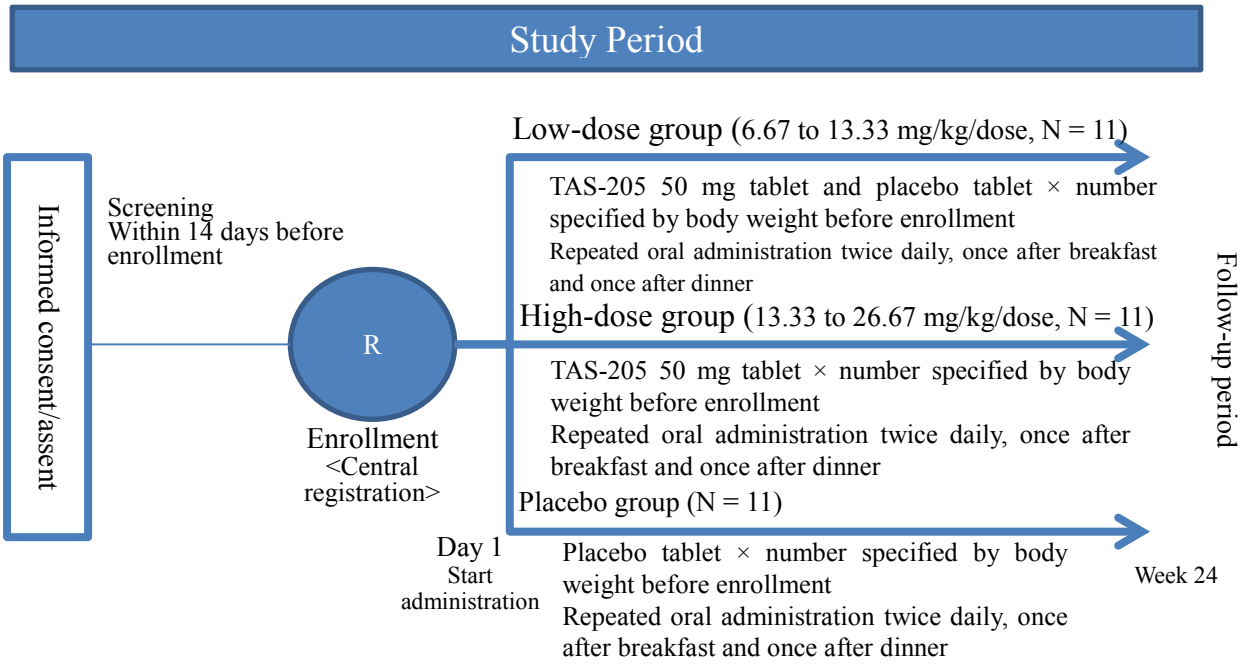

Figure 3-1 Study Design

3.1 Study Period

Study start day (planned): February, 2016

Study completion day (planned): August, 2017

Patient enrollment period (planned): May, 2016 to October, 2016

Implementing countries: Japan only

3.1.1 Definitions of Periods in the Study for Individual Subjects

The periods described in this protocol will be defined as follows:

Study period:	Period from the day of written informed consent by the legal representative of the patient to the end of the follow-up period
Screening period:	Period from the day of written informed consent until before enrollment (within 14 days before enrollment)
Baseline period:	Period from after enrollment to the first dose of the investigational product (after dinner on Day 1) (in principle, within 14 days after enrollment)
Administration period:	Period from after the first dose of the investigational product (after dinner on Day 1) to the end of the last dose of the investigational product (standard: after breakfast on Day 169) or discontinuation
Follow-up period:	21 days from the day of last dose of the investigational product (permissible range: standard ± 7 days). Safety follow-up test will be performed.
Hospitalization period[*1]:	
	- Initial hospitalization period[*1] Period from the hospitalization on Day -2 to the discharge on Day 6 (8 days and 7 nights; in principle, the end day of pooled urine initiated on Day -1 will be Day 1)
	- 2nd hospitalization period[*1] Period from the hospitalization on Day 83 ± 7 days (Day 76 to Day 90) to the discharge after 3 days and 2 nights (subjects who visit the site from afar may be discharged on the day after the efficacy evaluations [4 days and 3 nights])
	- 3rd hospitalization period[*1] Period from the hospitalization on Day 167 ± 7 days (Day 160 to Day 174) to the discharge after 3 days and 2 nights (subjects who visit the site from afar may be discharged on the day after the efficacy evaluations [4 days and 3 nights])

*1 In view of the conditions of pediatric subjects, if it is not possible due to an adverse event or other reasons to perform the efficacy evaluations or to start the investigational product administration on the end day of pooled urine, the efficacy evaluations may be started within the end day of pooled urine + 2 days or the administration may be started on Day 1. In such case, the increase in the number of hospitalization days (excluding prolonged hospitalization due to inpatient treatment) will not be assessed as a serious adverse event.

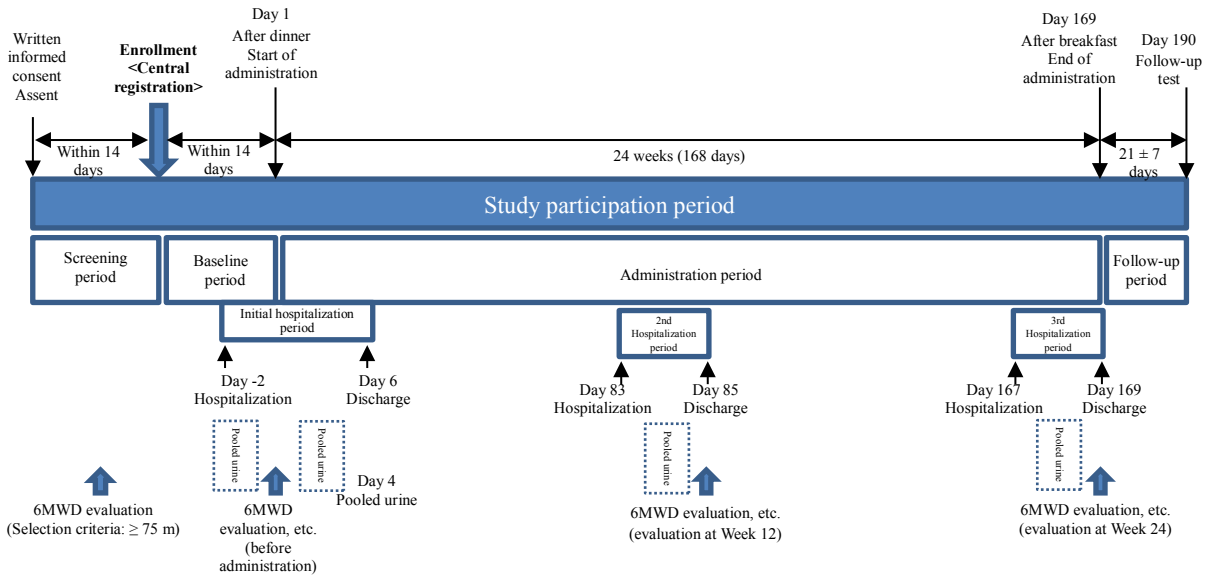

Figure 3.1-1 Study Participation Period for Individual Subjects

3.2 Subject Randomization and Blinding

3.2.1 Randomization Method

This study is a randomized study.

After providing due explanation to each prospective patient and his legal representative, the investigator or subinvestigator will obtain written informed consent/assent, and then prepare a screening log of patients whose legal representative consented to participate in the study in order to check the patient enrollment in the study. After confirming that the prospective patient is deemed eligible by meeting all of the inclusion criteria and none of the exclusion criteria, all necessary information will be entered the Interactive Web Response System (IWRS) and submitted to the Enrollment Center.

Upon completion of enrollment after confirmation of subject eligibility, the subjects will be randomly assigned to the low-dose group, high-dose group, or placebo group in a ratio of 1:1:1 via IWRS based on a dynamic randomization method (minimization method).

Data will be entered in accordance with the description in the IWRS procedure.

The subjects will be stratified by the following randomization adjustment factors:

- Age (between 5 and 6 years, 7 years or older)
- Presence or absence of concomitant steroid use

The above-mentioned enrollment and randomization will be centrally managed; after completion of the enrollment procedure, each subject will be assigned to a treatment group and given an investigational product number to be initially prescribed (for 6-week administration) by the enrollment system.

The investigational product numbers corresponding to subject randomization will be given and reported to the study site with instructions on the investigational product prescription via IWRS. For more detailed information, refer to the IWRS procedure.

If an investigational product not corresponding to the number given via IWRS is prescribed to a subject in error, the IWRS help desk must be notified immediately. In addition, the cause of the erroneous prescription of the investigational product must be recorded at the study site.

If a subject receives the investigational product for a different treatment group due to an error in the investigational product number allocation or prescription, the subject will continue to receive the investigational product for the rest of the study period.

If any of the discontinuation criteria for individual subjects specified in Section 4.3 is met, the condition related to the discontinuation will be entered in the IWRS promptly. In addition, any dose suspension or reduction will be promptly recorded in the IWRS with the start and end days of the suspension, the start day of the reduction, etc.

3.2.2 Allocation of the Investigational Product Number

3.2.2.1 Allocation of the Investigational Product Number at Enrollment

After enrollment, each subject will be assigned to a treatment group and provided an investigational product number (boxes) to be initially prescribed (for 6-week administration) via IWRS (1st allocation). The first dose after enrollment will start within 14 days after enrollment.

3.2.2.2 Second and Subsequent Allocation of the Investigational Product Number (at Visit 4 and Thereafter)

At the 2nd allocation of the investigational product number, the study site staff will enter necessary information into the IWRS after confirming that there are no problems for continuous administration of the investigational product after medical examination at Visit 4 (Week 4). Based on the information entered, the investigational product numbers (boxes) necessary for a total of 8 weeks of administration from Week 7 to Week 14 should be given to the study site via IWRS (2nd allocation).

Similarly, at the 3rd allocation, the study site staff will enter necessary information into the IWRS after confirming that there are no problems for continuous administration of the investigational product during hospitalization (after medical examination) at Visit 6 (Weeks 11 to 12), and then, based on the information entered, the investigational product numbers (boxes) necessary for a total of 6 weeks of administration from Week 15 to Week 20 should be given to the study site via IWRS.

At the 4th allocation, the study site staff will enter necessary information into the IWRS after confirming that there are no problems for continuous administration of the investigational product after medical examination at Visit 7 (Wees 18), and then, based on the information entered, the investigational product numbers (boxes) necessary for a total of 6 weeks of administration from Week 21 to the day of last dose [taking into consideration the 3rd hospitalization on Day 174 (the latest permissible hospitalization day) and the end day of pooled urine (Day 176) + 2 days (Day 178: the latest permissible day of the efficacy evaluations)] should be given to the study site via IWRS.

Table 3.2-1 Allocation of the Investigational Product Number (at Enrollment and Visit 4 and thereafter)

Allocation of the investigational product number	1st	2nd	3rd	4th
Number of tablets prescribed to subjects[*1]	For a total of 6 weeks of administration	For a total of 8 weeks of administration	For a total of 6 weeks of administration	For a total of 4 weeks + 2 weeks[*2] of administration
Prescription time point	Before administration after the 1st hospitalization (Day -2 to Day 1 before first dose)	Visit 4 (Week 4)	Visit 6 (Weeks 11 to 12; at the 2nd hospitalization)	Visit 7 (Week 18)
Duration of administration period of the investigational product prescribed (planned)	Day 1 to Week 6	Week 7 to Week 14	Week 15 to Week 20	Week 21 to Week 24 (+ 2 weeks[*2])
Timing of IWRS completion and the investigational product number allocation	Enrollment	Visit 4 (after medical examination)	During hospitalization at Visit 6 (after medical examination)	Visit 7 (after medical examination)

*1: Since the investigational product will be supplied in boxes, the subjects will be prescribed at least the number of boxes that include necessary number of tablets.

*2: 2 weeks are added in consideration of the permissible range of the 3rd hospitalization (± 7 days) as well as the efficacy evaluation day at Week 24 (end day of pooled urine + 2 days).

The investigational product numbers given at the 1st (at enrollment) and subsequent allocation will be the same as the numbers corresponding to the treatment group assigned at enrollment at the 1st allocation.

If a subject is administered the investigational product for a different treatment group during the administration period due to an error in the 2nd (Visit 4) or subsequent investigational product number allocation or prescription, the medical expert and the sponsor will discuss the action to be taken promptly.

3.2.3 Blinding

This study is a double-blind study. During the study, all subjects, the investigator, the subinvestigator, the trial collaborator, and the sponsor will be blinded to the treatment groups. According to the investigational product allocation procedure, the key codes will be prepared, broken, and managed by the investigational product allocation manager.

The codes will not be broken unless otherwise needed for the management of the medical condition of the subject. If the investigational product has to be identified in case of emergency to manage the medical condition of a subject, the investigator or subinvestigator will discuss the condition of the applicable subject with the sponsor before code breaking via IWRS. If discussion before code breaking is not possible, the investigator will notify the sponsor of the code breaking as soon as possible. In case the code breaking occurs, the investigator or subinvestigator must record the date of and reason for the code breaking.

The codes will be broken to identify the investigational product group after completion of the study period and the analysis data lock.

4. Patient Inclusion/Exclusion and Subject Discontinuation Criteria

4.1 Inclusion Criteria

Patients who meet all of the criteria below at the enrollment will be included in the study.

The rationale is described in Section 14.3.

(1) A legal guardian (legal representative) of a male pediatric patient with the ability to give consent provides written informed consent to participate in the study (whenever possible, informed voluntary assent should also be obtained personally from the patient after all information has been given in a way that suits the patient's level of understanding).

(2) Patients with a diagnosis of dystrophinopathy as determined by a dystrophin genetic test or muscle pathology findings, symptoms or signs characteristic to DMD (e.g., proximal muscular weakness, waddling gait, Gowers sign), and progressive walking difficulty at the time of informed consent.

(3) Patients aged 5 years or more at the time of informed consent

(4) Patients weighing ≥ 7.5 kg and < 60 kg within 14 days before enrollment

(5) Patients who can rise from the floor or a chair and walk by themselves at the screening test (confirmed by medical interview, actual performance, etc.), with 6MWD of 75 m or more (use of wheelchair in daily activities is permissible)

(6) Patients who can stay in the hospital for the time period specified in the study

(7) Patients who can continue with administration of the specified number of tablets

(8) If the patient is receiving oral steroids for DMD treatment, he had begun the treatment more than 6 months before informed consent, and his symptoms remain stable with no change in the prescription-based dosage regimen of steroids within 3 months

4.2 Exclusion Criteria

Patients who meet any of the following criteria at the enrollment will be excluded from the study. Patients who meet any of the following criteria (except for criterion (2)) during the baseline period after enrollment cannot receive the administration of the investigational product during the period.

The rationale is described in Section 14.4.

(1) Patients who have serious concomitant drug hypersensitivity

(2) Patients with FVC of < 50% of the predicted value[*1] based on the spirometric reference value in Japanese children (developed by the Lung Function Review Committee of the Japanese Society of Pediatric Pulmonology in 2008)[6] within 14 days before enrollment

*1 FVC will be predicted using the following formula:

FVC prediction: $2.108 + (-0.1262) \times \text{age (years)} + 0.00819 \times \text{age (years)}^2 + (-3.118) \times \text{height (m)} + 2.553 \times \text{height (m)}^2$

(3) Patients who continuously use mechanical ventilation (except for use while sleeping)

(4) Patients with a left ventricular EF of < 40% or left ventricular FS of < 25% on the cardiac ultrasonography (echocardiography) performed within 14 days before enrollment

(5) Patients who have been confirmed to have clinically significant symptoms of cardiac failure or respiratory failure

(6) Patients receiving immunosuppressive medications (other than corticosteroids for DMD treatment)
(7) Patients who have used COX-1 or COX-2 inhibitors, or NSAIDs during 7 days before the 6MWD test in the screening period
(8) Patients who have a history of surgery that may affect muscle strength or motor function within 6 months before enrollment or who will undergo surgery during the study
(9) Patients who have incurred an injury (trauma/damage) that may affect muscle strength or motor function within 3 months before enrollment or who have an uncured injury (trauma/damage) that may affect muscle strength or motor function at the enrollment
(10) Patients with systemic allergic disease, chronic inflammatory disease, or other diseases that may prevent correct interpretation of efficacy or safety data (excluding allergic rhinitis, localized or mild atopic dermatitis, eczema, etc.)
(11) Patients who have received gene-/cell-based therapy or stop-codon readthrough therapy with antisense oligonucleotides, or who have participated in another clinical trial and received an investigational product within 90 days before investigational product administration in the present study
(12) Participants of another clinical trial or participants of another clinical research or another study in which they may undergo a motor function test during 7 days before a motor function test scheduled in the present study
(13) Patients who have been confirmed to be HBs antigen-, HCV antibody-, or HIV antigen- or antibody-positive before enrollment
(14) The patient's legal representative is unwilling to agree that the patient will use appropriate contraception throughout the study period and for 180 days after the end of the study.
    1) The investigator or subinvestigator will discuss appropriate contraception with the patient and his legal representative, and instruct the patient to avoid pregnancy of a partner without fail using a double barrier method (condom plus diaphragm) or intrauterine contraceptive device throughout the study participation or contraception period if applicable.
(15) Patients who are judged by the investigator or subinvestigator to have brain dysfunction, including intellectual disability, tendency of autism, and attention deficit hyperactivity disorder that may affect the evaluation of motor function
(16) Patients with QTc of 450 msec or more on the 12-lead ECG performed within 14 days before enrollment (corrected by Fridericia’s formula)
(17) Patients who are deemed not eligible for the study by the investigator or subinvestigator for any other reason

4.3 Discontinuation Criteria for Individual Subjects

Subjects who meet any of the following conditions will be withdrawn from investigational product administration:

- An adverse event that, in the opinion of the investigator, requires discontinuation of investigational product administration occurs.
- The subject or his legal representative requests to discontinue participation in the study (investigational product administration) (e.g., withdrawal of consent).
- There is a significant deviation from the study procedures.
- The subject cannot remain in the study because of residence change, hospital change, commitment to other tasks, etc.
- The subject requires persistent use of mechanical ventilation.
- The subject must use walking aids during the efficacy evaluations, including that of motor function.
- The dose was suspended for more than a total of 50 days during the specified administration period (missed dose[*1] will also be included; missed dose in a morning or evening will be counted as 0.5 days of dose suspension).

  *1 Only the missed dose of all tablets per dose will be counted.
- The investigator deems it necessary to discontinue the subject from the study for any other reason.

5. Evaluations and Tests in the Study

Evaluations and tests to be performed in the study are listed in Table 5-1. In addition, a detailed implementation schedule for clinical assessments at each visit is shown in Table 1.

All information specified in the protocol shall be recorded. Data from any evaluation/test performed as specified within 14 days before enrollment can be used as screening data, even if obtained before informed consent.

Table 5-1 Medical Evaluations/Tests

Written informed consent and assent Consent to study participation Legal guardian (legal representative): required, patient: whenever possible			
Subject ID code assignment			
Day of diagnosis of DMD determined • Day of diagnosis of dystrophinopathy determined (Day of diagnosis determined based on dystrophin genetic test or muscle pathology) • Clinical symptoms or signs characteristic to DMD and symptoms of progressive walking difficulty (e.g., proximal muscular weakness, waddling gait, Gowers sign)			
Subject characteristics Gender Body weight Current medication History of steroid use Rehabilitation status	Date of birth (age) Motor function (6MWD) Previous/present participation in clinical researches Previous medical history	Height History of surgery Previous participation in clinical trials Concurrent illness	
Patient enrollment		Investigational product accountability (subject medication diary)	
Medical examination (medical interview, inspection, auscultation, palpation)			
Blood pressure (systolic, diastolic), pulse rate, body temperature (axilla)			
ECG 12-lead ECG (at rest)		Heart rate, QTcF interval, findings	
Hematology Red blood cell count White blood cell count Eosinophils	Hemoglobin Basophils	Hematocrit Lymphocytes	Platelet count Neutrophils Monocytes
Biochemistry Total protein Direct bilirubin LDH Cystatin C Triglycerides Sodium (Na) Magnesium (Mg)	Albumin AST CK Creatinine (Cre) Total cholesterol Potassium (K) Phosphate (P)	A/G ALT γ-GTP Glucose (blood sugar) HDL-C Chlorine (Cl)	Total bilirubin ALP BUN Uric acid CRP Calcium (Ca)
Endocrinology Cortisol	ACTH		
Urinalysis Protein	Glucose	Urobilinogen	
Cardiac ultrasonography (echocardiography) EF,FS			
Concomitant medication/therapy		Evaluation of adverse events	
Motor function 6MWD test, time to rise from the floor test, Timed 10-m walk/run test, Timed Up & Go test			
Evaluation of muscle volume Skeletal muscle CT		BIA	
Lean body mass			
Quantitative muscle strength assessments Measured with a hand-held dynamometer (hip flexion/extension, knee flexion/extension, ankle extension/flexion)			
Pulmonary function test Measured with a spirometer (measured VC, FVC,* FEV1.0, and FEV1.0%) *Only FVC (including measured value, predicted value, and % of predicted value) will be measured during the screening period.			
Pharmacodynamic and exploratory evaluations (pooled urine) Urine tetranor-PGDM and tetranor-PGEM concentrations, urine creatinine and creatine concentrations [Creatine in urine (%) *1], urine volume (urine specific gravity and urine weight)*2			

*1 Creatine in urine (%) will be calculated by the sponsor based on the urine creatinine concentration, urine creatine concentration, and urine volume described on the case report form (CRF).

*2 Urine volume (mL) will be calculated from the urine specific gravity (g/mL) and urine weight (g) measured at the study site and recorded on the CRF at the study site.

5.1 Study Procedures

The results of the evaluations/tests in Sections 5.1.1 to 5.1.13 must be recorded in the source documents of subjects. The muscle volume in the skeletal muscle CT and the urine tetranor-PGDM and tetranor-PGEM concentrations in the pharmacodynamic evaluation will be measured and recorded by the muscle volume evaluation committee and the Pharmacokinetics Research Laboratories, respectively.

5.1.1 Informed Consent

Informed consent will be obtained from the legal representative of the patient, and assent from the patient whenever possible, within 14 days before enrollment (screening period), followed by eligibility confirmation.

5.1.2 Subject ID Code Assignment

Subject ID code will be assigned after obtaining written informed consent at the study site. Subject ID code shall be composed of the study site number (2 digits) - order of informed consent obtained at each site (2 digits) (e.g., study site number 0X and order of informed consent obtained 1st: 0X-01).

5.1.3 Subject Characteristics

The necessary items for subject characteristics shown in Table 5-1 will be entered in the CRF within 14 days before enrollment.

5.1.4 Motor Function/Muscle Volume/Lean Body Mass/Muscle Strength Evaluations and Pulmonary Function Test

Motor function, muscle volume, and muscle strength evaluations and pulmonary function test will be performed for all subjects at the time points specified in the clinical assessment schedule in Table 1.

Skeletal muscle CT will be performed as a muscle volume evaluation. Diagnostic radiology central review (measurement and evaluation) will be performed by the muscle volume evaluation committee in accordance with a separately specified procedure.

5.1.5 Pregnancy Test

This test is not applicable, because the target population is male pediatric patients.

5.1.6 Drug Accountability

The investigator or subinvestigator will collect the subject medication diary at each visit and confirm the accountability of TAS-205 by medical interview, checking medication records in the subject medication diary, etc., from the start to end of the administration. If the subject medication diary is left behind at home, it may be collected at the subsequent visit. Confirmed drug accountability will be recorded on the CRF in reference to the “Instructions for Completing the CRFs and Making Changes or Corrections to the CRFs.”

Any subject who consults another department or hospital for other diseases will inform his treating physician of his participation in this study. Any subject who is required to use other medications after the consultation will be instructed to inform the investigator or subinvestigator.

5.1.7 Blood Pressure, Pulse Rate, Body Temperature, Height, and Body Weight

Data on blood pressure, pulse rate, body temperature, and body weight will be collected at the time points specified in Table 1 and Section 5.1.10. Height will measured only during the screening period to calculate predicted FVC, an exclusion criterion.

Blood pressure and pulse rate will be measured after the subject is confirmed to be at rest in a supine or sitting position for several minutes, and the measurement on the efficacy evaluation day will be performed before the evaluation. Pulse rate, blood pressure, and body temperature will always be measured at the same site of the same arm whenever possible. The measurement will be immediately repeated if any abnormality is observed. Any clinically significant change from baseline will be recorded as an adverse event specified in Section 12.1.

5.1.8 ECG, Cardiac Ultrasonography (Echocardiography)

The investigator or subinvestigator will be responsible for assessment of the result of ECG and cardiac ultrasonography (echocardiography).

The measurement will be performed after the subject is confirmed to be at rest for several minutes. The measurement on the efficacy evaluation day will be performed before the evaluation. Any clinically significant change from baseline must be recorded as an adverse event specified in Section 12.1. Data on 12-lead ECG at rest will be collected at the time points specified in Table 1 and Section 5.1.10.

5.1.9 Laboratory Values

The investigator or subinvestigator must evaluate all laboratory values to determine whether they are clinically significant events.

Laboratory tests will be performed while subjects are at rest and fasted whenever possible. The measurement on the efficacy evaluation day will be performed before the evaluation.

Any laboratory value determined to be clinically significant shall be followed up and reported as an adverse event specified in Section 12.1. In addition, the laboratory value will be repeatedly evaluated until the value resolves to baseline level or becomes resolving, or is determined to be difficult to follow-up due to a reason described in Section 12.1.7, “Follow-up of Adverse Events.”

Outline of the laboratory parameters is shown in Table 5-1.

As shown in Section 11.7.1, only the serum CK concentration during the hospitalization period will be used for the efficacy evaluation.

5.1.9.1 Hematology

Blood samples for hematology will be collected at the time points specified in Table 1 and Section 5.1.10.

5.1.9.2 Biochemistry

Blood samples for biochemistry will be collected at the time points specified in Table 1 and Section 5.1.10.

5.1.9.3 Endocrinology

Blood samples for endocrinology will be collected at the time points specified in Table 1 and Section 5.1.10 (during the hospitalization only).

5.1.9.4 Urinalysis

Urine samples for qualitative urinalysis will be collected at the time points specified in Table 1 and Section 5.1.10.

5.1.10 Timing for Individual Evaluations/Tests

- Screening period (for eligibility confirmation): Performed within 14 days before enrollment
- Baseline period (for baseline evaluation): Performed within 14 days after enrollment
- Administration period:
  - Day 4: Performed within ± 1 day (pooled urine may also be started on Day 4 ± 1 day)
  - Day 6: Performed on the day
  - Day 15: Performed within + 5 days[*1]

    *1 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.
  - Day 29: Performed within ± 5 days
  - Day 57, 127: Performed within ± 7 days
  - Day 85, 169: Performed within ± 7 days (if hospitalization is within the permissible range of ± 7 days)
- Follow-up period: Follow-up test (21 days after the end of investigational product administration): Performed within ± 7 days

5.1.11 Concomitant Medication/Therapy

Information on all medications (prescribed and over-the-counter drugs) and therapies concomitantly used during the time from the informed consent to the end of the follow-up test will be collected. This will include information on the medications used for treatment of adverse events or serious adverse events. Test or diagnostic agents, or solvents or solutions for injections need not to be recorded on the CRF. The current concomitant medications will be recorded in the source documents.

5.1.12 Report of Adverse Events

As shown in Table 1, at each visit from the informed consent to the end of the follow-up test and during the hospitalization period, presence of any unfavorable medical event (adverse event or serious adverse event), including adverse drug reaction, will be confirmed. Any serious adverse event developed will be reported in accordance with the procedure presented in Section 12.2.2.

The investigator or subinvestigator will report to the sponsor after the end of the follow-up period any serious medical event reported or observed, including adverse event and death, for which relationship with the investigational product cannot be ruled out.

5.1.13 Sampling for Pharmacokinetic and Pharmacodynamic Analyses

The pharmacokinetics of TAS-205 will not be evaluated in this study. Details of sampling for pharmacodynamic analysis are provided in Section 8.2.

5.2 Evaluation/Test Parameters for Individual Visits

5.2.1 Screening Period

5.2.1.1 Before Enrollment (Day -14 to Day -1)

- Informed consent/assent
- Subject ID code assignment
- Subject characteristics (evaluation items are shown in Table 5-1 Medical Evaluations/Tests)
- Day of diagnosis of DMD determined
- Medical examination
- Pulse rate, blood pressure, body temperature
- Hematology, biochemistry
- Urinalysis
- 12-lead ECG (Heart rate, QTcF interval, findings)
- Cardiac ultrasonography (echocardiography)
- Pulmonary function test [FVC (measured value, predicted value, and % of predicted value) only]
- Motor function evaluation (6MWD only)
- Evaluation of adverse events
- Concomitant medication/therapy

5.2.2 Baseline Period

- Hospitalization, medical examination, investigational product prescription, and explanation for/supply of subject medication diary
- Pulse rate, blood pressure, body temperature, and body weight
- Hematology, biochemistry, endocrinology
- Urinalysis
- 12-lead ECG (heart rate, QTcF interval, findings)
- Pulmonary function test
- Motor function/muscle volume (skeletal muscle CT, BIA)/muscle strength evaluation
- Lean body mass
- Urine creatine concentration measurement (pooled urine)
- Urine tetranor-PGDM/-PGEM concentrations, urine creatinine concentration, urine volume measurement (pooled urine)
- Evaluation of adverse events
- Concomitant medication/therapy

5.2.3 Evaluation During the Investigational Product Administration Period (Excluding Hospitalization Period)

- Medical examination, additional prescription of the investigational product
- Pulse rate, blood pressure, body temperature, and body weight
- Hematology, biochemistry
- Urinalysis

- 12-lead ECG (Heart rate, QTcF interval, findings)
- Pulmonary function test
- Muscle volume evaluation (BIA only)
- Lean body mass
- Evaluation of adverse events
- Concomitant medication/therapy
- Current administration of the investigational product [collection of empty boxes of the investigational product (as needed) and subject medication diary as well as drug accountability check using subject medication diary]

5.2.4 Evaluation During (Hospitalization Period) and at the End of the Investigational Product Administration Period

- Hospitalization, medical examination, additional prescription of the investigational product
- Pulse rate, blood pressure, body temperature, and body weight
- Hematology, biochemistry, endocrinology
- Urinalysis
- 12-lead ECG (Heart rate, QTcF interval, findings)
- Cardiac ultrasonography (echocardiography)
- Pulmonary function test
- Motor function/muscle volume (skeletal muscle CT, BIA)/muscle strength evaluation
- Lean body mass
- Urine creatine concentration (pooled urine)
- Urine tetranor-PGDM/-PGEM concentration measurement (pooled urine), urine creatinine concentration measurement (pooled urine): Day 4 in the initial hospitalization, the day after hospitalization in the 2nd hospitalization, and the day after hospitalization in the 3rd hospitalization
- Evaluation of adverse events
- Concomitant medication/therapy
- Current administration of the investigational product [collection of empty boxes of the investigational product, unused investigational products (at the end of the period), and subject medication diary as well as drug accountability check using subject medication diary]

5.2.5 Evaluation in the Follow-up Period (Follow-up Test, Discontinuation Test)

Follow-up test before the end of the study (including discontinuation test) will be performed 21 days after the last dose of the investigational product (permissible range: standard ± 7 days). In addition, data on any adverse event developed at and after the follow-up test that is determined to be related to the investigational product will be reported.

- Medical examination
- Pulse rate, blood pressure, body temperature, and body weight
- Hematology, biochemistry, endocrinology[*1]

*1 Endocrinology will be performed only if an abnormal change (adverse event) is observed in the test on the discharge day of the 3rd hospitalization.

- Urinalysis
- 12-lead ECG (Heart rate, QTcF interval, findings)
- Cardiac ultrasonography (echocardiography)
- Evaluation of adverse events (including confirmation of presence of the follow-up of adverse events)
- Concomitant medication/therapy
- Collection of empty boxes of the investigational product, unused investigational products, and subject medication diary (only if previously uncollected)

6. Investigational Product

The sponsor will provide TAS-205 and control (placebo) until the end of the study period.

6.1 Name of the Investigational Product, etc.

The physical and chemical properties of the active ingredient of TAS-205 are shown in Table 6.1-1 and Table 6.1-2.

Table 6.1-1 Overview of TAS-205 [Study Drug]

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

Table 6.1-2 Overview of Control (Placebo)

Dosage form	Oral placebo tablet identical to TAS-205 in appearance
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

6.2 Packaging and Labeling of the Investigational Product

The investigational product label will include the following information:

(1) Sponsor name
(2) Sponsor address
(3) Storage
(4) Quantity
(5) Product number

[redacted]

6.3 Management of the Investigational Product

The investigational product storage manager at the study site will manage all investigational products provided to the site in accordance with the ICH and applicable regulatory requirements in Japan. The investigational product storage manager at the study site will follow the "Written Procedure for Management and Handling of Investigational Products." All investigational product prescriptions will be recorded in the investigational product accountability log.

The investigational product will be used only in this study.

6.4 Instruction to Subjects Regarding the Handling of the Investigational Product

The investigator will instruct each subject and his legal representative to take the investigational product in a specified method during the study period. If the subject or his legal representative does not follow the specified method, the investigator or sponsor may discontinue the subject's participation in the study. The subject's drug accountability will be confirmed by reference to the record in the investigational product accountability log and the consistency with the subject medication diary or source documents.

The investigator will instruct each subject and his legal representative regarding the handling of the investigational product as follows:

- Store the investigational product at room temperature (1 to 30°C).
- Take necessary number of tablets from the PTP sheet at the time of medication and take them without crushing, with several cups of cool or lukewarm water.
- Do not take tablets for next medication from the PTP sheet in advance.
- Take the investigational product within 30 minutes after meals (breakfast and dinner), with approximately 8-hour or more interval between breakfast and dinner whenever possible.
- Take the investigational product as scheduled.
- When visiting the study site from afar, bring the investigational product to take after meals of the day without fail, if applicable.
- When eating out during the administration period (all meals excluding those at home), bring the investigational product to take after meals of the day without fail.
- Do not take missed doses of the investigational product, but indicate and report them in the subject medication diary. Return the missed doses of the investigational product to the study staff as unused investigational product.
- Return the empty boxes of the investigational product (including empty packages and sheets) to the study staff not only at the end of the study (at the follow-up test), but also at applicable time points (visits).
- When vomited after taking the investigational product, do not additionally take the amount vomited.

- Keep the investigational product in a place safe and out of reach of children other than the subject.
- Do not discard, but store all unused investigational product appropriately until recovery. Record and report any lost investigational product (especially the lost date and time, number of tablets lost, etc.) in the subject medication diary.

7. Method of Administration

Subjects will receive the investigational product orally twice daily for 24 consecutive weeks, with the first dose after dinner on Day 1 and the last dose after breakfast on the efficacy evaluation day at Week 24, until the end day of the study or the subjects meet any of the discontinuation criteria specified in Section 4.3.

The administration of the investigational product will be started within 14 days after enrollment (Day 1) (if Note 14 in Table 1 is applicable, the administration may be started within up to 16 days after enrollment). Any suspended or missed dose during the administration period will not be administered later than administration after breakfast on the efficacy evaluation day at Week 24.

7.1 Administration Procedures

7.1.1 Method of Administration

The investigational product will be initially prescribed before start of the administration after hospitalization in the baseline period (Day -2 to before start of the first dose on Day 1) under management of the subject's legal representative (the study staff may manage the prescribed investigational product for each subject during hospitalization).

Subjects will receive the investigational product under management of their legal representatives or study staff (the subject or his legal representative will record drug accountability in the subject medication diary at each medication), without crushing, with cool or lukewarm water. Since the number of tablets per dose differs by subject, the amount of water to be taken with the tablets will not be specified, but kept sufficient. The number of tablets of the investigational product corresponding to the dosage by body weight within 14 days before enrollment shown in Table 7.1.1-1 will be administered within 30 minutes after breakfast and dinner. The time for administration per dose (time from the 1st to last tablet administration per dose specified) will be within 5 minutes whenever possible.

No dose increase/decrease will be considered (re-calculated) according to body weight increase/decrease during the study in any of the 3 groups.

The investigational product will be additionally prescribed in accordance with Table 3.2-1.

For hospitalization within the permissible range of standard hospitalization day at Week 24 (Day 167) ± 7 days (Day 160 to Day 174), the investigational product will not be administered after the efficacy evaluations.

Table 7.1.1-1 Dosage of the Investigational Product by Body Weight (Within 14 Days Before Enrollment)

Treatment group	Body weight before enrollment	Dosage (mg/dose)	Dosage[*1] (mg/kg/dose)	Number of tablets/dose		
				TAS-205 50 mg tablet	Placebo tablet	Total
Low-dose group	≥ 7.5 kg and < 15 kg	100	6.67 ~ 13.33	2	2	4
	≥ 15 kg and < 30 kg	200	6.67 ~ 13.33	4	4	8
	≥ 30 kg and < 45 kg	400	8.89 ~ 13.33	8	8	16
	≥ 45 kg and < 60 kg	600	10.00 ~ 13.33	12	12	24
High-dose group	≥ 7.5 kg and < 15 kg	200	13.33 ~ 26.67	4	0	4
	≥ 15 kg and < 30 kg	400	13.33 ~ 26.67	8	0	8
	≥ 30 kg and < 45 kg	800	17.78 ~ 26.67	16	0	16
	≥ 45 kg and < 60 kg	1200	20.00 ~ 26.67	24	0	24
Placebo group	≥ 7.5 kg and < 15 kg	-	- ~ -	0	4	4
	≥ 15 kg and < 30 kg	-	- ~ -	0	8	8
	≥ 30 kg and < 45 kg	-	- ~ -	0	16	16
	≥ 45 kg and < 60 kg	-	- ~ -	0	24	24

*1 The values are rounded to 2 decimal places.

7.1.2 Criteria for Changing the Administration Plan

If any change in the administration plan is made, necessary items specified in Section 3.2.1 will be entered in the IWRS promptly.

7.1.2.1 Dose Suspension/Resumption Criteria

The dose suspension/resumption criteria are shown in Table 7.1.2.1-1. The dose of the investigational product will be suspended or resumed according to the criteria below. The rationale for the dose suspension criteria is described in Section 14.9.

(1) Dose suspension/resumption procedures

- The investigator or subinvestigator must suspend the dose if any adverse event specified in Table 7.1.2.1-1 occurs.
- After dose suspension, an early subject visit other than the visits specified in this protocol will be scheduled to confirm whether the adverse event is resolved or resolving, for the earliest possible dose resumption.
- Even if the resumption criteria is met, however, the dose cannot be resumed if prolonged dose suspension is determined to be necessary by the investigator or subinvestigator for the safety of the subject.
- The dose may be suspended even in the absence of any adverse event specified in Table 7.1.2.1-1 if the dose suspension is determined to be necessary by the investigator or subinvestigator due to any other adverse event.
- Any dose suspension determined by the investigator shall be recorded with the detailed medical reason/rationale in the source documents.
- Dose suspension determined by the investigator due to the subject's complaint of the number of tablets to be taken will not be permitted.

Table 7.1.2.1-1 Dose Suspension/Resumption Criteria

Item	Dose suspension criteria	Dose resumption criteria
Adverse event	Onset of the following symptoms of glucocorticoid deficiency (severity: any): Hyponatraemia (< 130 mEq/L), hypoglycaemia (< 50 mg/dL), and orthostatic hypotension	Hyponatraemia, hypoglycaemia: Resolved to the baseline level or site reference level and orthostatic hypotension: resolved
	Onset of severe adverse events[a]	Resolving to mild or lower in severity

a Excluding cases in which the relationship with the investigational product is definitely ruled out [e.g., injury associated with the motor function disorder due to DMD (underlying disease), including fractures, sprain, bruise, and contusion]

7.1.2.2 Dose Reduction Criteria

The dose reduction criteria are shown in Table 7.1.2.2-1. The dose of the investigational product will be reduced according to the criteria below. The rationale for the dose reduction criteria is described in Section 14.10.

(1) Dose reduction procedures

- The investigator or subinvestigator must reduce the dose after dose suspension or resumption if any of the dose reduction criteria specified in Table 7.1.2.2-1 is met.
- Even if none of the dose reduction criteria specified in Table 7.1.2.2-1 is met, the dose may be reduced after dose suspension or resumption (including the time of dose resumption) if determined to be necessary by the investigator or subinvestigator due to any adverse event.
- Any dose reduction determined by the investigator shall be recorded with the detailed medical reason/rationale in the source documents.
- Dose increase after dose reduction will not be permitted.
- Any dose reduction shall be recorded with the details of the applicable dose in the source documents.
- Dose reduction for certain reasons of the subject or his legal representative, including complaint about the number of tablets to be taken, will not be permitted.
- Dose reduction only by halving the number of tablets specified will be permitted.
- For subjects administered at a reduced dose, the efficacy and safety will be analyzed as randomized at the enrollment. Any expelled dose or partial dose of the specified number of tablets due to vomiting or other reasons will be assessed as the dose of the specified number of tablets.

Table 7.1.2.2-1 Dose Reduction Criteria

Item (Reason for dose suspension before dose reduction)	Dose reduction criteria	Proportion of dose reduction
Onset of severe adverse drug reactions	Dose suspension (per day) continued for 2 weeks or more[b]	Take half the amount of tablets specified
Onset of severe adverse events[a]	Dose was suspended after the same adverse event specified in the left occurred twice	
Onset of the following symptoms of glucocorticoid deficiency (severity: any): Hyponatraemia (< 130 mEq/L), hypoglycaemia (< 50 mg/dL), and orthostatic hypotension	Dose suspension (per day) continued for 2 weeks or more[b] or Dose was suspended after the same adverse event specified in the left occurred twice	

a: Excluding cases in which the relationship with the investigational product is definitely ruled out [e.g., injury associated with the motor function disorder due to DMD (underlying disease), including fractures, sprain, bruise, and contusion]

b Dose will be suspended for a day if both morning and evening doses fail. 2 weeks or more means a total of 28 or more consecutive morning and evening doses.

7.1.3 Time of Dose Resumption

Subjects who meet any of the dose suspension and dose resumption/reduction criteria specified in Table 7.1.2.1-1 and Table 7.1.2.2-1 may resume administration with the unchanged or reduced dose during the study period.

7.2 Volume of Blood Collected During the Study Period

The volume of blood collected at each time point during the study period (standard) is shown in Table 7.2-1. Total volume of blood collected by each subject will be approximately 80 mL.

Table 7.2-1 Volume of Blood Collected During the Study Period

Item	Number of blood collections	Volume of blood per collection (mL)	Total volume of blood collected (mL)
Laboratory tests	10	Approximately 8	Approximately 80
Total	10	Approximately 8	Approximately 80

7.3 Restrictions

7.3.1 Physical Activity

Subjects will be prohibited from engaging in excessive physical activity, especially excessive exercise (including excessive rehabilitation, gymnastics class, and motor function evaluation in clinical research or a trial that may affect the efficacy evaluations in the study), during 7 days before the physical function evaluations specified for the study period (screening evaluation, baseline evaluation, Week 12 evaluation, and Week 24 evaluation). In addition, subjects will avoid continuous excessive exercise beyond daily activities whenever possible, stay rested and calm, and sleep sufficient hours during the study period. Study staff will instruct the subjects on appropriate levels for these daily physical activities.

7.3.2 Fasting

Subjects will be kept at rest and fasted for 3 to 4 hours (standard) before blood collection for laboratory tests whenever possible.

7.3.3 Foods and Beverages

Subjects will be prohibited from taking the following from 7 days before the start of the investigational product administration to the end of the follow-up test:

- Foods and beverages containing grapefruit or St. John's Wort (including supplements)

7.4 Concomitant Medication/Therapy

7.4.1 Prohibited Concomitant Medications/Therapies

The concomitant medications/therapies specified below will be prohibited during the study period. The rationale is described in Section 14.6.

- Immunosuppressive medications (other than corticosteroids for DMD treatment)
- Persistent use of COX-1 and COX-2 inhibitors (excluding acetaminophen or other drugs that primarily centrally inhibit COX-3) and NSAIDs (temporary use for as-needed or other purpose is permissible)
- Other investigational product/therapy under study (medical device under development, etc.)
- Persistent use of mechanical ventilation (excluding non-persistent use or use while sleeping)

- Use of walking aids other than plantar orthosis (ankle foot orthosis, knee ankle foot orthosis, walker, etc.) in the 6MWD test and other motor function evaluations (use of wheelchair in daily activities is permissible)
- Rehabilitation proposed as a new program that obviously affects the present study (general or daily rehabilitation is permissible)
- Medications continuously used obviously for the improvement of the deterioration of physical function
- Sedatives used for skeletal muscle CT

The following concomitant medications (including temporary use for as-needed or other purpose) or therapies will be completely prohibited during 7 days before the motor function test:

- COX-1 and COX-2 inhibitors and NSAIDs
- Motor function test in another clinical research or trial

7.4.2 Concomitant Medications/Therapies Requiring Precaution

The use of the concomitant medications requiring precaution specified below will be avoided whenever possible; if used, care should be taken, especially when used with the investigational product. The rationale is described in Section 14.7.

- Potent cytochrome P450 (CYP) 3A4 inhibitors including itraconazole, ketoconazole, atazanavir, indinavir, nelfinavir, ritonavir, and saquinavir
- P-glycoprotein (P-gp) inhibitors including ketoconazole, erythromycin, and diltiazem

Concomitant therapies requiring precaution will not be set.

7.4.3 Restricted Concomitant Medications/Therapies

The dosage regimen (dosage and administration) of the following concomitant medications will be restricted during the study period: The rationale is described in Section 14.8.

- Oral steroids for DMD treatment:
  In principle, the prescription-based dosage regimen will not be changed after obtaining informed consent (This will not be applied if the dose must be reduced or suspended due to an adverse event or other reasons, nor will this be applied if change in the dosage regimen for the subject with unexpectedly marked increase in body weight associated with growth is determined to be necessary by the investigator from an ethical viewpoint. Any change in the dosage regimen shall be recorded with the detailed medical rationale/reason in the source documents.).

Restricted concomitant therapies will not be set.

8. Pharmacokinetic/Pharmacodynamic and Exploratory Evaluations

The pharmacokinetics of TAS-205 will not be evaluated in this study. The urine samples for pharmacodynamic evaluation will be collected and treated in accordance with the separately prepared "Procedures for Treatment of Samples for Urine Tetranor-PGDM/-PGEM Concentration Measurement."

8.1 Blood Sampling

Not applicable.

8.2 Urine Sampling

Time points of pooled urine for measurement of individual concentrations and other parameters for pharmacodynamic and exploratory endpoints will be as follows:

- From immediately after waking on the day after initial hospitalization to immediately after waking on the efficacy evaluation day at baseline (the day after start of pooled urine);
- From immediately after waking on Day 4 to immediately after waking on Day 5;
- From immediately after waking on the day after the 2nd hospitalization to immediately after waking on the efficacy evaluation day (Week 12 evaluation); and
- From immediately after waking on the day after the 3rd hospitalization to immediately after waking on the efficacy evaluation day (Week 24 evaluation).

The urine samples will be stored under refrigeration (approximately 4°C) during pooled urine. At each time point of pooled urine described above, parts of the urine will be transferred to urine containers (approximately 4-mL each) and stored frozen (at or below approximately -70°C) at the study site as samples for urine tetranor-PGDM/-PGEM concentration measurement. The frozen samples will then be collected by an externally contracted carrier and analyzed at the Pharmacokinetics Research Laboratories of Taiho Pharmaceutical Co., Ltd.

In addition, at each time point of pooled urine described above, the urine volume (mL) will be calculated from the separately measured urine weight (g) and urine specific gravity (g/mL), and approximately 4-mL each of the urine collected in 2 containers as samples for urine creatinine and creatine concentration measurement at the study site. Urine creatinine and creatine concentrations will be measured at the study site.

For details regarding the collection and treatment of samples for urine tetranor-PGDM/-PGEM concentration measurement, the separately prepared "Procedures for Treatment of Samples for Urine Tetranor-PGDM/-PGEM Concentration Measurement" will be followed.

8.3 Pharmacokinetic Analysis of TAS-205

Not applicable.

8.4 Pharmacodynamic Analysis of TAS-205

The pharmacodynamic analysis is intended to evaluate the inhibitory effect of TAS-205 on PGD_2 production through HPGDS inhibition as the mechanism of the pharmacological effect, based on the measured tetranor-PGDM/-PGEM concentrations in the urine samples (pooled urine). Details of the analytical method will be specified in the Statistical Analysis Plan.

8.4.1 Calculation of Pharmacodynamic and Exploratory Endpoints

Urinary excretion of tetranor-PGDM, urine tetranor-PGDM/Cre concentration ratio, urinary excretion of tetranor-PGEM, and urine tetranor-PGEM/Cre concentration ratio will be calculated as pharmacodynamic endpoints, and urinary creatinine excretion, urinary creatine excretion, and creatine in urine (%) will be calculated and summarized as exploratory endpoints. Any other calculation of pharmacodynamic and exploratory endpoints will be specified in the Statistical Analysis Plan.

8.4.2 Pharmacodynamic and Exploratory Evaluations

The parameters specified below will be evaluated (refer to Section 13.1.3.4, "Analysis of Pharmacodynamic and Exploratory Endpoints") using the pharmacodynamic and exploratory endpoints during pooled urine (refer to Section 8.4.1, "Calculation of Pharmacodynamic and Exploratory Endpoints"). Any evaluation of the detailed analytical method or other parameters will be specified in the Statistical Analysis Plan.

(1) Effect of TAS-205 on the pharmacodynamic and exploratory endpoints

(2) Relationship of pharmacodynamic and exploratory endpoints with efficacy endpoints

8.4.3 Bioanalytical Method in the Pharmacodynamic Analysis

Urine tetranor-PGDM/-PGEM concentrations will be measured using a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) assay at the Pharmacokinetics Research Laboratories of Taiho Pharmaceutical Co., Ltd. Urine creatinine and creatine concentrations will be measured using a validated bioanalytical method at the study site.

The urine tetranor-PGDM-/-PGEM and creatinine concentrations will be measured in all subjects in the placebo, low-dose, and high-dose groups.

9. Pharmacogenomics

Pharmacogenomic research will not be performed in this study.

10. Early Termination or Completion of the Study

10.1 Criteria for Discontinuation of Participation of the Study Site

If the proper conduct of the study is or could be undermined because of significant or continuous non-compliance with GCP or the protocol by the investigator or subinvestigator, the sponsor or the investigator may terminate the study site's participation in the study. In this case, the sponsor or the investigator will report promptly to the Investigational Review Board (IRB) in accordance with the relevant Standard Operating Procedure (SOP) of the study site.

10.2 Criteria for Discontinuation of the Study

The sponsor has the right to discontinue the study, regardless of the timing, for administrative reasons. The sponsor will discontinue the whole or part of the study in an appropriate manner if any condition requiring discontinuation is found during the study. In this case, the sponsor will inform the head of the study site of the decision and the reason promptly in writing. The head of the study site will report the decision to the IRB and the investigator promptly in writing. In addition, the investigator or subinvestigator will notify subjects promptly, and change their therapy. The sponsor will notify the regulatory authorities of discontinuation of the study promptly.

10.3 Investigations for Individual Subjects at Discontinuation

If a subject is discontinued from the study as specified in Section 4.3, “Discontinuation Criteria for Individual Subjects,” the investigator or subinvestigator will take appropriate measures as needed and perform clinical assessments specified for Day 169 (immediately after the end of the administration period) or follow-up test (discontinuation during the follow-up period) (clinical assessments for the safety endpoints) whenever possible. Any adverse event will be followed up whenever possible, as specified in Section 12.1.7, “Follow-up of Adverse Events.”

11. Efficacy Evaluation

Among the efficacy endpoints, the motor function and muscle strength of subjects will be evaluated by the sponsor and the master physical therapist in the study in accordance with the evaluation procedure separately prepared. The muscle volume of subjects and other efficacy endpoints will also be evaluated by the sponsor and the muscle volume evaluator in the study in accordance with the evaluation procedure separately prepared.

For efficacy evaluation of serum CK concentration, only the values measured during the hospitalization period will be used in the evaluation.

11.1 Training and Prior Certification of Evaluators for Individual Study Sites Before Study Initiation

The evaluators for individual study sites in this study will participate in training on the standardization of motor function and other evaluations in advance. In the training, the reliability of the measurement techniques of evaluators will be assessed, and prior evaluator certification will then be awarded accordingly. The evaluators for individual study sites will preferably be physical therapists; however, if there are limited study staff or other reasons, evaluators with experience in caring for patients with DMD (physicians, occupational therapists, etc.) will be acceptable. The standardized evaluation methods will be specified in separate procedure documents.

11.2 Order of the Efficacy Evaluations

The various efficacy evaluations will be performed in each subject in a day in the following order:

(1) Evaluation of muscle volume by BIA, and of lean body mass (evaluations using a body composition monitor; the order of these evaluations will not matter)
(2) 6MWD test
(3) Time to rise from the floor test
(4) Timed Up & Go test
(5) Timed 10-m walk/run test
(6) Quantitative muscle strength assessments

The pulmonary function test, muscle volume evaluation by skeletal muscle CT, and serum CK concentration measurement shall be performed by the start of (2) 6MWD test (before start of the motor function test). The evaluations will, in principle, be performed in a consistent order to avoid difference in the order (for all items) for individual subjects in each evaluation period.

11.3 Evaluation of Motor Function

The need for repetition of each evaluation (data recollection) will be determined by the evaluator. Any repeated evaluation determined to be necessary for reasons described below will be performed whenever possible, taking into consideration the subject's condition, etc. In this case, the measurement data obtained before the repeated evaluation will not be assessed.

Cases judged to require repeated evaluation: Definite non-compliance with the instruction, marked deviation from the track during the test, reversal of direction of the track, discontinuation during the test for reasons other than fatigue, etc.

11.3.1 6MWD Test

The distance the subject can walk as fast as possible in 6 minutes will be evaluated.

The test will be performed using a flat, straight. 25-m track wider than a specified width (a quiet indoor hallway, etc.; the distance will be measured accurately with a tape measure, with marks affixed at both ends and cones placed). The subject will go back and forth along the 25-m distance until completion of the test is announced 6 minutes later (passage time of each 25 m will be recorded). The passage time will be read out to the subject while walking, in a specified timing according to the evaluation procedure. The 6-minute walk distance will be recorded in metric units (distance less than 1 meter will be rounded down). For any subject who falls, information on the time of the fall will be recorded. For details of the preparation, implementation procedures, important points, safety considerations, etc., the evaluation procedure will be followed.

For subjects with 6MWD of less than 75 m in the baseline period, before start of administration in this study, investigational product administration will be started as scheduled (Day 1), and the 6MWD tests after administration (at Weeks 12 and 24) will be performed.

11.3.2 Time to Rise from the Floor Test

The time required for the subject to rise from a supine position on the floor as quickly as possible will be evaluated.

The time from start of rising from a supine position to the judgment of standing up (standing posture with arms parallel to the body) will be measured with a stopwatch (unit: second, time measured to 2 decimal places). There is no time restriction for the test. For details of the preparation, implementation procedures, important points, safety considerations, etc., the evaluation procedure will be followed.

11.3.3 Timed Up & Go Test

This test will assess the extent of the subject's composite mobility, including standing up, walking, repositioning the body, and balancing.

The time required for the subject to stand up from a sitting position on a table (chair), walk to a cone placed 3 m ahead as quickly as possible, and then return to the table will be evaluated.

With the table stabilized against a wall (0-m point will be the front center of the table) and the back of the subject leaning against a backrest (wall) at the start, the time from the start call to the subject's return with his back against the backrest after going around the cone will be measured with a stopwatch (unit: second, time measured to 2 decimal places). There is no time restriction for the test. For details of the preparation, implementation procedures, important points, safety considerations, etc., the evaluation procedure will be followed.

11.3.4 Timed 10-m walk/run test

The time required for the subject to run or walk as quickly as possible a 10 m-wide passage with marks affixed on the floor will be evaluated. The test will be performed using more than a specified width of flat straight line (a quiet indoor hallway, etc.). 10 meters will be measured with a tape measure, and marks affixed to both the 0-m (start line) and 10-m (goal line) ends. With the subject in a standing position just behind the start line at the start, the time from the start call to the subject's leg passing the goal line will be measured with a stopwatch (unit: second, time measured to 2 decimal places). There is no time restriction

for the test. For details of the preparation, implementation procedures, important points, safety considerations, etc., the evaluation procedure will be followed.

11.4 Evaluation of Muscle Volume

11.4.1 Skeletal Muscle CT

To estimate the skeletal muscle volume using muscle CT, muscle volume index (MVI), %MVI, and net muscle volume_CT (nMV_CT), which indicate the cross-sectional area of the middle of a muscle, muscle survival rate (proportion), and CT-based skeletal muscle volume in a given section, respectively, will be used. MVI, which is the cross-sectional area of the middle of a muscle (unit: cm^2), will be measured in both legs. As %MVI, which is intended to estimate the skeletal muscle volume based on the CT values in the cross-section of a middle thigh, the muscle survival rate (proportion of actual muscle in the cross-section of the original muscle, unit: %) will be measured in only 1 leg (right leg in principle) using an estimator.[11)] In addition, nMV_CT, which is the skeletal muscle volume in a given section of the middle thigh (unit: cm^3), will be measured in both legs using an estimator.[11, 12)] All parameters will be measured in the lower leg as well as the middle thigh. The obtained CT images (DICOM data) will be submitted to the sponsor by each study site. Based on the data submitted to the sponsor, the images will be centrally evaluated by the muscle volume evaluator. For details of the measurement method, measured site, and evaluation method, the evaluation procedure will be followed.

11.4.2 BIA

The skeletal muscle volume (unit: kg, 2 decimal places) at the left and right sites (in each limb) will be measured by BIA (TANITA body composition monitor: Inner Scan® 50V model BC-622). Since the lower age limit for skeletal muscle measurement is 6, subjects aged 5 at the baseline evaluation will be handled as those aged 6 for the measurement. For all subjects, the age at the baseline evaluation will be used for the measurement throughout the study period. For details of the measurement method and evaluation method, the evaluation procedure will be followed.

11.5 Lean Body Mass

Lean body mass (kg) will be calculated by deducting the body fat that is calculated from the body fat percentage measured by BIA (TANITA body composition monitor: Inner Scan® 50 V model BC-622) from the body weight. The lean body mass calculation formula shall be as follows: body weight (kg, 1 decimal place) - [body weight (kg, 1 decimal place) × body fat percentage (%, 1 decimal place)] = lean body mass (kg, the value shall be rounded to 1 decimal place).

11.6 Evaluation of Muscle Strength

11.6.1 Quantitative Muscle Strength Assessments

Quantitative muscle strength assessments will be performed using a hand-held dynamometer (Nihon Medix microFET2™; manual muscle measurement/evaluation equipment will be specified). Muscle strength for hip flexion/extension, knee flexion/extension, ankle extension/flexion will be evaluated [measurement unit: newton (N), 1 decimal place]. For details of the preparation, implementation procedures, important points, safety considerations, etc., the evaluation procedure will be followed.

11.7 Other Efficacy Evaluations

11.7.1 Serum CK Concentration

Since CK, a muscle-specific enzyme, is known to leak out of muscle cells of a damaged muscle tissue and is released into the blood, plasma CK concentration may reflect the extent of muscle damage. For this purpose, serum CK concentration will be measured and evaluated using blood samples collected for biochemistry. Only the serum CK concentration measured during the hospitalization period will be used for the efficacy evaluation. The rationale is described in Section 14.1.

11.7.2 Pulmonary Function Test

Noninvasive vital capacity measurement will be performed using a spirometer, and the measured values of VC (unit: L), FVC (unit: L), FEV1.0 (forced expiratory volume in first second, unit: L), and FEV1.0% (percent ratio of FEV1.0 to FVC; FEV1/FVC, unit: %) will be evaluated.

12. Safety Evaluation

12.1 Adverse Events

12.1.1 Definition of Adverse Event

An adverse event is defined as any unfavorable medical event that occurs in a subject participating in the study, regardless of whether it is considered related to the investigational product.

A diagnosis will be recorded as an adverse event wherever possible. If no definite diagnosis can be established, signs or symptoms will be recorded.

Symptoms associated with DMD or concurrent illnesses and abnormal laboratory or other test findings that have been present since before the study initiation will not be assessed as adverse events. However, any new symptoms or worsening of concurrent illnesses will be assessed as adverse events.

All clinically or medically significant abnormal test values will be reported as adverse events. Symptoms derived from a diagnosis already reported as an adverse event by the investigator or subinvestigator will not be assessed as adverse events.

Abnormal laboratory test values assessed as adverse events are:

- those requiring medical treatment
- those requiring prolonged administration, discontinuation, or dose reduction of the investigational product
- those deemed medically significant by the investigator or subinvestigator for any other reason

For report on the follow-up of pregnancy of the subject's partner or definition and report of medication errors, misuses, and drug interactions, refer to Section 12.7, "Other Information."

Adverse events will be evaluated from the time of informed consent, while those developed or worsened after start of investigational product administration will be collected on the CRFs. For any other details of recording, the "Instructions for Completing the CRFs and Making Changes or Corrections to the CRFs" will be referred to.

For each efficacy evaluation parameter (serum CK concentration will be applicable only during the hospitalization period), any clinically or medically significant change will not be assessed as adverse event.

12.1.2 Severity of Adverse Events

One of the following severities of adverse events will be selected and evaluated [semicolon (;) means "or"]:

Mild:

Mild; no symptom or mild symptom; only clinical or test finding; requiring no treatment

Moderate:

Moderate; requiring minimum/local/non-invasive treatment; limiting age-appropriate activities of daily living except for self-care*

Severe:

Severe or medically significant, but not immediately life-threatening; requiring hospitalization or prolongation of existing hospitalization; disability; limiting self-care activities.** An event leading to

life-threatening consequences or requiring emergency intervention, or death due to adverse event is also assessed as severe.

* "Activities of daily living except for self-care" refers to meal preparation, shopping for daily goods and clothing, use of a telephone, financial management, etc.

** "Self-care activities" refers to bathing, dressing/undressing, food intake, use of a bathroom, and oral drug intake without being bedridden.

12.1.3 Causal Relationship to the Investigational Product

The causal relationship of an adverse event to the investigational product will be assessed as one of 2 categories as described below, based on various factors (e.g., the subject's condition, previous medical history, concomitant medications, temporal association between investigational product administration and the onset of the adverse event).

(1) There is a reasonable possibility: The onset of the adverse event is temporally associated with investigational product administration, and meets any of the following conditions:
- The event resolved by dose suspension: The event improved or resolved after (temporary or permanent) suspension of investigational product administration.
- The event recurred after dose resumption: The event recurred after resumption of investigational product administration.
- The event cannot be explained reasonably based on the subject's clinical symptoms and/or therapies other than the investigational product.
- The event is known to occur, although scarcely, after medication (e.g., angioedema, Stevens-Johnson syndrome).

(2) There is no reasonable possibility: There is no evidence of causal relationship of the adverse event to the investigational product.

The adverse event is assessed to have no reasonable possibility under the following conditions:
- The adverse event occurred before administration of the investigational product.
- There is no reasonable possibility that the administration of the investigational product caused the adverse event.
- The onset of the adverse event is not temporally associated with investigational product administration, and may be due to concurrent illness, concomitant medications, clinical symptoms, etc., of the subject

12.1.4 Definition of Adverse Drug Reaction

An adverse event (including an abnormal laboratory value) assessed by the investigator, subinvestigator, or the sponsor as reasonably related to the investigational product will be regarded as an adverse drug reaction in this study.

12.1.5 Outcome of Adverse Events

(1) Resolved: The symptom or finding resolved or returned to the baseline level.

(2) Resolving: The symptom or finding nearly resolved or returned to the baseline level.
(3) Not resolved: The symptom or finding is unchanged with no resolve.
(4) Resolved with sequelae: The symptom resolved, but with evidence of adverse event-related dysfunction interfering with daily life.
(5) Death: The subject died due to the adverse event.

12.1.6 Reporting of Adverse Events

Adverse events will be reported from the day of informed consent by the subject's legal representative or the subject to the end of the evaluation in the follow-up test described in Section 5.2.5. All adverse events will be recorded in the source documents.

Any adverse event determined to be related to the investigational product by the investigator or subinvestigator will be collected, regardless of the time of onset.

12.1.7 Follow-up of Adverse Events

If an adverse event occurs, the investigator or subinvestigator will take appropriate measures immediately and follow up the event until it is confirmed to have resolved or to be resolving. If follow-up of an adverse event cannot be continued for any of the reasons listed below, the reason will be described on the CRF.

- The causal relationship between the event and the investigational product cannot be determined due to another treatment given to the subject.
- Further follow-up is impossible, due to hospital change, etc.
- The subject and his legal representative refuse follow-up.
- The subject died.
- The adverse event is not resolved or resolving, but the investigator or subinvestigator concludes that the event is stable or there will be no further improvement.

12.2 Serious Adverse Events

12.2.1 Definition of Serious Adverse Event

A serious adverse event is defined, regardless of the dosage of the investigational product, as any adverse event that:

(a) Results in death.
(b) Is life-threatening.
Note: "Life-threatening" serious adverse event refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
(c) Requires hospitalization or prolongation of existing hospitalization for the treatment. However, the following will not be assessed as hospitalization in the evaluation of seriousness of adverse events:
- Visit to the emergency department less than 24 hr after the event
- Previously scheduled hospitalization
- Hospitalization to receive tests related to the study
(d) Results in persistent or significant disability/incapacity.

(e) Results in congenital anomaly/birth defect. (where exposure to the investigational product immediately before or during pregnancy adversely affected the fetus)

(f) Is an important medical event.

Note: This refers to an important medical event that is not immediately life-threatening or fatal, or does not result in hospitalization, but may expose the subject to danger or require intervention or treatment to prevent the results described in above (a) to (e).

This includes, for instance, allergic bronchospasm requiring intensive care at the emergency department, home, etc.; blood disorder or spasm that does not result in hospitalization; and drug dependence or abuse.

12.2.2 Reporting of Serious Adverse Events

Serious adverse events will be reported to the sponsor within 24 hr from the time the investigator or subinvestigator first becomes aware of the event. The causal relationship and seriousness shall be carefully determined, and the comprehensive information obtained at the first reporting of the event (e.g., clinical course, previous medical history, concomitant medications) reported.

After the first reporting of the serious adverse event to the sponsor, any significant additional information on the event (diagnosis, outcome, evaluation of the causal relationship, certain test results, etc.) will be reported whenever it is obtained.

The investigator will respond to any request for further necessary information by the sponsor, the head of the study site, or IRB.

All serious adverse events that occur during the study period will be reported to the sponsor.

Any serious adverse event (including death) that occurs outside the study period will be reported to the sponsor only if the relationship of the event to the investigational product is indicated by the investigator.

[Emergency contact (sponsor)]

Clinical Development Division, Taiho Pharmaceutical Co., Ltd.

[redacted]

(from 8:40 am to 5:30 pm, except weekends, holidays, and December 29 to January 4)

After office hours, contact the product leader or clinical team leader.

For contact information of the product leader and clinical team leader, see the attachment.

12.2.3 Follow-up of Serious Adverse Events

If a serious adverse event occurs, the investigator or subinvestigator will take appropriate measures and follow up the event until it is confirmed to have resolved or to be resolving. If follow-up of a serious adverse event cannot be continued for any of the reasons listed below, the reason will be recorded on the Serious Adverse Event Report and CRF.

- The causal relationship between the event and the investigational product cannot be determined due to another treatment given to the subject.
- Further follow-up is impossible, due to hospital change, etc.
- The subject and his legal representative refuse follow-up.

- The subject died.
- The serious adverse event is not resolved or resolving, but the investigator or subinvestigator concludes that the event is stable or there will be no further improvement.

12.3 Worsening of Underlying Disease

Worsening of underlying disease will not be used as an adverse event term. For worsening of underlying disease, the associated signs, symptoms, or concurrent illnesses will be reported as adverse events, or as serious adverse events if any of the seriousness criteria are met. In any case, the relationship of the signs, symptoms, or concurrent illnesses to the worsening of underlying disease will be clarified.

12.4 Reporting of Death

Any death, including that due to worsening of underlying disease, during the study period will be reported to the sponsor within 24 hr from the time the investigator or subinvestigator first becomes aware of the event, following the same procedure as for serious adverse events.

Since death is an outcome of an adverse event, it will not be used as an adverse event or serious adverse event term.

12.5 Adverse Events of Special Interest

12.5.1 Definition of Adverse Events of Special Interest

Adverse events of special interest will not be defined in this study.

12.6 Predictability

Since no serious adverse drug reactions have occurred with TAS-205, all adverse events that occur in this study will be handled as “unexpected” events.

12.7 Other Information

12.7.1 Follow-up of Pregnancy

Any pregnancy or outcome of the pregnancy of a subject’s partner during participation in this study that is found by the investigator or subinvestigator will be reported promptly.

The information on pregnancy will be recorded on a pregnancy evaluation sheet and reported to the sponsor via e-mail or fax.

Any new information and/or correction of the previous information obtained after submission of the pregnancy evaluation sheet will be newly recorded on another pregnancy evaluation sheet and reported to the sponsor via e-mail or fax.

The investigator or subinvestigator will follow up the pregnancy of the subject’s partner and report the outcome. Outcome of the pregnancy such as stillbirth, congenital disorder/birth defect, or serious maternal event, will be reported to the sponsor as a serious adverse event. In addition, the investigator or subinvestigator will follow up the child and convey any information indicative of involvement of the investigational product to the sponsor even after study completion.

12.7.2 Medication Errors

In this study, a medication error is defined as any unintended error, for instance, in the prescription, dispensing, or administration of the investigational product, that occurs under the management of a health

care provider or a subject. Medication errors may occur in association with administration of a different drug, property or administration route of the investigational product, or dosage or number of doses specified in the protocol.

The following procedure shall be followed:

The investigator or subinvestigator will report any medication error with TAS-205 that occurs, regardless of the onset of adverse events (even if the definition of a serious adverse event is not met), to the sponsor promptly.

12.7.3 Misuse

In this study, misuse is defined as any intended misuse of the investigational product (including abuse and use of more than the right dose) that increase risks. Any intended administration of the investigational product to subjects for whom the product is contraindicated will also be included. Any misuse found by the investigator or subinvestigator will be reported to the sponsor promptly.

12.7.4 Drug Interaction

In this study, drug interaction is defined as any interaction that occurs between the investigational product and concomitant medications affecting the pharmacokinetic profile and/or efficacy/adverse drug reactions, meals, or lifestyle habits (e.g., smoking, alcohol intake), etc. Any drug interaction found by the investigator or subinvestigator will be reported to the sponsor promptly.

13. Statistical Analysis

Statistical analysis will be performed in accordance to the plan described below. Details be specified in a separately prepared Statistical Analysis Plan.

13.1 Analysis Plan

13.1.1 Timing of Statistical Analysis

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

13.1.2 Analysis Sets and Criteria for Handling Subject Data

13.1.2.1 Analysis Sets

The analysis sets in this study are defined as below.

Table 13.1.2-1 Definition of Analysis Sets

Analysis set	Definition
Enrolled subjects	All subjects enrolled in the study
Subjects administered the investigational product	All enrolled subjects who received at least 1 dose of the investigational product
Full Analysis Set (FAS)	All subjects administered the investigational product 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 (administration 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 inclusion in the analysis sets, the handling of such subject will be determined through discussion between the sponsor and the medical expert before data lock.

13.1.2.2 Criteria for Handling Subject Data

The criteria for handling subject data in this study are shown below.

If it is questionable beyond the criteria shown below 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 code breaking.

(1) 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.

(2) Deviation from investigational product assignment
- 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 subjects administered the investigational product or PPS.
- In the analysis of FAS, the data will be handled as data for the randomized investigational product.

13.1.3 Statistical Analysis Methods

The methods of main statistical analyses for the primary and secondary purposes of this study are described below.

13.1.3.1 Subject Disposition and Characteristics

(1) Subject disposition
- The number of subjects randomized to each group will be totaled in a manner so as to clarify inclusion of subjects in each analysis set, and a list of subjects excluded from each analysis set will be provided with the reason for exclusion.

(2) Subject characteristics
- For each analysis set, excluding enrolled subjects, distribution of main subject and disease characteristics will be summarized.

13.1.3.2 Analysis of the Primary Endpoint

The following analyses will be performed for the primary endpoint, defined as the change from baseline in 6MWD at Week 24:

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

(2) Sensitivity analysis for the primary analysis
- The analysis described in (1) will be performed in the FAS.

(3) Secondary analyses of the primary endpoint

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

- 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.
- 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.
- 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.

13.1.3.3 Analysis of the Secondary Endpoints

13.1.3.3.1 Efficacy Analysis

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

(1) 6MWD

- Summary statistics will be calculated at each time point for each treatment group.
- A 2-sample t-test will be performed between each treatment group and placebo group at Week 12. This analysis will be performed with and without the LOCF imputation.
- The time course by each time point will be plotted for each treatment group.

(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%):

- 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. This analysis will be performed with and without the LOCF imputation.
- The treatment effect will be estimated using the MMRM.
- 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 time course by each time point will be plotted for each treatment group.

13.1.3.3.2 Safety Analysis

The analyses described below will be performed in subjects administered the investigational product for each treatment group.

(1) Adverse events

- The incidence of adverse events will be calculated.
- For each adverse event type, the number and proportion of subjects with adverse events will be calculated by severity.

- 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 the outcome 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

- For each laboratory parameter, summary statistics at each evaluation time point will be shown.
- 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 shown.
- 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 shown.
- For each QTcF interval will be categorized, the frequency at each evaluation time point will be tabulated.
- Change in QTcF interval from immediately before Day 1 dose will be categorized, and for each category, the frequency at each evaluation time point will be tabulated.
- The proportion of subjects with abnormal change in 12-lead ECG and the two-sided 95% confidence interval will be calculated. A list of subjects with abnormal change in 12-lead ECG will also be created.

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

- For systolic blood pressure, diastolic blood pressure, pulse rate, and body temperature (axilla), summary statistics at each evaluation time point will be shown.
- For 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 shown.
- 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.

13.1.3.4 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:

- 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. This analysis will be performed with and without the LOCF imputation.
- The treatment effect will be estimated using the MMRM.
- 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 correlation coefficient (Pearson, Spearman) between the change rate from baseline at each time point in each treatment group and the change from baseline in each item specified in (1) and (2) of Section 13.1.3.3.1 will be calculated.
- The time course by each time point will be plotted for each treatment group.

13.1.3.5 Current Administration

The following analyses by treatment group will be performed in subjects administered the investigational product:

(1) Current administration

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

(2) Completed administration

- Summary statistics of the administration rate of TAS-205 will be calculated.
- The rate of completed administration of TAS-205 (proportion of subjects who were administered TAS-205 as in a specified schedule) will be calculated.
- The presence or absence of and the reasons for study discontinuation will be summarized.

13.1.4 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.

14. Rationale

14.1 Rationale for the Endpoints

The 6MWD test, used for the measurement of the primary endpoint, is a self-paced test that has achieved a global consensus in the statement of the American Thoracic Society (ATS) in 2002.[13] The test was developed for evaluation of motor function in patients with metabolic or cardiopulmonary diseases.

In the field of DMD in Japan, the *Practical Guideline for Duchenne Muscular Dystrophy (DMD) 2014* was published in 2014 jointly by the Muscular Dystrophy Clinical Trial Site Preparation and Comprehensive Practical Guideline Research Group, the Japanese Society of Neurology, and the Japanese Society of Child Neurology, while no guidelines for clinical evaluation have been created yet. Similarly, no firm guidelines for clinical evaluation recommending efficacy endpoints in this field have been established in other countries.

In the above-mentioned practical guideline, the 6MWD test is described to "be a useful item for the measurement of motor function through strict condition adjustment and evaluator training, but with many issues to be discussed, including the burdens to patients."[14] While issues on the difficulties in evaluating motor function in pediatric patients and the various confounders remain unsolved, the 6MWD test may be expected to be used as a primary method for the measurement of motor function by eliminating the issues as much as possible, through strict specification of the conditions and procedures or provision of evaluator training before study initiation, etc. The 6MWD test has been widely used as a primary endpoint in the international joint clinical trials of exon-skipping, readthrough, and other similar therapies being developed for treatment of DMD.

Based on these circumstances, the 6MWD test for the evaluation of motor function was selected as the efficacy primary endpoint in the present study.

Since the present study is positioned as a small-scale early Phase II study with the nature of a pilot study to evaluate the efficacy of TAS-205 in an exploratory manner, the 6MWD test in the study may be performed without the necessity to determine statistical significances. The target sample size, therefore, was not determined statistically. On the premise that the efficacy of TAS-205 will be determined in terms of the numerical trends in an appropriate manner, the sample size was determined from the viewpoint of feasibility. Given the development status of similar therapies to date and the future study plan of TAS-205, etc., it may be difficult to determine the efficacy of TAS-205 appropriately based only on the 6MWD and other evaluations of motor function in the early Phase II study; therefore, other efficacy endpoints, including the evaluations of muscle volume, lean body mass, or muscle strength, were added to these evaluations to ensure comprehensive assessment of the efficacy of TAS-205. In addition, the muscle volume will be evaluated using skeletal muscle CT in the present study. In consideration of the radiation effects, the evaluation will be limited to lower extremities and only 2 time points, before start (baseline period) and at the end (end of the administration period) of investigational product administration, in consideration of number of measurements. For serum CK concentration, unlike the evaluation during the hospitalization period, which involves relatively low patient burden, including physical activities, and rested conditions, the outpatient evaluation may be subject to various effects/confounders during daily activities; therefore, only the values measured during the hospitalization period will be used for the efficacy evaluation.

14.2 Rationale for the Method of Administration

Since Study 10053030 demonstrated that TAS-205, after repeated oral administration twice daily after meals for 7 consecutive days, decreased the total excretion of tetranor-PGDM and tetranor-PGDM/Cre concentration ratio with increasing dose, the repeated oral administration twice daily, once after breakfast and once after dinner, was selected for the present study. In addition, based on the development of DMD in subjects and the planned evaluation duration (48 weeks) of a confirmatory study positioned as the next study, a minimum 24-week administration period, in which the POC of TAS-205 may be evaluated in an exploratory manner, was selected in the present study.

14.3 Rationale for the Inclusion Criteria

(1) This criterion was set to ensure ethical conduct of the study in accordance with GCP and the principles of the Declaration of Helsinki by including only subjects from whom informed consent can be obtained in an appropriate manner through their legal guardians (legal representatives).

(2) This criterion was set to identify patients with DMD or with symptoms characteristic of DMD to ensure appropriate evaluation of the study.

(3) Age 5 was set as the minimum age for inclusion because this is considered the minimum age at which specified study procedures can be performed and a definitive diagnosis of DMD can be made.[15)] In addition, only male pediatric patients will be included in this study on the grounds that DMD is usually seen in boys, although no nonclinical study of fertility and early embryonic development has been conducted.

(4) The lower and upper limits of body weight were set based on an expected body weight distribution of the ambulatory patients with DMD.

(5) This criterion was set to select patients who can complete individual motor function evaluations of the efficacy endpoints.

(6) This criterion was set to select patients who can stay in the hospital during the hospitalization period specified in the study, because approximately 24-hr (1 day) pooled urine is required a total of 4 times during the study period (baseline period, Day 4, Week 12, and Week 24).

(7) This criterion was set to ensure proper conduct of the study in consideration of the formulation of the investigational product.

(8) The only currently available drug therapy for DMD is treatment with Predonine® Tablets 5 mg[16)] (a synthetic corticosteroid), for which approval has been only obtained for additional indication in September 2013 following its public knowledge-based application in February in the same year, and rehabilitation and management of concurrent illnesses, etc., remain the mainstays of treatment. Under ethical considerations in view of the scarcity of drug therapy options, the concomitant use of steroids will be allowed in patients who are on corticosteroids at the time of informed consent as far as no changes are made to their dosage regimen after informed consent.

14.4 Rationale for the Exclusion Criteria

(1) to (6), (8), (9) These criteria were set to ensure subject safety and proper conduct of the efficacy and safety evaluations in this study.

(7) Since the use of COX-1 or COX-2 inhibitors, or NSAIDs is completely prohibited during 7 days before the motor function test during the study period (including the screening period), this criterion was set to exclude patients who are on such drug before enrollment.

(10) This criterion was set to exclude patients who may undermine appropriate pharmacodynamic evaluation on the grounds that PGD_2 is a chemical mediator involved in inflammatory response and thus associated with various allergic diseases.

(11) This criterion was set because, for subjects who received another investigational product that produces dystrophin protein, the effects of the another investigational product cannot be ruled out regardless of the administration period. In addition, this criterion was set for patients who have received investigational products other than that described above, in accordance with "General Considerations for Clinical Trials," in which it is stated that repeated enrollment of the same subject in clinical studies without adequate washout to ensure safety and eliminate carry-over effects is not desirable.

(12) It is known that a relatively high proportion of patients with DMD participate in clinical research or trials on motor function, etc., independently performed by rehabilitation or other departments. Since excluding all these patients from the present study may impair recruitment of patients with DMD, a rare disease, this criterion was set to exclude at least patients who undergo a motor function test at the same timing as the present study to avoid any effect on the study.

(13) This criterion was set to exclude patients who are HBs antigen-, HCV antibody-, or HIV antigen- or antibody-positive before enrollment to ensure the safety of personnel handling blood samples and other subjects in this study involving blood collection.

(14) Since no upper limit of age for subjects is set for the present study, although this is a study in pediatric patients, and no study of fertility or early embryonic development has been conducted with TAS-205 in nonclinical studies, this criterion was set to select patients who can give consent for the use of appropriate contraception throughout the study period and for 180 days after the end of the study through their legal guardians (legal representatives) who are required to provide written informed consent for the study.

(15) This criterion was set because there was a need to select only patients who can understand and follow the instructions of the study staff properly during evaluation of motor function, which is subject to various confounders.

(16) This criterion was set to ensure subject safety and proper conduct of the safety evaluations in this study, because TAS-205 will be administered for a long term of 24 consecutive weeks, although no effects on the QTc or other 12-lead ECG findings have been demonstrated after repeated administration twice-daily for 7 days in Study 10053030.

(17) This criterion was set to exclude patients who may impair subject safety or prevent the study from being conducted in compliance with the protocol.

14.5 Rationale for Randomization Adjustment Factors

- Since DMD, a progressive muscular dystrophy, develops with increasing age, age was set as a randomization adjustment factor. The age classification (between 5 and 7 years, 7 years or older) was set by reference to the reports on a stratified analysis of 6MWD in the placebo

group administered a similar drug[17] and on a 36-month natural course data in ambulatory patients with DMD.[18] The presence or absence of concomitant steroid use was also set as a randomization adjustment factor because the concomitant use of steroid can considerably affect the efficacy evaluation.

14.6 Rationale for the Prohibited Concomitant Medications/Therapies

- All of the prohibited concomitant medications/therapies were set because they may impair appropriate efficacy and safety evaluations of TAS-205 during the study.
- In particular, persistent use of COX inhibitors involved in arachidonic acid cascade or NSAIDs was included because it may affect the efficacy evaluation of TAS-205. The use of prohibited concomitant medications/therapies, including as-needed use, was completely prohibited during 7 days before the motor function test. However, since this study may be affected by COX-1 and COX-2 inhibitors, which are known to be primarily involved in peripheral anti-inflammatory activity, but not by COX-3 inhibitors, which primarily act centrally and hardly inhibit peripheral prostaglandin synthesis, the use of acetaminophen, etc., is not prohibited.

14.7 Rationale for the Concomitant Medications Requiring Precaution

- [redacted]

14.8 Rationale for the Restricted Concomitant Medications

- In this study, the efficacy of TAS-205 in patients will be evaluated. In addition, urine tetranor-PGDM/PGEM concentrations will be measured for pharmacodynamic evaluation. Restricted concomitant medications were defined to ensure that these study endpoints can be evaluated appropriately.

14.9 Rational for the Dose Suspension Criteria

- [redacted]

[redacted]

- In case of severe adverse events, excluding those definitely unrelated to the investigational product, the efficacy of TAS-205 will also be evaluated with close attention to safety, with thorough dose suspension measures taken to ensure subject safety.

14.10 Rationale for the Dose Reduction Criteria

- If a severe adverse event occurs as an adverse drug reaction of TAS-205, the same adverse drug reaction is expected to recur after dose resumption. Since severe adverse reactions requiring at least 2 consecutive weeks of washout per period may indicate that the dosage for the subject is not appropriate to continue administration or ensure subject safety, the dose reduction measure is included.
- In addition, since severe adverse events not reasonably related to the investigational product may be possibly related to the investigational product (the causal relationship will be reassessed depending on the situation) if they recur after dose suspension or resumption, and thus may indicate that the dosage for the subject is not appropriate to continue administration or ensure subject safety, the dose reduction measure is included.
- Similarly, since any symptom of glucocorticoid deficiency requiring at least 2 consecutive weeks of washout or resulting in recurrence of the same syndrome may indicate that the

dosage for the subject is not appropriate to continue administration or ensure subject safety, the dose reduction measure is included.

14.11 Rationale for the Contraception Period

- Since no study of fertility and early embryonic development has been conducted with TAS-205 in nonclinical studies, the contraception period of 180 days after the end of investigational product administration was set as a period sufficiently exceeding the expected duration of spermatogenesis (growth from spermatogonia to sperm takes approximately 10 weeks) and sperm retention up to ejaculation.

14.12 Rationale for the Restrictions on Foods and Beverages

- [redacted]

15. Case Report Forms

A CRF will be completed for all subjects enrolled in this study (enrolled subjects).

The investigator or subinvestigator will complete the CRFs as specified in the "Instructions for Completing the CRFs and Making Changes or Corrections to the CRFs."

Data on the CRFs must be consistent with the source documents. Any inconsistency must be explained by the investigator in writing and submitted to the sponsor; the investigator will retain a copy.

15.1 Recording of CRFs

The investigator or subinvestigator will complete the CRFs as specified in Section 15.3, "Instructions for Completing Case Report Forms." After completion, the CRFs will be signed/sealed or signed and dated. If the subinvestigator or trial collaborator completes the CRFs, the investigator will review the CRFs for completeness before data lock, and sign/seal or sign and date the CRFs before submission to the sponsor. The investigator will retain a copy of the submitted CRFs at the study site.

Adverse events that develop or worsen after start of investigational product administration will be collected on the CRFs.

15.2 Changes to or Correction of the Case Report Forms

The investigator, subinvestigator, and trial collaborator will make any change or correction to a CRF as specified in Section 15.3, "Instructions for Completing Case Report Forms."

The investigator will add a "Record of Changes and Corrections to the CRFs" to the CRF, and submit the CRF to the sponsor. In addition, the investigator will retain a copy.

15.3 Instructions for Completing Case Report Forms

(1) The sponsor will create the "Instructions for Completing the CRFs and Making Changes or Corrections to the CRFs" and deliver it to the investigator and subinvestigator (and trial collaborator). The investigator or subinvestigator will complete the CRFs and make any change, correction, or addition to the CRFs in accordance with the instructions. In addition, the trial collaborator may help with completion the CRFs in accordance with the instructions in cases of simple mechanical operation requiring no medical judgment.

(2) A ballpoint pen, etc. will be used so that the entries cannot be easily erased.

(3) To protect the privacy of subjects, each subject in the study will be identified by a unique subject ID code.

(4) Any correction to the CRF will include striking out the corrected text with a double-line so that the original information can be read, and will be sealed or signed with the date of correction. For significant change or correction, the reason should additionally be included. If any change, correction, or addition to the CRF is required after submission to the sponsor, the change, correction, or addition will be made directly to the CRF, and the date of change, correction, or addition, and reason for the change, correction, or addition (if necessary) will be described. The investigator will confirm the change, correction, or addition, and sign or sign/seal and date the record.

[Significant change or correction]

1) Change or correction to the description of informed consent and assent

2) Change or correction to the assessment of abnormal change in 12-lead ECG, cardiac ultrasonography (echocardiography), blood pressure, pulse rate, or body temperature

3) Change or correction to an adverse event term and the description of causal relationship to the investigational product

(5) Signatures and seals must be consistent with those in a list submitted to the sponsor beforehand.

(6) Any blank field must be struck out or completed with “Not performed,” “No,” etc., as appropriate to clarify that the blank field is not a failure to fill it in.

(7) After the CRFs are completed, the investigator will cross-check the CRFs against the medical record (medical chart), etc., and sign or sign/seal and date the CRFs.

16. Compliance with, Deviations from, and Amendments to the Protocol

16.1 Compliance with the Protocol

The investigator will sign or sign/seal and date the protocol or equivalent together with the sponsor to declare that the investigator agrees with the sponsor on the protocol and sample CRF, and that the investigator agrees to comply with the protocol.

In the event that the protocol or sample CRF is revised or corrected by order of the head of the study site based on the recommendation of the IRB, the investigator will do as described above.

16.2 Deviations from the Protocol

Significant deviations from the protocol will be defined as below. However, item (1) will be applicable only if the safety of a subject is definitely endangered.

(1) Prohibited concomitant medications/therapies were administered.
(2) The subject did not withdraw from the study although he met the discontinuation criteria.
(3) The dose for the subject was not suspended or reduced although the subject met the dose suspension or reduction criteria.

The protocol must not be changed without prior written agreement between the investigator and the sponsor or prior written approval from the IRB based on a review.

The investigator must submit a report of every change to the study that may significantly affect the implementation of the study or increase the risk to subjects to the sponsor and the head of the study site, and to the IRB through the head of the study site, without delay.

The investigator may deviate from the protocol or change the protocol without prior written agreement with the sponsor or the prior approval from the IRB if the medical situation inevitably requires the action, for instance, to avoid an emergency risk to a subject. In such a case, the investigator must promptly report the details of the deviation or change and the reason to the sponsor and the head of the study site, and submit the report to the IRB through the head of the study site to obtain written approval.

The investigator must record all protocol deviations, irrespective of the reason.

16.3 Amendments to the Protocol

If any amendment to the protocol or sample CRF is deemed necessary, the sponsor must submit the revised protocol or sample CRF to the investigator. The investigator must review the revised protocol or sample CRF thoroughly.

The sponsor must obtain agreement from the investigator to revise the protocol or sample CRF.

The sponsor must submit the revised protocol or sample CRF to the head of the study site and obtain approval from the IRB through the head of the study site promptly.

However, amendment due to only a change in administrative affairs (e.g., change of the sponsor’s organization or structure, change of name of the study site or department, change of address or phone number of the study site or the sponsor, change of job title of the investigator, or change of layout of the CRF) will require no new agreement.

17. Direct Access to Source Documents

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

17.1 Source Documents

Source documents refer to original documents, data, and records (e.g., hospitalization records, medical records, test records, memoranda, checklists for subject evaluation, medication records, recorded data of automatic measuring instruments, CT image data, subject files, records retained at the Pharmacy Department, Inspection Department, and medical engineering departments involved in this study, IWRS-related materials, etc.).

Specific details of source documents for this study will be recorded in the list of source documents, etc. (or any documents to replace it) after preview with the investigator, and a copy of the list will be provided to the investigator.

Items listed below are “materials to be entered directly into the CRFs and regarded as source data.”

- Diagnosis
- Presence or absence of previous medical history or concurrent illness that is considered to have a significant effect on the study in the opinion of the investigator or subinvestigator
- History of steroid use (age of initiation of use)
- Assessment of the presence or absence of abnormal change in blood pressure, pulse rate, body temperature, 12-lead ECG, or cardiac ultrasonography (echocardiography)
- Reasons for use of any concomitant medications or therapies (including steroids), their route of administration, and names or therapies and routes of administration of any drugs prescribed at another hospital
- Presence or absence of adverse events, names of the adverse events, severity (intensity), serious/non-serious, action concerning the investigational product, outcome, reason for completion of follow-up, and causal relationship to the investigational product
- Presence or absence of withdrawal/dropout and reason
- Comments

17.2 Direct Access

The sponsor's monitor will cross-check the CRFs against the source documents to ensure the items listed below. For any inconsistency with a source document, a document that explains the reason must be obtained from the investigator.

- Data required by the protocol are accurately described on the CRFs or Serious Adverse Event Report and are consistent with the source documents.
- All changes in the regimen or treatment are described on the CRFs.
- Adverse events are described on the CRFs in accordance with the protocol.
- For subjects enrolled, all withdrawals and dropouts are described with the reasons on the CRFs.

18. Study Quality Control and Quality Assurance

The duties related to the quality control and quality assurance of the study will be implemented as described below, in accordance with the sponsor's SOPs.

18.1 Study Quality Control

The sponsor will control the quality of the study in accordance with the respective SOPs for clinical trials and the monitoring plan of this study. The main responsibilities are as follows:

- To explain the method for selecting subjects, methods for investigating and evaluating efficacy/safety, etc., to the investigator, subinvestigator, or trial collaborator through protocol explanatory meetings, etc.
- To make periodic monitoring visits to the study site to ensure that the study is being conducted in compliance with the protocol and GCP
- To inspect the source documents to ensure that the entries on the CRFs are accurate; and to create the “Instructions for Completing the CRFs and Making Changes or Corrections to the CRFs” and make a request to the investigator or subinvestigator for a change or correction if necessary
- To check the entries on the CRF
- To ensure that relevant essential documents are appropriately retained at the study site
- To document and report the study management, data collection, data management, statistical analyses, analyses of adverse events, etc., in accordance with the sponsor's SOPs, and check the completeness

18.2 Audits by the Sponsor and Inspection by the Regulatory Authorities

The investigator will accept audits by the sponsor and inspection by the regulatory authorities to ensure thorough compliance with the protocol, GCP, and applicable regulatory requirements.

The investigator will agree to the direct access of the auditors and inspectors to the study records. The auditors and inspectors must not disclose personal information or personal medical information on any individual evaluated.

The investigator will make efforts to cooperate in implementation of audits and inspections as far as possible, including approval of access to all necessary facilities as well as data and materials related to the study. The investigator will promptly inform the sponsor of information obtained from the regulatory authorities or the IRB regarding any scheduling of inspection. The investigator will report any results of the inspection to the sponsor promptly. The investigator will take appropriate measures requested by the sponsor and perform corrective actions for all issues indicated in the audits and inspections.

19. Data Handling and Record Retention

19.1 Data Handling

All information provided by the sponsor to the investigator, including the protocol, CRFs, investigator's brochure, etc., created during the study, and any results obtained in the process of this study, is confidential. The study personnel will agree not to refer to such information by any means without prior written approval of the sponsor.

The personal data of the subjects, the investigator, or subinvestigator that may be reflected in the sponsor’s database will be handled in compliance with all applicable laws and regulations.

If the sponsor processes or retains the personal data of the subjects, the investigator, or subinvestigator, the sponsor will take all appropriate measures to protect these data from access by any unauthorized third party.

19.2 Record Retention

19.2.1 Investigator/Study Site

The investigator/study site is responsible for retaining all study-related documents in accordance with the applicable regulatory requirements and the ICH E6 Guideline (Part 4.9.4, 4.9.5).

The investigator/study site will agree to inform the sponsor of any intention to delete or destroy any study-related record in writing. Before informing the sponsor, the investigator/study site must confirm that the record meets the applicable regulatory requirements for record retention. The sponsor will approve the destruction of the record in writing to the investigator/study site.

If the sponsor requests longer management of the record, although all requirements for record retention are met, the investigator/study site will make additional adjustment.

19.2.2 Sponsor

The sponsor must retain essential documents to be retained by itself in compliance with the regulatory requirements applied in countries in which the investigational product is approved or application for approval is planned.

If the development of the investigational product is discontinued, the sponsor must retain essential documents to be retained by itself in accordance with the applicable regulatory requirements.

20. Compensation for Injury

The sponsor will obtain insurance in accordance with the applicable regulatory requirements, and submit an outline of the compensation scheme to the study site.

In preparation for compensation requests for any injury that may occur during the study, for which the sponsor is found not to be legally responsible, excluding those that occur due to malpractice or negligence, the sponsor will specify a policy and payment procedure for any study-related injury in the outline of the compensation.

Compensation for subjects will be made in accordance with the outline of the compensation.

21. Publication and Secondary Use of Data

21.1 Publication

The sponsor has the right to make use of the results of this study and submit them to the governments or regulatory authorities.

The results of this study may be presented in academic conferences or published in scientific journals only after review by the sponsor in accordance with the applicable guidelines for publications or financial agreement.

The timing of publication and persons involved in the publication will be determined through discussion between the coordinating investigator and the sponsor.

21.2 Secondary Use of Data

The sponsor has the right for secondary use of the study data. Secondary use of data means the use of data collected in this study for purposes other than the study (including provision to third parties).

The primary examples of secondary use of data are as follows:

- Use in another clinical study
- Integrated analysis with the relevant clinical studies
- Independent analysis by or information sharing among regulatory authorities
- Use for epidemiological research

22. Ethics

22.1 Ethical Matters

The protocol, the ICH Guideline, the ethical principles that have their origin in the Declaration of Helsinki, and all applicable regulatory requirements must be followed and any information be updated to ensure that all measures are taken for protection of subjects.

22.2 Approval of the Institutional Review Board (IRB)

As required in the ICH E6 Guideline (Part 3), the study must be approved by the appropriately established IRB. The conduct of the study must be approved by the head of the study site after review and approval by the IRB.

During the study, the qualifications of the investigator must be reviewed on an ongoing basis. The review will be updated in accordance with the IRB requirements, while at least once a year of review is required by regulation. At the completion of the study, the completion and results of the study will be reported to the IRB.

22.3 Procedure for Obtaining Informed Consent

Informed consent must be obtained in compliance with the Declaration of Helsinki, the ICH E6 Guideline, and applicable regulatory requirements.

The investigator will create an informed consent/assent form based on a draft informed consent/assent form provided by the sponsor. If an amendment to the informed consent/assent form is required, the investigator will discuss with the sponsor and create revisions, and obtain approval from the IRB.

The investigator or subinvestigator will provide sufficient explanation about all matters related to the study to the legal representative of each patient. The investigator or subinvestigator will provide sufficient explanation to all the legal representatives using simple sentences. Sufficient explanation will also be provided to each patient in a way that suits his level of understanding, using simple sentences depending on the situation.

Prior to participation in the study, the legal representative of each patient, the patient, and the person who provided explanation about the informed consent will sign and date the informed consent form. A copy of the informed consent/assent form signed and dated by the legal representative of each patient or the patient will be provided to the legal representative or the patient before any study-related procedure described in the informed consent form is implemented. The informed consent/assent form approved by the IRB will be used.

The legal representative of each patient will be deemed to have consented to participate in the study by signing and dating the informed consent form before implementation of the study procedures specified in the protocol. However, voluntary will of the patient will be fully respected, considered, and given priority. If a patient becomes able to give consent during the study, his willingness to continue to participate in the study will be newly confirmed and his written consent obtained.

22.4 Administration of the Investigational Product After the Study Period

Continued administration of the investigational product after the end (discontinuation) of the administration period in this study will not be permitted.

23. Clinical Study Organization

Details of the clinical study organization are described in the Attachment.

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