Study Protocol

A Phase 1/2 Study of DS-5141b

- Open-label Study of DS-5141b in Patients with Duchenne Muscular Dystrophy -

Sponsor: Daiichi Sankyo Company, Limited

Version 03.04.000/Date of report: 11 Jun 2020

PROTOCOL SYNOPSIS

Protocol Number	DS5141-A-J101
Investigational substance code	DS-5141b
Generic Name	renadirsen (INN)
Study Title	A Phase 1/2 Study of DS-5141b - Open-label Study of DS-5141b in Patients with Duchenne Muscular Dystrophy -
Study Phase	Phase 1/2
Indication under Investigation	Duchenne muscular dystrophy (DMD)
Study Objectives	The objective of the study is to assess the safety, tolerability, efficacy, and pharmacokinetics of DS-5141b in DMD patients. The study is also intended to assess the dose to be used in the next-phase studies.
Study Design	A multicenter, uncontrolled, open-label study
Study Duration	01 Oct 2015 to 31 Dec 2020
Study Sites	2 sites
Planned Sample Size	6 subjects in each part
Subject Eligibility Criteria	[Inclusion Criteria] 1) Patients who have been confirmed to have an out-of-frame deletion that can be corrected by exon 45 skipping of the dystrophin gene, to thus restore the in-frame deletion. 2) Those who have been confirmed to have a DNA sequence that forms a double strand with DS-5141b in the exon 45 of the dystrophin gene. 3) Those who have intact muscles of adequate quality for biopsy to allow evaluation of the efficacy of the study drug. 4) Boys aged from 5 to <11 years at the time of registration. 5) Those who are able to walk at least 325 meters in the 6-minute walk test. 6) Steroid-naive patients or patients who have been treated with steroids for at least 6 months prior to

registration in the study without a dosage change for at least 3 months prior to registration.

7) Those who are able to follow the instructions on the scheduled admission, visits, treatment plan, tests/observations, and other study procedures set in the protocol while participating in the study.
8) Those who have voluntarily provided written informed consent or have received adequate explanations about the study involving their decision-making about participation in the study.
9) Those whose legal representatives have voluntarily provided written informed consent in an appropriate manner.

[Exclusion Criteria]

1) Patients with a gene mutation which is not expected to produce the dystrophin protein by exon 45 skipping.
2) Concurrent illness other than DMD that can cause muscle weakness and/or impairment of motor function.
3) Current or previous severe disorder involving the liver, kidneys, blood, hypersensitivity, respiratory system, gastrointestinal system, circulatory system, central nervous system, etc.
4) Left ventricular ejection fraction <55% on the echocardiogram.
5) Fridericia-corrected QT interval (QTc) >0.45 seconds on the 12-lead electrocardiogram.
6) Those who require treatment of the respiratory system, eg, respiratory physical therapy or mechanical respiratory support.
7) Those who have a positive result for the hepatitis B surface (HBs) antigen, hepatitis C virus (HCV) antibody, or human immunodeficiency virus (HIV)

	antibody tests. 8) Those who have participated in another clinical study and have received an investigational product within 3 months prior to registration in this study. 9) Those who are considered ineligible for the study by the investigator or subinvestigator.
Dose and Route of Administration	<Part 1> DS-5141b will be subcutaneously administered at the following dose levels once weekly for 2 weeks. The dose level will be increased stepwise. DS-5141b will be administered at Dose Level 1 and Dose Level 3 in Cohort 1 and at Dose Level 2 and Dose Level 4 in Cohort 2. • Dose Level 1: 0.1 mg/kg • Dose Level 2: 0.5 mg/kg • Dose Level 3: 2.0 mg/kg • Dose Level 4: 6.0 mg/kg <Part 2> DS-5141b will be subcutaneously administered at 2 dose levels, determined based on the results of Part 1, once weekly for 12 weeks. <Part 2-Extension> Based on the results of Part 2, DS-5141b will be subcutaneously administered at 2 dose levels (2.0 mg/kg and 6.0 mg/kg) that had been administered in Part 2, once weekly for 48 weeks. Based on the results of nonclinical studies in mice, the study drug administration was temporarily discontinued. <Part 2-Extension-2> Based on the results of Part 2, DS-5141b will be subcutaneously administered at 2 dose levels (2.0 mg/kg and 6.0 mg/kg) that had been administered in Part 2, once weekly for 48 weeks (a total of 48 doses).
Prohibited Concomitant Drugs	Concomitant use of the following drugs is prohibited during the period from registration in the study to the

	end of the follow-up period in Part 2, and during the period from the day of informed consent for Part 2-Extension to the end of the follow-up period in Part 2-Extension-2 (during the period from registration in the study to the end of the follow-up period in Part 2-Extension-2 for subjects participating in the study from Part 2-Extension or Part 2-Extension-2; and to the start of study drug administration for subjects participating in the long-term extension study). 1) Other anti-DMD drugs than the study drug used in this study and steroids 2) Other investigational products 3) Chloroquine and hydroxychloroquine
Prohibited Concomitant Therapy	The use of the following therapy is prohibited from registration in this study to the end of the follow-up period in Part 2-Extension-2 (or to the start of study drug administration in the long-term extension study for subjects participating in the long-term extension study). 1) HAL® (Hybrid Assistive Limb®)
Study Procedures	See Appendix 3.
Study Endpoints	[Safety Endpoints] Adverse events, laboratory data, body weight, vital signs, 12-lead electrocardiogram, and CCI [redacted]. [Pharmacokinetic Endpoints] Pharmacokinetic parameters [Major Efficacy Endpoints] • Expression of the dystrophin protein in the muscle tissue • Production of exon 45-skipped dystrophin mRNA in the muscle tissue
Statistical Analyses	[Safety Endpoints] The incidence of adverse events will be calculated by dose level. The frequency of adverse events will also be counted by event. For laboratory data, body weight, vital signs, 12-lead electrocardiogram results, and CCI [redacted]

	CCI findings, summary statistics will be calculated and frequency will be counted by the dose level. [Pharmacokinetic Endpoints] For pharmacokinetic parameters, summary statistics will be calculated by the dose level. [Efficacy Endpoints] The dystrophin protein levels in the muscle tissue relative to the normal muscle and their change will be calculated for each subject.

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List of Abbreviations

Abbreviation	Unabbreviated term
A/G	albumin/globulin
ALP	alkaline phosphatase
ALT (GPT)	L-alanine aminotransferase (glutamic pyruvic acid transaminase)
AON	antisense oligonucleotide
APTT	activated partial thromboplastin time
AST (GOT)	L-aspartate aminotransferase (glutamic oxaloacetic acid transaminase)
BMD	Becker muscular dystrophy
BUN	blood urea nitrogen
CK (CPK)	creatine kinase (creatine phosphokinase)
CPF	cough peak flow
CRP	C-reactive protein
CT	computerized tomography
DMD	Duchenne muscular dystrophy
DNA	deoxyribonucleic acid
E/A	early diastolic filling velocity/atrial filling velocity
EDC	electronic data capturing
ENA	2'-*O*,4'-*C*-ethylene bridged nucleic acids
FEV1	forced expiratory volume in 1 second
FVC	forced vital capacity
GCP	good clinical practice
gamma-GT	gamma-glutamyl transferase
HBs	hepatitis B surface
HCV	hepatitis C virus
HED	human equivalent dose
hERG	human ether-a-go-go related gene
HIV	human immunodeficiency virus
HPF	high power field
ICH	international conference on harmonisation
IHC	immunohistochemistry
IRB	Institutional Review Board
LDH	lactic acid (lactate) dehydrogenase
LPF	low power field
MCH	mean cell hemoglobin
MCHC	mean cell hemoglobin concentration
MCV	mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
miR-	micro-RNA-
MRI	magnetic resonance imaging

Abbreviation	Unabbreviated term
MTD	maximum tolerated dose
mRNA	messenger ribonucleic acid
NAG	N-acetyl-β-D-glucosaminidase
NOAEL	no-observed-adverse-effect
non-Tg	non-transgenic
PEF	peak expiratory flow
PT	preferred term
PT-INR	prothrombin time-international normalized ratio
QTc	corrected QT interval
QTcB	corrected QT interval using Bazett's formula
QTcF	corrected QT interval using Fridericia's formula
RNA	ribonucleic acid
RT-PCR	reverse transcription-polymerase chain reaction
SOC	system organ class
WB	western blot

–: No applicable notation

List of Pharmacokinetic Parameters

Abbreviation	Unabbreviated term
AR	observed accumulation ratio
AUC168h	area under the plasma concentration-time curve up to 168 hours
AUCinf	area under the plasma concentration-time curve up to infinity
AUClast	area under the plasma concentration-time curve up to the last quantifiable time
AUCtau	area under the plasma concentration-time curve during dosing interval
Cavg	average plasma concentration
CL/F	apparent total body clearance
CLss/F	apparent total body clearance at steady state
Cmax	maximum plasma concentration
Kel	elimination rate constant associated with the terminal phase
MRTinf	mean residence time up to infinity
t1/2	terminal elimination half-life
Tmax	time to reach maximum plasma concentration
Vz/F	apparent volume of distribution based on the terminal phase

1. INTRODUCTION

1.1 Background to Development

Duchenne muscular dystrophy (DMD) is a serious, rare, X-linked regressive genetic disease caused by a mutation (such as deletion or duplication) in the dystrophin gene, leading to dystrophin deficiency. In its clinical course, patients at 3 to 5 years old fall over easily, and are often unable to run, and their motor function reaches a peak around the age of 5 years. After this, muscle atrophy and muscle weakness gradually progress, and in many cases, patients lose ambulation at around the age of 10 years. As motor function decreases, joint contracture or scoliosis appears, and generally, from the age of 10 years onwards, respiratory failure and cardiomyopathy start to appear. Due to recent advances in medical technology such as respiratory management, patients now have a life expectancy of over 30 years.[1]

Steroid therapy is the only pharmacotherapy for DMD with available evidence for the prevention of progression, and has been shown to improve muscle strength and function in a period of 6 months to 2 years. However, its mechanism of action is unknown, and side effects are commonly reported. In addition, there is insufficient evidence about effects of steroid on parameters such as respiratory function or cardiac function in long-term use after loss of ambulation.[2] As a non-pharmacotherapy, rehabilitation to maintain motor function, respiratory care such as respiratory physiotherapy and treatment of myocardial disorder, etc. are available, but current therapy including steroids is symptomatic treatment, and is not based on the cause of DMD. Therefore, more effective, new therapies are desired.

In 2006, it was discovered that an antisense oligonucleotide (AON) induced exon skipping, resulting in the synthesis of dystrophin protein in DMD patients.[3] At present, multiple modified AONs such as 2'-*O*-methyl RNA and morpholino nucleic acid that skip an exon such as exon 51, 53 or 45 of the 79 exons in the dystrophin gene are being developed both in Japan and overseas. The exon 51 skipping drug eteplirsen was approved in 2016, and the exon 53 skipping drug golodirsen was approved in 2019, in the US, but their target populations are different from that of DS-5141b, which is an AON that induces dystrophin exon 45 skipping. DS-5141b is a modified oligonucleotide consisting of 2'-*O*,4'-*C*-ethylene-bridged nucleic acids (ENA) and 2'-*O*-methyl RNA, and was discovered and formulated in Japan by Daiichi Sankyo Company, Limited in collaboration with PPD of the PPD, Kobe University Graduate School of Medicine (PPD , Kobe Gakuin University), etc.. Modified

oligonucleotides containing ENAs have dramatically increased affinity for complementary strands of nucleic acid compared with conventional modified nucleic acids such as 2'-*O*-methyl RNA or morpholino nucleic acid, and have superior nuclease resistance[4]. Therefore, ENA-containing modified oligonucleotides are expected to be useful for treating DMD by inducing skipping more strongly.
To confirm the pharmacological activity of DS-5141b, dystrophin mRNA was analyzed in an in vitro study using myotubes derived from a DMD patient, and DS-5141b was confirmed to induce exon 45 skipping. And the expression of dystrophin protein was confirmed by Western blot. In an in vivo study using a murine model of muscular dystrophy (*mdx* mice), DS-5141b induced exon 45 skipping of dystrophin mRNA in the anterior tibial muscle, diaphragm, and heart.
Given the above, it is possible that, by inducing skipping of exon 45, DS-5141b causes expression of dystrophin protein in DMD patients with genetic abnormalities amenable to exon 45 skipping therapy. As DS-5141b has a different mechanism of action from other therapeutic drugs, we consider that if it is co-administered with existing therapies, DS-5141b is expected to maintain motor function, respiratory function and cardiac function in DMD patients over a long period, and therefore, we decided to pursue development of DS-5141b.

1.2 Summary of Significant Findings Obtained from Nonclinical Studies and Clinical Studies

1.2.1 Pharmacological Action

Exon 45 skipping was observed at concentrations CCI and the expression of dystrophin protein was confirmed at a concentration of CCI when cultured myotubes derived from a DMD patient were transfected with DS-5141b. Exon 45 skipping was confirmed in the anterior tibial muscle, diaphragm, and heart by reverse transcription-polymerase chain reaction (RT-PCR) of mRNA after subcutaneous administration of DS-5141b to mdx mice once weekly for 4 weeks. The exon 45-skipped bands were detected in approximately half of the animals at CCI and in all animals at CCI According to these results, DS-5141b is expected to cause exon 45 skipping also in humans.

1.2.2 Safety Pharmacology

For in vitro safety pharmacology study in the cardiovascular system, the human ether-a-go-go related gene (hERG) current study was conducted using

hERG-transfected human embryonic kidney 293 cells. DS-5141b did not affect hERG currents at concentrations up to [redacted] but mildly reduced hERG currents at [redacted] (corrected suppression rate [redacted]). However, in a 1-month intermittent subcutaneous dose (once weekly) toxicity study with a 3-month recovery period in cynomolgus monkeys and a 9-month intermittent subcutaneous dose (once weekly) toxicity study with a 3-month recovery period in cynomolgus monkeys, DS-5141b had no effects on the cardiovascular system including blood pressure and electrocardiograms at doses up to [redacted] In a 1-month intermittent subcutaneous dose (twice weekly) toxicity study with a 3-month recovery period in mice, DS-5141b had no effects on the central nervous system or respiratory system up to the maximum dose of [redacted] In a 1-month intermittent subcutaneous dose (once weekly) toxicity study with a 3-month recovery period in cynomolgus monkeys, DS-5141b had no effects on the central nervous system up to the maximum dose of [redacted] Thus, DS-5141b has no clinically relevant safety pharmacological effects on the central nervous system, respiratory system, or cardiovascular system.

1.2.3 Pharmacokinetics and Drug Metabolism

After a single subcutaneous administration to cynomolgus monkeys, DS-5141b was rapidly absorbed, and the mean Tmax of plasma DS-5141a concentration ranged from [redacted]. Then, the plasma DS-5141a concentration decreased in a biphasic manner. The mean AUClast increased with dose increment and tended to increase more than dose proportionally. The absolute bioavailability was [redacted] at [redacted] and DS-5141b was absorbed well after subcutaneous administration. After a single subcutaneous administration of [^{14}C]DS-5141b at [redacted] to albino mice, the radioactivity was detected broadly throughout the entire body except the central nervous system at [redacted] after administration. High radioactivity was detected especially in the kidney and bladder (including the urine), suggesting the urinary excretion as the major elimination pathway. While radioactivity in the blood was eliminated below the lower limit of quantitation at [redacted] after administration, the increased radioactivity was detected over time in many tissues, suggesting DS-5141b was cleared from circulation by distribution to tissues during this period. The remaining radioactivity in the whole-body at [redacted] after administration were [redacted] of the administered dose, respectively, indicating that DS-5141b is slowly eliminated over time. Radioactivity remained in many tissues, including the muscle tissues that are the target of the pharmacological

effect (the skeletal muscles, diaphragm, and heart), at [redacted] after administration. In pigmented mice, the distribution to the skin and eyeballs was observed. However, similar distribution was also observed in albino mice, suggesting that the distribution of radioactivity to the skin and eyeballs is not dependent on melanin binding.
Plasma protein binding was high, [redacted], in each species, mice, cynomolgus monkeys, and humans, and no difference between species or concentration dependency were noted.
No metabolites were detected either in an in vitro metabolism study using cryopreserved hepatocytes from mice, cynomolgus monkeys, and humans or in analysis of urine samples after a single subcutaneous administration to mice, suggesting DS-5141b was metabolically stable. The major component in plasma and urine samples after a subcutaneous administration of DS-5141b to humans was the unchanged drug, and no peaks which corresponded to metabolites were detected.
In an excretion study in mice, after a single subcutaneous administration of 10 mg/kg of [^{14}C]DS-5141b to male albino mice, the radioactivity in the urine, feces, and expired air was measured over time. The cumulative radioactivity excreted in the urine, feces, and expired air were [redacted] of the dose, respectively, up to [redacted] after administration, suggesting that urinary excretion is the major elimination pathway. Excretion was slow, and approximately [redacted] of the administered radioactivity remained in the body even at [redacted] after administration.
DS-5141b showed no major inhibitory or inducing effect on the cytochrome P450 (CYP) isoforms. DS-5141b also showed no inhibitory effect on the major transporters.

1.2.4 Toxicity

1.2.4.1 Repeated-Dose Toxicity Studies

In a 1-month intermittent subcutaneous dose toxicity study with a 3-month recovery period in mice (doses: 10, 30, 100, and 300 mg/kg, twice weekly), [redacted] was observed at 1 hour after administration on Days 11, 15, and 18, but disappeared at 4 hours after administration at ≥100 mg/kg. In the histopathological examination, [redacted] at ≥30 mg/kg, and [redacted] ≥100 mg/kg were observed. Each of the findings showed reversibility after a 3-month recovery period. Therefore, the no-observed-adverse-effect level (NOAEL)

was determined to be 10 mg/kg. In a 6-month intermittent subcutaneous dose toxicity study with a 3-month recovery period in mice (doses: 1, 3, 10, and 100 mg/kg, twice weekly), in the histopathological examination, CCI [redacted] at dose levels of ≥10 mg/kg were observed. At 100 mg/kg, CCI [redacted] were observed CCI [redacted], and in the histopathological examination, CCI [redacted] was observed. All of the findings tended to recover after a 3-month recovery period. Therefore, the NOAEL was determined to be 3 mg/kg. In a 1-month intermittent subcutaneous dose toxicity study with a 3-month recovery period in cynomolgus monkeys (doses: 10, 30, and 100 mg/kg, once weekly), no toxicity findings were observed up to 100 mg/kg, and the NOAEL was determined to be 100 mg/kg. In a 9-month intermittent subcutaneous dose toxicity study with a 3-month recovery period in cynomolgus monkeys (doses: 10, 30, and 100 mg/kg, once weekly), CCI [redacted] was observed at ≥30 mg/kg. At 100 mg/kg, CCI [redacted] was observed, and CCI [redacted], which were considered to be secondary changes related to CCI [redacted], were also noted. All the findings showed reversibility after a 3-month recovery period. Therefore, the NOAEL was determined to be 10 mg/kg.

1.2.4.2 Genotoxicity Studies

In genotoxicity studies, a bacterial reverse mutation study, a chromosome aberration study using Chinese hamster lung cells, and a mouse bone marrow micronucleus study had negative results. Therefore, DS-5141b is determined to have no potential to induce genotoxicity. In the mouse bone marrow micronucleus study, decreased CCI [redacted] at ≥125 mg/kg, and CCI [redacted] at ≥500 mg/kg were observed. And after 48 hours after administration in the 1000 mg/kg group, CCI [redacted] was significantly lower than that in the negative control group.

1.2.4.3 Reproductive and Developmental Toxicity Studies

In a fertility and early embryonic development study in male mice (doses: 30, 100, and 300 mg/kg) decreased CCI [redacted] was observed at

approximately 30 minutes after administration in the 300 mg/kg group, but these findings always disappeared at 1 to 2 hours after administration. No toxicologically significant changes were noted in body weight, body weight gain, food consumption, copulation rate, copulatory interval, fertility rate, necropsy, organ weight (testes or epididymides), or sperm examination. At 100 and 30 mg/kg groups, no test article-related changes were noted in the above test items, including clinical signs. In addition, no test article-related changes were noted in the number of corpora lutea, number of implantations, implantation rate, preimplantation loss rate, number of live embryos, embryonic viability rate, number of postimplantation losses, or postimplantation loss rate, in all test article groups. Therefore, the NOAELs were determined to be 100 mg/kg for general toxicity and 300 mg/kg for reproductive function and early embryonic development.

1.2.4.4 Dose Range Finding Study for Carcinogenicity Study

In a 1-month intermittent subcutaneous dose toxicity study in non-transgenic (non-Tg) littermates of Jic:CB6F1-Tg rasH2@Jcl (rasH2-/-, non-Tg) mice (doses: 0, 30, 100, and 300 mg/kg, twice weekly), CCI [redacted] at ≥30 mg/kg, CCI [redacted] at 100 mg/kg, and CCI [redacted] at 300 mg/kg were noted. The maximum tolerated dose (MTD) was determined to be 30 mg/kg. In the clinical signs, CCI [redacted] at ≥100 mg/kg and CCI [redacted] at 300 mg/kg were noted. In a 3-month intermittent subcutaneous dose toxicity study in rats (doses: 30, 100 and 300 mg/kg, once weekly), CCI [redacted] at ≥30 mg/kg and CCI [redacted] at ≥100 mg/kg, and CCI [redacted] at 300 mg/kg were noted. The MTD was determined to be 100 mg/kg.

1.2.5 Synopsis of Investigation of CCI [redacted] Observed in Nonclinical Studies

1.2.5.1 Study to Find the Mechanism of Occurrence of CCI [redacted] in Mice

The mechanistic studies for CCI [redacted] were conducted, because CCI [redacted] were observed in a dose range finding study for carcinogenicity study using non-Tg mice (a

1-month intermittent subcutaneous dose toxicity study).

1.2.5.1.1 Time of Occurrence of [redacted] in Mice

In a single subcutaneous dose study in non-Tg mice (dose: 300 mg/kg), [redacted] after administration, [redacted] after administration, and also [redacted] after administration were observed. In a 2-week-maximum intermittent subcutaneous dose study in non-Tg mice (dose: 300 mg/kg, twice weekly), similar changes were also observed in animals in [redacted] after the start of administration, but no major differences were noted [redacted]
In a single subcutaneous dose study in Crl:CD1(ICR) mice (ICR mice) (doses: 500 and 1000 mg/kg), [redacted] were observed at ≥500 mg/kg, and [redacted] after a single administration, and [redacted] after administration were observed at 1000 mg/kg. In a 2-week-maximum intermittent subcutaneous dose study in ICR mice (doses: 500 and 1000 mg/kg, twice weekly), similar [redacted] were observed in animals in [redacted] after the start of administration ([redacted] after the start of administration at 1000 mg/kg), and no major differences were noted [redacted]. The [redacted] observed at ≥500 mg/kg of DS-5141b in ICR mice were qualitatively comparable to those observed in non-Tg mice.

1.2.5.1.2 [redacted] Distribution

The concentrations of in the [redacted] were measured [redacted] after a single subcutaneous administration (doses: 30 and 300 mg/kg) to non-Tg mice. At the 30 mg/kg, the DS-5141a concentration [redacted] was below the limit of quantitation [redacted]. [redacted] DS-5141a was observed at 300 mg/kg, although the [redacted] was extremely low.
The DS-5141a concentrations in the [redacted] were measured [redacted] after a single subcutaneous administration to ICR mice (doses: 30, 300, 500, and 1000 mg/kg). The DS-5141a concentrations in the [redacted] increased with dose increment. [redacted] DS-5141b in ICR mice was comparable to that in non-Tg mice at the same doses, and thus no major difference is noted [redacted]

[redacted] between murine strains.
To assess the [redacted] of DS-5141b, [redacted] obtained by [redacted] was conducted using samples from a 1-month intermittent subcutaneous dose study in non-Tg mice (a dose range finding study for carcinogenicity study) and a 1-month intermittent subcutaneous dose toxicity study in ICR mice. In non-Tg mice, [redacted] were [redacted] at ≥30 mg/kg, and the [redacted] broadened with dose increment. The [redacted] was also observed in [redacted] at 300 mg/kg. In ICR mice, [redacted] was also observed in [redacted] at ≥100 mg/kg, and also in [redacted] at 300 mg/kg. No major strain difference was noted for the [redacted] of DS-5141a between non-Tg mice and ICR mice. Because [redacted] of DS-5141b was observed from the dose levels that [redacted] were not noted at, and the [redacted] of DS-5141b did not necessarily correspond to [redacted] DS-5141b-[redacted] was considered not to be caused by [redacted] of DS-5141a [redacted]

1.2.5.1.3 [redacted] (In Vitro)

To assess the [redacted] of DS-5141b, DS-5141b was transfected to mouse primary [redacted] The [redacted] was assessed by measuring the [redacted] of the cells at 48 hours after transfection of DS-5141b (5, 15, 50, and 150 nmol/L) using transfection reagent to [redacted] derived from 2 strains of mice (C57BL and ICR) seeded on a 96-well plate at concentrations ≥8.3 × 10^4 cells/well. No [redacted] was observed in any of the [redacted]

1.2.5.1.4 Association Between Murine [redacted] and [redacted]

In both non-Tg and ICR mice, at dose levels that led to the [redacted] (non-Tg mice: ≥100 mg/kg; ICR mice: ≥500 mg/kg), the [redacted] of decreased [redacted] were observed immediately after administration of DS-5141b [redacted] after administration). [redacted] did not necessarily correspond to the occurrence [redacted] but in

individuals with [redacted] was observed.

1.2.5.1.5 Other Studies Relating to [redacted]

After a single subcutaneous administration of 1000 mg/kg of DS-5141b to ICR mice, the [redacted] was assessed by [redacted] observed in 2 of 4 animals at [redacted] after administration. In analysis of [redacted] of ICR mice, [redacted] in the group of [redacted] related to [redacted], which is reported to be activated [redacted], was observed [redacted] after a single subcutaneous administration of 500 and 1000 mg/kg. [redacted] after administration to ICR mice, [redacted], was observed [redacted] was observed. In addition, when the [redacted] to ICR mice, followed by a single subcutaneous administration of 500 mg/kg of DS-5141b, [redacted] were observed in any animals. In addition, [redacted] were observed.

From the above, based on the following; [redacted] often occurred [redacted] the results of [redacted] analysis and [redacted] and complete suppression [redacted], DS-5141b-induced [redacted]. Because [redacted] did not affect the [redacted] to DS-5141b, the [redacted] of DS-5141b-induced [redacted] was considered to be related to the [redacted].

1.2.5.2 Differences Between Species

After a single subcutaneous administration of 300 mg/kg of DS-5141b to rats and 100 mg/kg of DS-5141b to cynomolgus monkeys, the DS-5141a concentrations in the [redacted] were measured [redacted] after administration, respectively [redacted]. In both rats and cynomolgus monkeys, [redacted] of DS-5141b was observed, but the [redacted] was low.

CCI using samples from a 3-month intermittent subcutaneous administration dose toxicity study in rats (a dose finding study for carcinogenicity study) and a 9-month intermittent subcutaneous dose toxicity study in cynomolgus monkeys was conducted. In both rats and cynomolgus monkeys, CCI was observed in the CCI at ≥30 mg/kg, and the CCI broadened with dose increment.

To investigate whether the CCI observed in mice are specific to mice, CCI were examined and CCI and CCI were measured CCI After a single subcutaneous administration of 1000 and 2000 mg/kg to unanesthetized unconstrained rats, necropsy was conducted at 24 hours after administration and pathological tests CCI were conducted. At doses up to 2000 mg/kg, no effect was observed in CCI or CCI and CCI was observed.

Based on the above, DS-5141b transferred to CCI and distributed also in rats and cynomolgus monkeys like in mice. However, DS-5141b-induced CCI are considered to be mouse-specific, because no pathological findings were observed in CCI up to 2000 mg/kg in rats and 100 mg/kg in cynomolgus monkeys.

1.2.5.3 Safety Margin

Based on that CCI observed in mice after a subcutaneous administration of DS-5141b is CCI and does not worsen by CCI Cmax is considered appropriate for calculating the safety margin in humans.

In comparison of the exposure (Cmax) to DS-5141a at the NOAEL for CCI in each animal strains/species with that at 6 mg/kg in humans, the safety margin is CCI in the most sensitive murine strain, non-Tg mice, and CCI in ICR mice, rats, and cynomolgus monkeys.

1.2.6 Clinical Studies

As of 30 Aug 2019, no clinical studies have been completed, and 1 study (this study) is in progress.

As of 19 Mar 2018, Part 2 is complete, and a total of 7 subjects have received DS-5141b.

The primary efficacy endpoint, expression of dystrophin protein in muscle tissue, was positive in 1 of 7 subjects, and the secondary efficacy endpoint, production of exon 45-skipped dystrophin mRNA in muscle tissue, was observed in all subjects.
During the Part 2-Extension, based on the result of nonclinical studies using mice shown in Section 1.2.4.4, the study drug administration and the Part 2-Extension were temporarily discontinued.
As of 30 Aug 2019, Part 2-Extension-2 is in progress. A serious adverse event, appendicitis, has been observed in 1 of 7 subjects. The severity was mild, and the event was considered unrelated to the study drug and was confirmed to be resolved.
No adverse events leading to withdrawal from administration of the study drug or a change in the dose of the study drug were observed. Common adverse events (those that occurred in 3 or more subjects) were injection site reaction (7 subjects), nasopharyngitis (6 subjects), alpha 1 microglobulin increased and beta 2 microglobulin urine increased (4 subjects each) and influenza and pyrexia (3 subjects each). The severity of each of these was mild.
Based on analysis of the safety information from sources including nonclinical studies, clinical study and publications about other nucleic acid medications, we newly selected “injection site reaction” and “alpha 1 microglobulin urine increased” as other identified risks. Based on the findings observed in the carcinogenicity and dose finding study in mice, we newly selected CCI [redacted] as an important potential risk and CCI [redacted] as another potential risk.

2. STUDY OBJECTIVES

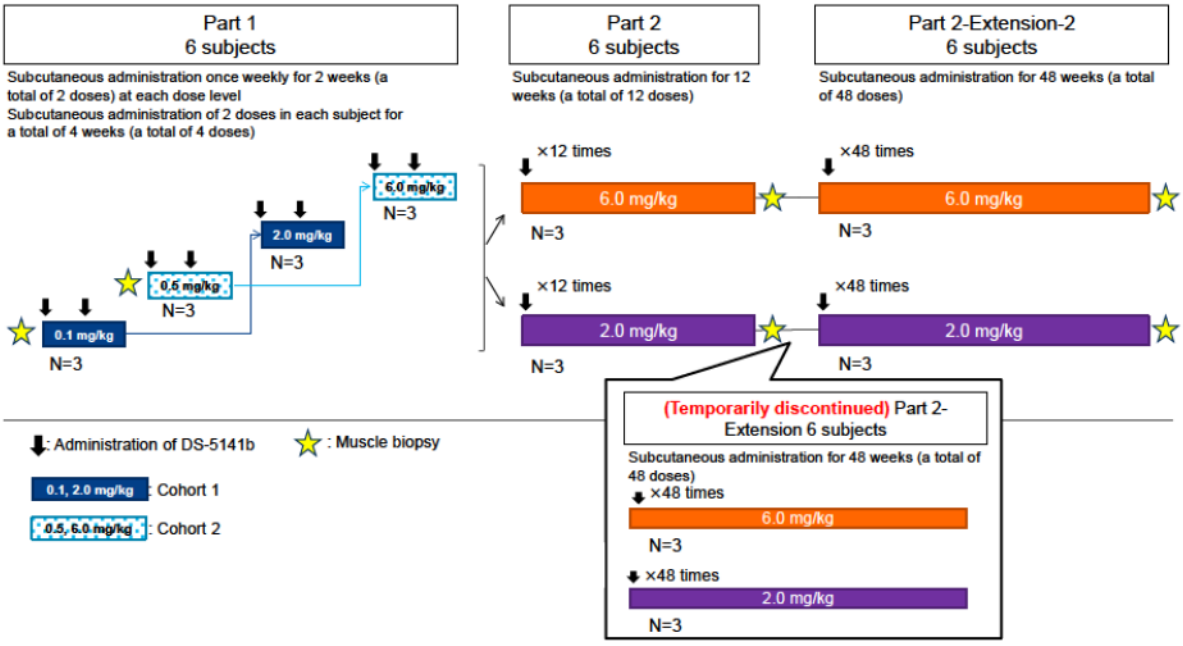
The objective of the study is to assess the safety, tolerability, efficacy, and pharmacokinetics of DS-5141b in DMD patients. The study is also intended to assess the dose to be used in the next-phase studies.

3. STUDY DESIGN

This study is a multicenter, uncontrolled, open-label, phase 1/2 study consisting of Part 1, Part 2, Part 2-Extension, and Part 2-Extension-2. The study design is shown in Figure 3-1.

Subjects who complete 48 weeks of study drug administration in Part 2-Extension-2 of this study and complete efficacy assessment after administration may participate in the long-term extension study (DS5141-A-J201).

Figure 3-1 Study Design



<Part 1>

The dose of DS-5141b will be increased stepwise, from Dose Level 1 (0.1 mg/kg) to Dose Level 4 (6.0 mg/kg). There will be 3 subjects in each cohort, and each of the 2 cohorts will be subcutaneously administered 2 dose levels, to investigate a total of 4 dose levels. Each dose level will be administered once weekly for 2 weeks (a total of 2 doses).

First, 3 subjects will be administered Level 1 (0.1 mg/kg) as Cohort 1. Next, another 3 subjects will be administered Level 2 (0.5 mg/kg) as Cohort 2. After this, the patients in Cohort 1 will be administered Level 3 (2.0 mg/kg), and finally the patients in Cohort 2 will be administered Level 4 (6.0 mg/kg).

<Part 2>
DS-5141b will be administered subcutaneously once weekly for 12 weeks (a total of 12 doses) at 2 dose levels determined based on the results of Part 1. Subjects who have finished Part 1 may participate, and 3 subjects will be assigned to each dose level. Any new subjects will be added according to the procedure in 5.8.
DS-5141b was administered at 2 dose levels (2.0 mg/kg and 6.0 mg/kg) based on the results of Part 1.

<Part 2-Extension>
DS-5141b will be administered subcutaneously once weekly for 48 weeks (a total of 48 doses) at 2 dose levels (2.0 mg/kg and 6.0 mg/kg) based on the results of Part 2. Subjects who have finished Part 2 may participate, and 3 subjects will be assigned to each dose level. Any new subjects will be added according to the procedure in 5.8.
Based on the results of nonclinical studies in mice, the study drug administration was temporarily discontinued.

<Part 2-Extension-2>
DS-5141b will be administered subcutaneously once weekly for 48 weeks (a total of 48 doses) at the 2 dose levels of DS-5141b administered in Part 2 (2.0 mg/kg and 6.0 mg/kg) based on the results of Part 2. Subjects who have finished Part 2 may participate, and 3 subjects will be assigned to each dose level. Any new subjects will be added according to the procedure in 5.8.
As a measure to prevent the spread of the novel coronavirus, administration by a guardian at home ("self-administration") will be allowed. Consent for self-administration will be obtained from the legally acceptable representative, and the guardian performing self-administration will be given training in the method of storing the study drug, the method of administering the study drug and the method for recording information in the "Self-Injection Diary" before self-administration starts.

<Rationale>
Since the number of target patients in this study is small, we selected a design that allows as much information for assessing DS-5141b as possible to be obtained from a limited number of patients. We selected 4 weeks as the duration of study drug administration for each subject in Part 1, since this is the period for which safety was confirmed in the nonclinical toxicology study. Specifically, we decided to administer

each dose level to a subject once weekly for 2 weeks (a total of 2 doses), so that 2 dose levels are administered, with a total of 4 doses over 4 weeks. We selected 12 doses in 12 weeks as the duration of study drug administration in Part 2 in order to confirm the expression of dystrophin protein. We plan to start Part 2 after safety has been confirmed in a nonclinical toxicology study with long-term repeated dosing.
We selected 48 doses in 48 weeks as the duration of study drug administration in Part 2-Extension and Part 2-Extension-2, in order to confirm the expression of dystrophin protein due to long-term administration of DS-5141b.

4. TARGET SUBJECTS

4.1 Selection of Subjects

DMD patients who meet all of the following inclusion criteria and do not meet any of the exclusion criteria at the time of registration in this study will be included in the study.

4.1.1 Inclusion Criteria

1) Patients who have been confirmed to have an out-of-frame deletion that can be corrected by exon 45 skipping of the dystrophin gene, to thus restore the in-frame deletion.
2) Those who have been confirmed to have a DNA sequence that forms a double strand with DS-5141b in the exon 45 of the dystrophin gene.
3) Those who have intact muscles of adequate quality for biopsy to allow evaluation of the efficacy of the study drug.
4) Boys aged from 5 to <11 years at the time of registration.
5) Those who are able to walk at least 325 meters in the 6-minute walk test.
6) Steroid-naive patients or patients who have been treated with steroids for at least 6 months prior to registration in the study without a dosage change for at least 3 months prior to registration.
7) Those who are able to follow the instructions on the scheduled admission, visits, treatment plan, tests/observations, and other study procedures set in the protocol while participating in the study.
8) Those who have voluntarily provided written informed consent or have received adequate explanations about the study involving their decision-making about participation in the study.
9) Those whose legal representatives have voluntarily provided written informed consent in an appropriate manner.

<Rationale>
1), 2), 3) These were selected to appropriately assess the efficacy of the study drug.
4) Lower age limit (5 years or older): The lower age limit was selected to be an age where the subject can follow the study procedures planned in this study with the cooperation of their families or guardians. Upper age limit (younger than 11 years): During the clinical course of DMD, many patients lose the ability to walk at around the age of 10 years.[1] The upper age limit was selected because it is not feasible to

perform muscle biopsy in patients who have lost the ability to walk.
5) It has been reported that patients with a result less than 325 m in the 6-minute walk test are likely to lose the ability to walk within 1 year.[5] This was selected because it is not feasible to perform muscle biopsy in patients who have lost the ability to walk.
6), 7) These were selected to appropriately assess the efficacy and safety of the study drug.
8), 9) These were selected due to ethical considerations about the handling of subjects.

4.1.2 Exclusion Criteria

1) Patients with a gene mutation which is not expected to produce the dystrophin protein by exon 45 skipping.
2) Concurrent illness other than DMD that can cause muscle weakness and/or impairment of motor function.
3) Current or previous severe disorder involving the liver, kidneys, blood, hypersensitivity, respiratory system, gastrointestinal system, circulatory system, central nervous system, etc.
4) Left ventricular ejection fraction <55% on the echocardiogram.
5) Fridericia-corrected QT interval (QTc) >0.45 seconds on the 12-lead electrocardiogram.
6) Those who require treatment of the respiratory system, eg, respiratory physical therapy or mechanical respiratory support.
7) Those who have a positive result for the hepatitis B surface (HBs) antigen, hepatitis C virus (HCV) antibody, or human immunodeficiency virus (HIV) antibody tests.
8) Those who have participated in another clinical study and have received an investigational product within 3 months prior to registration in this study.
9) Other patients who are considered ineligible for the study by the investigator or subinvestigator.

<Rationale>
1), 2), 8) These were selected to appropriately assess the efficacy and safety of the study drug.
3), 4), 5), 6), 7) These were selected out of consideration for the safety of subjects.
9) This was selected so that the investigator or subinvestigator can take other general factors into account.

4.2 Registration of Subjects

4.2.1 Subject Registration Procedure

After obtaining written informed consent (confirmation of intent) from a subjects or his legally acceptable representative (see 15.3), the investigator or subinvestigator will assign a subject identification code, prepare a subject screening list and confirm the eligibility of the subject. The investigator or subinvestigator will fill out the necessary items on the subject registration form (Appendix 1) for a subject determined to be eligible and send it to the sponsor by fax.

The sponsor will cross-check the contents of the subject registration form received with the inclusion criteria and exclusion criteria for this study and check the eligibility of the relevant subject. If the sponsor has any queries about the contents of the subject registration form, the sponsor will immediately contact the investigator or subinvestigator and check the contents. If the subject is confirmed to be eligible, he will be registered and assigned a subject number. The sponsor will immediately inform the investigator etc. of information including the eligibility assessment result, registration date, subject number and study drug dose level, for example by fax. If the sponsor determines that a subject is ineligible, the sponsor will immediately inform the investigator or subinvestigator of the reason for this. The investigator or subinvestigator must not prescribe the study drug until the subject is registered.

If any subject was not registered, the investigator or subinvestigator will explain the reason for this. Later, if the investigator or subinvestigator determines that the subject is suitable for this study, he or she will obtain written informed consent from the subject or legally acceptable representative again and perform registration of the subject according to the procedure specified in this section. The investigator etc. will record information including the registration date, subject number and study drug dose level in the case report form.

4.2.2 Notification If a Subject Is Receiving Treatment from Another Physician

The investigator or subinvestigator will check whether subjects are receiving treatment from another physician (another department at the study site or another medical institution). If a subject is receiving treatment from another physician, with the consent of the subject and his legally acceptable representative, the investigator or subinvestigator will notify the physician that the subject is participating in the study. The fact that this notification has been made will be recorded in medical records or the

like.

4.3 Withdrawal Criteria of Individual Subjects and Action on Withdrawal

If a subject meets any of the following criteria, the investigator or subinvestigator will promptly withdraw the relevant subject from the study and handle the subject appropriately. The investigator or subinvestigator will also follow up any abnormalities observed at the time of withdrawal and, as far as the cooperation of the subject and his legally acceptable representative can be obtained, will perform the physical examinations and tests specified in "6.5 Test Items on Withdrawal from the Study and their Timing" and make efforts to ensure the safety of the subject. If an adverse event occurs, the procedures in "9.5 Items to Investigate for Adverse Events" and "9.7 Action If an Adverse Event Occurs" will be followed.

Each subject's completion of/withdrawal from the study, the date of study completion or withdrawal/discontinuation, and the primary reason for early withdrawal/discontinuation will be recorded on the case report form.

- Continued study drug administration becomes difficult due to the occurrence of an adverse event
- A major deviation from the clinical study protocol is discovered
- The subject or legally acceptable representative makes a request to withdraw
- The study is terminated by the sponsor
- The investigator or subinvestigator determined that it is unsuitable to continue the subject's participation in the study for any other reason

5. METHODOLOGY

5.1 Study Drug

For details of the study drug and its handling, see the "Investigator's Brochure" and "Pharmacy Manual."

5.1.1 Investigational Drug

1) Investigational substance code: DS-5141b
2) Generic name: renadirsen (INN)
3) Content and dosage form:
   - DS-5141b for injection 100 mg is a lyophilized powder in a glass vial. It is white to light yellowish white cake-like mass, and each vial contains 100 mg of DS-5141b.
   - DS-5141b for injection 150 mg is a lyophilized powder in a glass vial. It is a white to light yellowish white cake-like mass, and each vial contains 150 mg of DS-5141b.
   - The accompanying reconstitution diluent for DS-5141b for injection (for 100 mg/mL) is a clear colorless liquid, and each vial (1.1 mL) contains 31 mg of glucose.
   - The accompanying reconstitution diluent for DS-5141b for injection (for 30 mg/mL) is a clear colorless liquid, and each vial (5.4 mL) contains 227 mg of glucose.
   - The accompanying reconstitution diluent for DS-5141b for injection (for 150 mg/mL) is a clear colorless liquid, and each vial (5.4 mL) contains 39 mg of glucose.
4) Lot number: Shown in "Pharmacy Manual."

5.1.2 Labeling and Packaging

Shown in "Pharmacy Manual."

5.1.3 Storage of the Study Drug

After a contract has been concluded, the sponsor will supply the study drug to the study site. The study drug manager will store "DS-5141b for injection 100 mg," "DS-5141b for injection 150 mg," "accompanying reconstitution diluent for DS-5141b for injection (for 100 mg/mL)," "accompanying reconstitution diluent for DS-5141b for injection (for 30 mg/mL)" and "accompanying reconstitution diluent for DS-5141b

for injection (for 150 mg/mL)" in a refrigerator (2°C to 8°C). The study drug will be managed and collected according to the "Pharmacy Manual."
If self-administration is performed as a measure to prevent the spread of the novel coronavirus, before distributing the study drug, the study drug manager will perform visual inspection to check whether there are foreign objects or discoloration in any vials. If foreign objects or discoloration are observed in a study drug, it must not be distributed. The study drug manager will check the quantities of study drug distributed to each subject on each visit day and the dates, the quantities of used and unused vials returned by subjects, and the "Self-Injection Diaries," and will record these in the Drug Accountability Record. If self-injection is performed, the study drug will be stored in the subjects' homes according to the "Self-Injection Guide."

5.2 Study Drug Administration Method

5.2.1 Dose

Doses will be calculated based on the subject's body weight. If the subject's body weight has changed by ≥10% since the last dose, the dose will be recalculated.

<Part 1>
This part will consist of the following dose levels.

Level	Dose	Number of doses, route of administration
1	0.1 mg/kg	Once weekly for 2 weeks (a total of 2 doses) Subcutaneous administration
2	0.5 mg/kg	
3	2.0 mg/kg	
4	6.0 mg/kg	

<Part 2>
The 2 dose levels of DS-5141b decided based on the results of Part 1 will be administered subcutaneously once weekly for 12 weeks (a total of 12 doses).

<Part 2-Extension>
Based on the results of Part 2, the 2 dose levels of DS-5141b administered in Part 2 (2.0 mg/kg, 6.0 mg/kg) will be administered subcutaneously once weekly for 48 weeks (a total of 48 doses).
Based on the results of nonclinical studies in mice, the study drug administration was temporarily discontinued.

<Part 2-Extension-2>
Based on the results of Part 2, the 2 dose levels of DS-5141b administered in Part 2 (2.0 mg/kg, 6.0 mg/kg) will be administered subcutaneously once weekly for 48 weeks (a total of 48 doses).

<Rationale>
We selected the first dose of 0.1 mg/kg with reference to "Guidance for Establishing Safety in First-in-Human Studies during Drug Development,[6]" by calculating the human equivalent dose (HED) for the NOAEL in murine toxicity studies, and taking the safety factor into consideration.
In a twice-weekly 1-month intermittent subcutaneous administration toxicity study in mice, vacuolization of the bladder transitional epithelium and thickening of the bladder mucosa were observed in groups administered doses ≥30 mg/kg, and therefore, we determined that the NOAEL was 10 mg/kg. Taking into account these toxicity findings and the severity and rarity of DMD, we selected 10 as the safety factor.
Since doses were administered twice weekly in the murine toxicity study, the dose per week at the NOAEL in mice was 10 mg/kg × 2 = 20 mg/kg per week, and the HED after body surface area conversion (conversion factor 0.09 [assuming a child's body weight to be 30 kg])[7] was calculated to be 1.8 mg/kg per week.
Based on the above, and taking into account that DS-5141b is a novel nucleic acid compound, we selected 0.1 mg/kg, a dose no greater than 1.8 mg/kg × 1/10 = 0.18 mg/kg, as the first dose level. We selected 0.5 mg/kg, 5 times the first dose level, as the second dose level, 2 mg/kg, 4 times the second dose level, as the third dose level, and 6 mg/kg, 3 times the third dose level, as the fourth dose level. The third dose level of 2 mg/kg is almost the same as 1.8 mg/kg, the HED of the dose per week at the NOAEL in mice, 20 mg/kg per week, and the maximum dose of 6 mg/kg is close to 5.4 mg/kg, the HED of the dose per week that was a toxic dose in mice, 60 mg/kg per week. Thus, since the third dose level and fourth dose level are between the NOAEL and toxic doses, the doses will be titrated cautiously, with careful monitoring to ensure the safety of subjects.
Since none of the 4 dose levels administered in Part 1 was associated with any problems with subject tolerability, the study drug was administered at dose levels of 2.0 mg/kg and 6.0 mg/kg in Part 2. In Part 2-Extension and Part 2-Extension-2, it will be administered at the same dose levels as in Part 2.

5.3 Method of Administration

The study drug will be administered once weekly by subcutaneous injection. In Part 2, Part 2-Extension and Part 2-Extension-2, if it cannot be administered once weekly, for example because of the circumstances of the subject, the administration day is allowed to be within ±2 days of the specified date. There will be intervals of at least 3 days between doses. The temperature of the solution for administration will be adjusted to approximately between room temperature and body temperature before administration. If 1 dose is administered at multiple locations, there will be distances of ≥4 cm between locations. The study drug will not be administered to the same location in consecutive weeks.

If self-administration is performed as a measure to prevent the spread of the novel coronavirus, the guardian performing self-administration will record the dose and date/time of administration in a "Self-Injection Diary." The investigator or subinvestigator will check the "Self-Injection Diary" on each visit day and provide retraining if necessary.

5.3.1 Method for Preparing the Solution for Administration

The dose of the study drug will be calculated based on the subject's body weight. The solution for injection will be prepared according to the relevant procedure in one of 1) to 3) below, depending on the dose. If the total dose cannot be obtained by performing the procedure once, the same procedure will be repeated until the total dose is obtained. The prepared solution for administration will be administered promptly after preparation.

1) If the dose is <3 mg
   An amount of 5.4 mL of the "accompanying reconstitution diluent for DS-5141b for injection (for 30 mg/mL)" will be added to "DS-5141b for injection 150 mg" to reconstitute it. After this, 1.0 mL of the obtained solution for administration (30 mg/mL) and 9.0 mL of Japanese Pharmacopoeia glucose for injection will be mixed in a sterilized vial to prepare 10 mL of 3 mg/mL solution for administration.
2) If the dose is ≥3 mg and <30 mg
   An amount of 5.4 mL of the "accompanying reconstitution diluent for DS-5141b for injection (for 30 mg/mL)" will be added to "DS-5141b for injection 150 mg" to reconstitute it, and 5.4 mL of 30 mg/mL solution for administration will be prepared.
3) If the dose is ≥30 mg

An amount of 1.0 mL of the "accompanying reconstitution diluent for DS-5141b for injection (for 150 mg/mL)" will be added to "DS-5141b for injection 150 mg" to reconstitute it, and 150 mg/mL solution for administration will be prepared. Alternatively, an amount of 1.1 mL of the "accompanying reconstitution diluent for DS-5141b for injection (for 100 mg/mL)" will be added to "DS-5141b for injection 100 mg" to reconstitute it, and 100 mg/mL solution for administration will be prepared.

5.4 Part 1 and Part 2

5.4.1 Start Time of Administration in Part 1

Administration of the study drug to the second subject at each dose level in Part 1 will be started after the second dose of the study drug has been administered to the first subject. If administration at Dose Level 3 (or 4) is started in a subject who has finished Dose Level 1 (or 2) in Part 1, there will be an interval ≥12 weeks between the stop date of administration of the study drug at Dose Level 1 (or 2) and the start date of administration of the study drug at Dose Level 3 (or 4).

5.4.2 Transition Between Dose Levels in Part 1

Transitions between dose levels in Part 1 will be made according to the following procedure.

1) The investigator will promptly report data relating to the safety and tolerability in each subject to the sponsor.
2) Whether to transition to the next dose level will be considered based on the data for 3 subjects at the time point 7 days after the second dose of the study drug to the third subject at the dose level being assessed. The sponsor will provide the data to a safety assessment committee member and request that the committee member considers whether it is possible to transition to the next dose level. Based on the opinion of the safety assessment committee member, the sponsor will consider whether it is possible to transition to the next dose level, and make a decision. During consideration, the details of adverse events observed at this dose level, their association with the study drug, dose dependence, their degree (severity), recoverability, and results such as pharmacokinetic results and the results of nonclinical toxicity studies will be taken into account. Reference will be made to "5.4.4 Criteria for Considering Whether to Transition Between Dose Levels in Part 1," and the investigator or medical expert will be consulted as

necessary.

3) When transitioning to the next dose level, to ensure the safety of subjects if action such as changing the contents or frequencies of tests or observations is necessary, the sponsor will change documents such as the clinical study protocol and informed consent form.
4) The sponsor will inform the investigator of the results of consideration about transitioning to the next dose level.

5.4.3 Transitioning from Part 1 to Part 2

Transitioning from Part 1 to Part 2 will be performed according to the following procedure.

1) The investigator will promptly report data relating to safety and tolerability in each subject to the sponsor.
2) Whether to transition to the next dose level and the doses to use in Part 2 will be considered based on the data for all dose levels at the time point 7 days after the second dose of the study drug to the third subject at the highest dose level assessed in Part 1. The sponsor will provide the data to a safety assessment committee member and request that the committee member considers whether it is possible to transition to Part 2 and the doses to use in Part 2. Based on the opinion of the safety assessment committee member, the sponsor will consider whether it is possible to transition to Part 2 and the doses to use in Part 2, and make a decision. During consideration, the details of adverse events observed in Part 1, their association with the study drug, dose dependence, their degree (severity), recoverability, and results such as pharmacokinetic results and the results of nonclinical toxicity studies will be taken into account. Reference will be made to "5.4.4 Criteria for Considering Whether to Transition Between Dose Levels in Part 1," and the investigator or medical expert will be consulted as necessary.
3) When transitioning to Part 2, to ensure the safety of subjects if action such as changing the contents or frequencies of tests or observations is necessary, the sponsor will change documents such as the clinical study protocol and informed consent form.
4) The sponsor will inform the investigator of the results of consideration about transitioning to Part 2. If the study will transition to Part 2, the sponsor will decide the dose levels administered to each subject in Part 2 and inform the investigator.

5.4.4 Criteria for Considering Whether to Transition Between Dose Levels in Part 1

If the following findings are observed at a dose level being assessed in Part 1, whether to transition between dose levels in Part 1 will be considered.

1) Adverse reactions corresponding to Grade 3 in "Seriousness Grading Criteria for Adverse Reactions to Pharmaceuticals" (Notification No. 80 of the Safety Division, PAB dated 29 Jun 1992, Appendix 2) (in ≥1 subject)
   For adverse reactions of the liver and kidneys, these criteria will not be used.
2) Severe adverse reactions (in ≥2 subjects)

If findings meeting any of the following criteria are observed at a dose level being assessed in Part 1, whether to transition between dose levels in Part 1 will be considered, taking a comprehensive view of information including the baseline value, other test findings and clinical findings.

<Liver>

1) ALT ≥10 times the site's upper limit of reference range and also total bilirubin ≥2 times the site's upper limit of reference range
2) ALT ≥10 times the site's upper limit of reference range and also PT-INR >1.5
3) ALT >twice the baseline value and also total bilirubin >twice the site's upper limit of reference range
4) ALT >twice the baseline value and also PT-INR >1.5
5) ALT ≥10 times the site's upper limit of reference range and also symptoms of hepatitis or hypersensitivity

<Kidneys>

1) Urine protein/creatinine ratio >0.5 g/gCr on 2 consecutive occasions
2) Serum cystatin C concentration ≥the site's upper limit of reference range and also ≥1.5 times the baseline value
3) Urine protein in 24-hour pooled urine >300 mg/day and also >twice the baseline value
4) Urine albumin in 24-hour pooled urine >50 mg/day and also >twice the baseline value
5) Newly occurring casts other than hyaline casts in urine sediment at ≥1 cast/LPF, or newly occurring hyaline casts at ≥21 casts/LPF

6) Newly occurring urine red blood cells at ≥5 cells/HPF

5.5 Randomization and Blinding

Randomization and blinding will not be performed in this study.

5.6 Concomitant Medications and Concomitant Therapy, and Other Restrictions

If concomitant medications are used during the period from registration in the study to the end of the follow-up period in Part 2, and during the period from the day of informed consent for Part 2-Extension to the end of the follow-up period in Part 2-Extension-2 (during the period from registration in the study to the end of the follow-up period in Part 2-Extension-2 for subjects participating in the study from Part 2-Extension or Part 2-Extension-2; and to the start of study drug administration for subjects participating in the long-term extension study), the drug name, administration method, dose, start date, stop date, and indication intended for will be recorded on the case report form. If concomitant therapy is performed, the treatment/procedure name, start date, stop date, frequency and indication intended for will be recorded on the case report form.

5.6.1 Prohibited Concomitant Drugs

Concomitant use of the following drugs is prohibited during the period from registration in the study to the end of the follow-up period in Part 2, and during the period from the day of informed consent for Part 2-Extension to the end of the follow-up period in Part 2-Extension-2 (during the period from registration in the study to the end of the follow-up period in Part 2-Extension-2 for subjects participating in the study from Part 2-Extension or Part 2-Extension-2; and to the start of study drug administration for subjects participating in the long-term extension study).

1) Other anti-DMD drugs than the study drug used in this study and steroids
2) Other investigational products
3) Chloroquine and hydroxychloroquine

<Rationale>

1) This was selected because it may affect assessment of efficacy and safety.
2) This was selected because the safety of other investigational products in development has not been established, and therefore, concomitant use with the

study drug is a safety problem.

3) This was selected because it may affect assessment of safety and efficacy. It was selected because, with the spread of the novel coronavirus, concomitant use of these drugs has become more likely.

5.6.2 Prohibited Concomitant Therapy

The use of the following therapy is prohibited from registration in this study to the end of the follow-up period in Part 2-Extension-2 (or to the start of study drug administration in the long-term extension study for subjects participating in the long-term extension study).

1) HAL® (Hybrid Assistive Limb®)

<Rationale>

1) This was selected because it may affect assessment of efficacy and safety.

5.6.3 Other Restrictions

During the period from registration in the study to the end of the follow-up period in Part 2, and during the period from the day of informed consent for Part 2-Extension to the end of the follow-up period in Part 2-Extension-2 (during the period from registration in the study to the end of the follow-up period in Part 2-Extension-2 for subjects participating in the study from Part 2-Extension or Part 2-Extension-2, and from the start of study drug administration for subjects participating in the long-term extension study), except in the following cases, newly starting steroids or changing the frequency or dose of steroids is prohibited.

- Temporary discontinuation or discontinuation due to the occurrence of adverse reactions to steroids
- Changes in dose due to variations in body weight
- Localized administration (such as the use of eye drops or inhalation) for purposes other than treatment of DMD

<Rationale>

This was selected because it may affect assessment of efficacy.

5.7 Subject Management

The duration of hospitalization will be as follows.

1) From the day before administration of the first dose of the study drug at each dose level in Part 1 (Day 0) to 3 days after study drug administration (Day 4)
2) From the date of administration of the second dose of the study drug at each dose level in Part 1 (Day 8) to 3 days after study drug administration (Day 11)
3) From the day before administration of the first dose of the study drug in Part 2 (Day 0) to the day after administration (Day 2)
4) From the day before administration of the last dose of the study drug in Part 2 (Day 77) to the day after administration of the last dose of the study drug (Day 79)
5) From the day before administration of the first dose of the study drug in Part 2-Extension (Week 0/ Day 0) to the day after administration (Week 1/ Day 2)
6) From the day before administration of the study drug in Week 13 of Part 2-Extension (Week 12/ Day 84), the day before administration of the study drug in Week 25 (Week 24/ Day 168) and the day before administration of the study drug in Week 37 (Week 36/ Day 252) to the day of administration
7) From the day before administration of the last dose of the study drug in Week 48 of Part 2-Extension (Week 47/ Day 329) to the day after administration of the last dose of the study drug (Week 48/ Day 331)
8) From the day before administration of the first dose of the study drug in Part 2-Extension-2 (Week 0/ Day 0) to the day after administration (Week 1/ Day 2)
9) From the day before administration of the study drug in Week 13 of Part 2-Extension-2 (Week 12/ Day 84), the day before administration of the study drug in Week 25 (Week 24/ Day 168) and the day before administration of the study drug in Week 37 (Week 36/ Day 252) to the day of administration
10) From the day before administration of the last dose of the study drug in Week 48 of Part 2-Extension-2 (Week 47/ Day 329) to the day after administration of the last dose of the study drug (Week 48/ Day 331)

For 5) to 7) and 9) to 10), hospitalization is not compulsory if tests and assessment can be performed appropriately, but in the case of subjects participating in the study from Part 2-Extension, hospitalization for 5) is compulsory.

If an adverse event that occurs during hospitalization continues until the planned discharge date, the investigator or subinvestigator will determine whether it is necessary to continue hospitalization, taking into account the need to ensure the subject's safety.

5.8 Addition of Subjects

In the following cases, subjects may be newly added in Part 1, Part 2, Part 2-Extension or Part 2-Extension-2. The sponsor will consult the medical expert if necessary before deciding whether it is necessary to add a subject.

1) There is a subject who is found not to meet the eligibility requirements after registration
2) There is a subject who was not administered the study drug or in whom administration of the study drug was not completed
3) It is considered necessary to add a subject for any other reason in order to assess the safety and efficacy of study drug

6. STUDY PROCEDURES

6.1 Listing of Examinations, Observations and Tests

The timing of examinations, observations and tests in this study is shown in Appendix 3. The investigator or subinvestigator will record the results of examinations, observations and tests and information such as the time of sample collection on the case report form. In this study, the period from the date of informed consent to the end of the follow-up period in Part 2, and during the period from the day of informed consent for Part 2-Extension to the end of the follow-up period in Part 2-Extension-2 (during the period from the date of informed consent for Part 2-Extension-2 to the end of the follow-up period in Part 2-Extension-2 for subjects participating in the study from Part 2-Extension-2) will be the "study duration" for each subject. Subjects who complete 48 weeks of study drug administration in Part 2-Extension-2 of this study and complete efficacy assessment after administration may participate in the long-term extension study. For subjects who participate in the long-term extension study, Week 52/ Day 358 will not be carried out, and the period until the start of study drug administration in the long-term extension study will be the "study duration" for this study. However, if it is difficult for a subject to continue the study, for example because the subject is unable to make visits, the study duration will end as of the relevant date, and will not continue until the end of the follow-up period.

6.2 Itemization of Vital Signs, Clinical Findings and Laboratory Tests

1) Vital signs

   Body temperature (axillary temperature), blood pressure (systolic blood pressure, diastolic blood pressure) and pulse rate will be measured, and the result and date/time of measurements will be recorded on the case report form. Blood pressure and pulse rate will be measured in the sitting position.

2) Clinical findings

   A physical examination including medical interview, visual examination, auscultation and palpation will be performed, and the result and date/time of the examination will be recorded on the case report form. In particular, neurological findings will be observed carefully, with reference to the "Pediatric Neurological Test Chart.[8]"

3) Blood tests and urinalysis

   The following items will be measured, and the test result, blood (or urine) collection date and fed/fasted state (blood chemistry tests and urinalysis only) will

be recorded on the case report form. The reference ranges at the measuring site will be used as reference ranges for laboratory data. On Day 1 (pre-dose), Day 4 and Day 11 of each dose level in Part 1, Day 1 (pre-dose) and Day 78 (pre-dose) of Part 2, Week 1/ Day 1 (pre-dose), Week 13/ Day 85 (pre-dose), Week 25/ Day 169 (pre-dose), Week 37/ Day 253 (pre-dose), and Week 48/ Day 330 (pre-dose) of Part 2-Extension, and Week 1/ Day 1 (pre-dose), Week 13/ Day 85 (pre-dose), Week 25/ Day 169 (pre-dose), Week 37/ Day 253 (pre-dose), and Week 48/ Day 330 (pre-dose) of Part 2-Extension-2, 24-hour urine pooling will be performed, starting on the previous day. On other specified dates, spot urine will be used. Spot urine before study drug administration, on the day after study drug administration, and during the follow-up period will be collected in the morning, as far as possible. Spot urine on Week 1/ Day 1 (from 4 hours post-dose), Week 13/ Day 85 (from 4 hours post-dose), Week 25/ Day 169 (from 4 hours post-dose), Week 37/ Day 253 (from 4 hours post-dose), and Week 48/ Day 330 (from 4 hours post-dose) of Part 2-Extension and Week 1/ Day 1 (from 4 hours post-dose), Week 13/ Day 85 (from 4 hours post-dose), Week 25/ Day 169 (from 4 hours post-dose), Week 37/ Day 253 (from 4 hours post-dose), and Week 48/ Day 330 (from 4 hours post-dose) of Part 2-Extension-2 will be sampled on the date of study drug administration, ≥4 hours after study drug administration, as far as possible.

Test contents	Test items
Hematology test	Red blood cell count, hemoglobin, hematocrit, white blood cell count, white blood cell differential count (neutrophil, lymphocyte, monocyte, eosinophil, basophil), platelet count, reticulocyte count, MCV, MCH, MCHC, APTT, PT-INR
Blood chemistry test	Total protein, albumin, A/G ratio, total bilirubin, direct bilirubin, AST, ALT, ALP, gamma-GT, LDH, CK, BUN, creatinine, uric acid, Na, K, Cl, Ca, P, Mg, total cholesterol, triglyceride, glucose, CRP, iron, total iron binding capacity, ferritin, cystatin C, cardiac troponin T
Urinalysis	Qualitative (glucose, protein, occult blood, ketone bodies, bilirubin, urobilinogen, specific gravity, pH), urinary sediment (red blood cell, white blood cell, casts, epithelial cells, crystals, bacteria), urine protein,[*1] urine creatinine,[*1] urine albumin,[*1] NAG,[*1] alpha-1 microglobulin,[*1] beta-2 microglobulin,[*1] volume of urine[*1]

*1: To be measured using 24-hour pooled urine on Day 1 (pre-dose), Day 4 and Day 11 of Part 1, Day 1 (pre-dose) and Day 78 (pre-dose) of Part 2, Week 1/ Day 1 (pre-dose), Week 13/ Day 85 (pre-dose), Week 25/ Day 169 (pre-dose), Week 37/ Day 253 (pre-dose) and Week 48/ Day 330 (pre-dose) of Part 2-Extension, and Week 1/ Day 1 (pre-dose), Week 13/ Day 85 (pre-dose), Week 25/ Day 169 (pre-dose), Week 37/ Day 253 (pre-dose) and Week 48/ Day 330 (pre-dose) of Part 2-Extension-2.

4) 12-lead electrocardiogram

A standard 12-lead electrocardiogram will be recorded after the subject has been rested for ≥5 minutes in the decubitus position. The investigator or subinvestigator will judge the overall test result as "normal," "abnormal, not clinically significant" or "clinically significant finding" and record this on the case report form. If the judgment is "clinically significant finding," this will be handled as an adverse event, and details will be recorded on the case report form. However, abnormalities already observed before study drug administration that have not worsened after study drug administration will not be handled as adverse events.

<12-lead electrocardiogram observation points>

- Part 1
  Day 1 (pre-dose, 2 hours and 6 hours post-dose), Day 2, Day 4, Day 8 (pre-dose, 2 hours and 6 hours post-dose), Day 9, Day 11, Day 15, Day 22, Day 36, Day 64
- Part 2
  Day 1 (pre-dose, 2 hours and 6 hours post-dose), Day 2, Day 22 (pre-dose), Day 50 (pre-dose), Day 78 (pre-dose, 2 hours, 4 hours, 6 hours, and 8 hours post-dose), Day 79, Day 85, Day 92, Day 106, Day 134, Day 162
- Part 2-Extension
  Week 1/ Day 1 (pre-dose and 4 hours post-dose), Week 1/ Day 2, Week 5/ Day 29 (pre-dose), Week 9/ Day 57 (pre-dose), Week 13/ Day 85 (pre-dose), Week 17/ Day 113 (pre-dose), Week 21/ Day 141 (pre-dose), Week 25/ Day 169 (pre-dose), Week 29/ Day 197 (pre-dose), Week 33/ Day 225 (pre-dose), Week 37/ Day 253 (pre-dose), Week 41/ Day 281 (pre-dose), Week 45/ Day 309 (pre-dose), Week 48/ Day 330 (pre-dose, 2 hours, 4 hours, 6 hours, and 8 hours post-dose), Week 48/ Day 331, Week 49/ Day 337, Week 52/ Day 358
- Part 2-Extension-2
  Week 1/ Day 1 (pre-dose and 4 hours post-dose), Week 1/ Day 2, Week 5/ Day 29 (pre-dose), Week 9/ Day 57 (pre-dose), Week 13/ Day 85 (pre-dose), Week 17/ Day 113 (pre-dose), Week 21/ Day 141 (pre-dose), Week 25/ Day 169 (pre-dose), Week 29/ Day 197 (pre-dose), Week 33/ Day 225 (pre-dose), Week 37/ Day 253 (pre-dose),

Week 41/ Day 281 (pre-dose), Week 45/ Day 309 (pre-dose),
Week 48/ Day 330 (pre-dose, 2 hours, 4 hours, 6 hours, and 8 hours post-dose),
Week 48/ Day 331, Week 49/ Day 337, Week 52/ Day 358

For each subject, at the first dose of the study drug (Day 1),*2 pre-dose and 2 hours, 4 hours, 6 hours, 8 hours, and 24 hours post-dose (Day 2), at the second dose at Dose Level 3 and Dose Level 4 of Part 1 (Day 8), pre-dose and 2 hours, 4 hours, 6 hours, 8 hours, and 24 hours post-dose (Day 9), at the 12th dose of the study drug in Part 2 (Day 78), pre-dose and 2 hours, 4 hours, 6 hours, 8 hours, and 24 hours post-dose (Day 79), in Part 2-Extension, on Week 1/ Day 1 (pre-dose and 4 hours post-dose), 24 hours post-dose (Week 1/ Day 2) and Week 48/ Day 330 (pre-dose, 2 hours, 4 hours, 6 hours, and 8 hours post-dose), 24 hours post-dose (Week 48/ Day 331), and in Part 2-Extension-2, on Week 1/ Day 1 (pre-dose and 4 hours post-dose), 24 hours post-dose (Week 1/ Day 2) and Week 48/ Day 330 (pre-dose, 2 hours, 4 hours, 6 hours, and 8 hours post-dose), 24 hours post-dose (Week 48/ Day 331), measurement will be performed 3 times at each planned time point, and the electrocardiogram will be sent electronically to an electrocardiogram analysis laboratory to measure the PR interval, QRS interval, QT interval, RR interval, and QTc.

*2: Including the first dose of the study drug in subjects participating in the study from Dose Level 3 or Dose Level 4 of Part 1, Part 2, Part 2-Extension or Part 2-Extension-2

5) CCI [redacted] The investigator or subinvestigator will judge the overall test result as “normal,” “abnormal, not clinically significant” or “clinically significant finding” and record this on the case report form. If the judgment is “clinically significant finding,” this will be handled as an adverse event, and details will be recorded on the case report form. However, abnormalities already observed before study drug administration that have not worsened after study drug administration will not be handled as adverse events.

6.3 Items and Timing of Tests Before Registration of Subjects

1) Items checked after informed consent and before registration

The following investigations, examinations, and tests will be performed, and the results will be recorded on the case report form.

- Day of informed consent (or confirmation of intent) by the subject for participation in this study
- Day of informed consent by the legally acceptable representative for participation in this study
- Subject identification code
- Baseline subject characteristics
  Race, country of residence at informed consent, sex, date of birth
- Medical history and complications
  Whether these are present or absent, whether they are ongoing (if ongoing: complications), and the findings and diagnoses will be checked. The medical history will list the symptoms and diseases from which the subject has recovered before study drug administration is started that the investigator or subinvestigator determines are necessary to report.
- History of participation in other studies
- Medical interventions by other physicians
- Method of genetic diagnosis
- Type of dystrophin gene mutation (for example, the region of the missing exon)
- DNA sequence of the site of DS-5141b double-strand formation in the dystrophin gene
- History of muscle biopsy
- History of steroid use

2) Items performed after informed consent and within a period of 28 days before registration

The following investigations, examinations, and tests will be performed. Data obtained before informed consent may also be used. For MRI or CT, motor function assessment (6-minute walk test), and cardiac function assessment (left ventricular ejection fraction), information such as the day of measurements will be recorded on the case report form.

- MRI or CT
  <Location of imaging>

Upper arm: MRI or CT (to confirm the location of muscle biopsy)
Thigh: MRI[*3]

- Motor function assessment (6-minute walk test)
- Cardiac function assessment (left ventricular ejection fraction)
- 12-lead electrocardiogram
- HBs antigen, hepatitis C virus antibody, HIV antibody test

*3: MRI of the thigh will be performed after informed consent and before the start of study drug administration.

6.4 Items and Timing of Tests After Registration

The following investigations, examinations, and tests will be performed, and the results will be recorded on the case report form.

6.4.1 Items to Be Performed After Registration up to the Day Before the First Dose of Study Drug (Day 0)

These will be performed after registration up to the day before the first dose of the study drug in each subject (Day 0). These items will also be performed in subjects participating in the study from Dose Level 3 or Dose Level 4 of Part 1, Part 2, Part 2-Extension or Part 2-Extension-2

<Items performed up to 28 days before the first dose of the study drug>

- Muscle biopsy, skin biopsy[*4]

<Items performed from 14 days before the first dose of the study drug up to the day before the first dose of the study drug (Day 0)>

1) Checking concomitant medications and concomitant therapy
2) Height and body weight
3) Vital signs and clinical findings
4) Blood tests and urinalysis
5) 12-lead electrocardiogram
6) CCI [redacted] [*5]
7) Motor function assessment[*6]
8) Respiratory function assessment[*7]
9) Cardiac function assessment[*7]
10) Quantitative muscle strength assessment[*6]
11) Blood collection

- Anti-dystrophin antibody
- Anti-DS-5141b antibody
- Blood cell dystrophin mRNA*4

12) Urine collection
- Urine protein
- Urine DS-5141b metabolites*8

*4: Not necessary in subjects participating in the study from Part 2-Extension or Part 2-Extension-2.
*5: To be performed in subjects participating in the study from Part 2-Extension-2. CCI will be performed after registration and before the first dose of the study drug.
*6: To be performed twice, at least 28 days after muscle biopsy.
*7: To be performed at least 28 days after muscle biopsy.
*8: Not necessary in subjects participating in the study from Part 2, Part 2-Extension or Part 2-Extension-2.

6.4.2 Part 1

6.4.2.1 Items to Be Performed Before the First Dose of the Study Drug at the Second Dosage

If subjects who have finished Dose Level 1 or 2 to continue to participate in Dose Level 3 or 4 of Part 1, the following will be performed from 14 days before the first dose of the study drug up to the day before the first dose of the study drug (Day 0).

1) Checking concomitant medications and concomitant therapy
2) Height and body weight
3) Vital signs and clinical findings
4) Blood tests and urinalysis
5) 12-lead electrocardiogram
6) Blood collection
   - Blood cell dystrophin mRNA
7) Urine collection
   - Urine protein

6.4.2.2 Items to Be Performed During the Treatment Period (Day 1 to Day 14) and Follow-Up Period (Day 15 to Day 64) for Each Dose Level

The visit window for items performed on Day 15 and Day 22 is ±2 days, and the visit window for items performed on Day 36 and Day 64 is ±7 days.

1) Checking the administration status of the study drug
   Whether the study drug was administered, date/time of study drug administration, dose level, actual dose (mg)
2) Investigating concomitant medications and concomitant therapy
3) Investigating adverse events
4) Body weight
   <Observation point>
   Day 15
5) Vital signs and clinical findings
   <Observation point>
   Day 1 (pre-dose and 1 hour, 2 hours, and 6 hours post-dose), Day 2, Day 4, Day 8 (pre-dose and 1 hour, 2 hours, and 6 hours post-dose), Day 9, Day 11, Day 15, Day 22, Day 36, Day 64
6) Blood tests and urinalysis
   <Observation point>
   Day 1 (pre-dose),[*8] Day 2, Day 4,[*8] Day 8 (pre-dose), Day 9, Day 11,[*8] Day 15, Day 36, Day 64
7) 12-lead electrocardiogram
   <Observation point>
   See 6.2
8) Blood collection
   - Pharmacokinetics
     <Blood collection point>
     See 6.7
   - Anti-dystrophin antibody
     <Blood collection point>
     Day 15
   - Anti-DS-5141b antibody
     <Blood collection point>
     Day 15
   - Blood cell dystrophin mRNA

<Blood collection point>
Day 15

9) Urine collection
- Urine protein
  <Urine collection point>
  Day 15
- Urine DS-5141b metabolites
  <Urine collection point>
  Day 9

*8: 24-hour urine pooling will be performed, starting on the previous day.

6.4.3 Part 2

6.4.3.1 Items to Be Performed Before the First Dose of Study Drug in Part 2

If subjects who have finished Part 1 continue to participate, the following will be performed from 14 days before the first dose of the study drug up to the day before the first dose of the study drug (Day 0). For subjects participating from Part 2, "6.4.1 Items to Be Performed After Registration up to the Day Before the First Dose of Study Drug (Day 0)" will be performed, and these tests will not be necessary.

1) Checking concomitant medications and concomitant therapy
2) Height and body weight
3) Vital signs and clinical findings
4) Blood tests and urinalysis
5) 12-lead electrocardiogram
6) MRI (only for subjects in whom MRI can be performed appropriately)
   <Location of imaging>
   MRI: Thigh
7) Motor function assessment[*9]
8) Respiratory function assessment
9) Cardiac function assessment
10) Quantitative muscle strength assessment[*9]
11) Blood collection
    - Anti-dystrophin antibody
    - Anti-DS-5141b antibody
    - Blood cell dystrophin mRNA
12) Urine collection

- Urine protein

*9: To be performed twice.

6.4.3.2 Items to Be Performed During the Treatment Period (Day 1 to Day 84) and Follow-Up Period (Day 85 to Day 162)

The visit window for items performed on Day 8 to Day 92 is ±2 days, and the visit window for items performed on Day 106, Day 134, and Day 162 is ±7 days.

1) Administration status of the study drug
   Whether the study drug was administered, date/time of study drug administration, dose level, actual dose (mg)
2) Investigating concomitant medications and concomitant therapy
3) Investigating adverse events
4) Body weight
   <Observation point>
   Day 29, Day 57, Day 85
5) Vital signs and clinical findings
   <Observation point>
   Day 1 (pre-dose and 1 hour, 2 hours, and 6 hours post-dose), Day 2, Day 8, Day 15, Day 22, Day 29, Day 36, Day 43, Day 50, Day 57, Day 64, Day 71, Day 78 (pre-dose and 1 hour, 2 hours, and 6 hours post-dose), Day 79, Day 85, Day 92, Day 106, Day 134, Day 162 (to be performed pre-dose on Day 8 to Day 78)
6) Blood tests and urinalysis
   <Observation point>
   Day 1,[*10] Day 2, Day 22, Day 50, Day 78,[*10] Day 85, Day 106, Day 134, Day 162 (to be performed pre-dose on Day 1 to Day 78)
7) 12-lead electrocardiogram
   <Observation point>
   See 6.2
8) MRI or CT
   <Location of imaging>
   Upper arm: MRI or CT (to confirm the location of muscle biopsy)
   Thigh: MRI
   <Investigation point>
   To be performed once in the period from Day 85 to Day 99.

9) Muscle biopsy
<Investigation point>
To be performed once in the period from Day 85 to Day 99. To be performed after MRI or CT, motor function assessment, respiratory function assessment, cardiac function assessment, and quantitative muscle strength assessment.

10) Motor function assessment
<Investigation point>
To be performed twice in the period from Day 85 to Day 99.

11) Respiratory function assessment
<Investigation point>
To be performed once in the period from Day 85 to Day 99.

12) Cardiac function assessment
<Investigation point>
To be performed once in the period from Day 85 to Day 99.

13) Quantitative muscle strength assessment
<Investigation point>
To be performed twice in the period from Day 85 to Day 99.

14) Blood collection

- Pharmacokinetics
  <Blood collection point>
  See 6.7
- Anti-dystrophin antibody
  <Blood collection point>
  Day 85
- Anti-DS-5141b antibody
  <Blood collection point>
  Day 85
- Blood cell dystrophin mRNA
  <Blood collection point>
  Day 85

15) Urine collection

- Urine protein
  <Urine collection point>
  Day 85

*10: 24-hour urine pooling will be performed, starting on the previous day.

6.4.4 Part 2-Extension

6.4.4.1 Items to Be Performed Before the First Dose of Study Drug in Part 2-Extension

If subjects who have finished Part 2 continue to participate, the following will be performed from 14 days before the first dose of the study drug up to the day before the first dose of the study drug (Day 0). For subjects participating from Part 2-Extension, "6.4.1 Items to Be Performed After Registration up to the Day Before the First Dose of Study Drug (Day 0)" will be performed, and these tests will not be necessary.

1) Day of informed consent (or confirmation of intent) by the subject for participation in Part 2-Extension
2) Day of informed consent by the legally acceptable representative for participation in Part 2-Extension
3) Checking concomitant medications and concomitant therapy
4) Height and body weight
5) Vital signs and clinical findings
6) Blood tests and urinalysis
7) 12-lead electrocardiogram
8) MRI (only for subjects in whom MRI can be performed appropriately)
   <Location of imaging>
   MRI: Thigh
9) Motor function assessment*11
10) Respiratory function assessment
11) Cardiac function assessment
12) Quantitative muscle strength assessment*11
13) Blood collection
   - Anti-dystrophin antibody
14) Urine collection
   - Urine protein

*11: To be performed twice.

6.4.4.2 Items to Be Performed During the Treatment Period (Week 1/ Day 1 to Week 48/ Day 336) and Follow-Up Period (Week 49/ Day 337 to Week 52/ Day 358)

The visit window for items performed on Week 2/ Day 8 to Week 50/ Day 344 is ±2 days, and the visit window for items performed on Week 52/ Day 358 is ±7 days.

1) Administration status of the study drug
   Whether the study drug was administered, date/time of study drug administration, dose level, actual dose (mg)
2) Investigating concomitant medications and concomitant therapy
3) Investigating adverse events
4) Height and body weight
   <Observation point>
   Week 13/ Day 85, Week 25/ Day 169, Week 37/ Day 253, Week 48/ Day 330
5) Vital signs and clinical findings
   <Observation point>
   Week 1/ Day 1 (pre-dose and 4 hours post-dose), Week 1/ Day 2, Week 2/ Day 8, Week 3/ Day 15, Week 4/ Day 22, Week 5/ Day 29, Week 6/ Day 36, Week 7/ Day 43, Week 8/ Day 50, Week 9/ Day 57, Week 10/ Day 64, Week 11/ Day 71, Week 12/ Day 78, Week 13/ Day 85 (pre-dose and 4 hours post-dose), Week 14/ Day 92, Week 15/ Day 99, Week 16/ Day 106, Week 17/ Day 113, Week 18/ Day 120, Week 19/ Day 127, Week 20/ Day 134, Week 21/ Day 141, Week 22/ Day 148, Week 23/ Day 155, Week 24/ Day 162, Week 25/ Day 169 (pre-dose and 4 hours post-dose), Week 26/ Day 176, Week 27/ Day 183, Week 28/ Day 190, Week 29/ Day 197, Week 30/ Day 204, Week 31/ Day 211, Week 32/ Day 218, Week 33/ Day 225, Week 34/ Day 232, Week 35/ Day 239, Week 36/ Day 246, Week 37/ Day 253 (pre-dose and 4 hours post-dose), Week 38/ Day 260, Week 39/ Day 267, Week 40/ Day 274, Week 41/ Day 281, Week 42/ Day 288, Week 43/ Day 295, Week 44/ Day 302, Week 45/ Day 309, Week 46/ Day 316, Week 47/ Day 323, Week 48/ Day 330 (pre-dose and 4 hours post-dose), Week 48/ Day 331, Week 49/ Day 337, Week 52/ Day 358 (to be performed pre-dose from Week 2/ Day 8 to Week 12/ Day 78, from Week 14/ Day 92 to Week 24/ Day 162, from Week 26/ Day 176 to Week 36/ Day 246, and from Week 38/ Day 260 to Week 47/ Day 323)

6) Blood tests
<Observation point>
Week 1/ Day 1, Week 1/ Day 2, Week 5/ Day 29, Week 9/ Day 57, Week 13/ Day 85, Week 17/ Day 113, Week 21/ Day 141, Week 25/ Day 169, Week 29/ Day 197, Week 33/ Day 225, Week 37/ Day 253, Week 41/ Day 281, Week 45/ Day 309, Week 48/ Day 330, Week 49/ Day 337, Week 52/ Day 358 (to be performed pre-dose on Week 1/ Day 1 and from Week 5/ Day 29 to Week 48/ Day 330)

7) Urinalysis
<Observation point>
Week 1/ Day 1 (pre-dose,[*12] from 4 hours post-dose), Week 1/ Day 2, Week 5/ Day 29, Week 9/ Day 57, Week 13/ Day 85 (pre-dose,[*12] from 4 hours post-dose), Week 17/ Day 113, Week 21/ Day 141, Week 25/ Day 169 (pre-dose,[*12] from 4 hours post-dose), Week 29/ Day 197, Week 33/ Day 225, Week 37/ Day 253 (pre-dose,[*12] from 4 hours post-dose), Week 41/ Day 281, Week 45/ Day 309, Week 48/ Day 330 (pre-dose,[*12] from 4 hours post-dose), Week 49/ Day 337, Week 52/ Day 358 (to be performed pre-dose on Week 5/ Day 29, Week 9/ Day 57, Week 17/ Day 113, Week 21/ Day 141, Week 29/ Day 197, Week 33/ Day 225, Week 41/ Day 281, Week 45/ Day 309)

8) 12-lead electrocardiogram
<Observation point>
See 6.2

9) MRI
<Location of imaging>
Upper arm: MRI or CT (to confirm the location of muscle biopsy)
Thigh: MRI
<Investigation point>
To be performed once in the period from Week 49/ Day 337 to Week 51/ Day 351.

10) Muscle biopsy
<Investigation point>
To be performed once in the period from Week 49/ Day 337 to Week 51/ Day 351.
To be performed after MRI or CT, motor function assessment, respiratory function assessment, cardiac function assessment, and quantitative muscle strength assessment.

11) Motor function assessment

<Investigation point>

To be performed once each in the period from Week 12/ Day 84 to Week 13/ Day 85 (pre-dose), the period from Week 24/ Day 168 to Week 25/ Day 169 (pre-dose), and the period from Week 36/ Day 252 to Week 37/ Day 253 (pre-dose), and twice in the period from Week 49/ Day 337 to Week 51/ Day 351.

12) Respiratory function assessment

<Investigation point>

To be performed once each in the period from Week 12/ Day 84 to Week 13/ Day 85 (pre-dose), the period from Week 24/ Day 168 to Week 25/ Day 169 (pre-dose), the period from Week 36/ Day 252 to Week 37/ Day 253 (pre-dose), and the period from Week 49/ Day 337 to Week 51/ Day 351.

13) Cardiac function assessment

<Investigation point>

To be performed once each in the period from Week 12/ Day 84 to Week 13/ Day 85 (pre-dose), the period from Week 24/ Day 168 to Week 25/ Day 169 (pre-dose), the period from Week 36/ Day 252 to Week 37/ Day 253 (pre-dose), and the period from Week 49/ Day 337 to Week 51/ Day 351.

14) Quantitative muscle strength assessment

<Investigation point>

To be performed once each in the period from Week 12/ Day 84 to Week 13/ Day 85 (pre-dose), the period from Week 24/ Day 168 to Week 25/ Day 169 (pre-dose), and the period from Week 36/ Day 252 to Week 37/ Day 253 (pre-dose), and performed twice in the period from Week 49/ Day 337 to Week 51/ Day 351.

15) Blood collection

- Pharmacokinetics

  <Blood collection point>

  See 6.7

- Anti-dystrophin antibody

  <Blood collection point>

  Week 49/ Day 337

- Anti-DS-5141b antibody
  <Blood collection point>
  Week 49/ Day 337

16) Urine collection
- Urine protein
  <Urine collection point>
  Week 13/ Day 85, Week 25/ Day 169, Week 37/ Day 253, Week 49/ Day 337

*12: 24-hour urine pooling will be performed, starting on the previous day.

6.4.5 Part 2-Extension-2

6.4.5.1 Items to Be Performed Before the First Dose of Study Drug in Part 2-Extension-2

If subjects who have finished Part 2-Extension continue to participate, the following will be performed from 14 days before the first dose of the study drug up to the day before the first dose of the study drug (Day 0). For subjects participating from Part 2-Extension-2, "6.4.1 Items to Be Performed After Registration up to the Day Before the First Dose of Study Drug (Day 0)" will be performed, and these tests will not be necessary.

1) Day of informed consent (or confirmation of intent) by the subject for participation in Part 2-Extension-2
2) Day of informed consent by the legally acceptable representative for participation in Part 2-Extension-2
3) Checking concomitant medications and concomitant therapy
4) Height and body weight
5) Vital signs and clinical findings
6) Blood tests and urinalysis
7) 12-lead electrocardiogram
8) CCI [redacted]
9) MRI (only for subjects in whom MRI can be performed appropriately)
   <Location of imaging>
   MRI: Thigh
10) Motor function assessment*13
11) Respiratory function assessment
12) Cardiac function assessment

13) Quantitative muscle strength assessment*13
14) Blood collection
- Anti-dystrophin antibody

15) Urine collection
- Urine protein

*13: To be performed twice.

6.4.5.2 Items to Be Performed During the Treatment Period (Week 1/ Day 1 to Week 48/ Day 336) and Follow-Up Period (Week 49/ Day 337 to Week 52/ Day 358)

The visit window for items performed on Week 2/ Day 8 to Week 50/ Day 344 is ±2 days, and the visit window for items performed on Week 52/ Day 358 is ±7 days.
Subjects who complete 48 weeks of study drug administration in Part 2-Extension-2 and complete efficacy assessment after administration may participate in the long-term extension study. For subjects who participate in the long-term extension study, Week 52/ Day 358 will not be performed.
As a measure to prevent the spread of the novel coronavirus, self-administration will be allowed. Consent for self-administration will be obtained from the legally acceptable representative, and the guardian performing self-administration will be given training in the method of storing the study drug and the method of administering the study drug before self-administration starts.

1) Administration status of the study drug
   Whether the study drug was administered, date/time of study drug administration, dose level, actual dose (mg), and checking the "Self-Injection Diary" if self-administration was performed
   <Time points at which self-administration is possible>
   Week 28/ Day 190, Week 30/ Day 204, Week 31/ Day 211, Week 32/ Day 218, Week 34/ Day 232, Week 35/ Day 239, Week 36/ Day 246, Week 38/ Day 260, Week 39/ Day 267, Week 40/ Day 274, Week 42/ Day 288, Week 43/ Day 295, Week 44/ Day 302, Week 46/ Day 316, Week 47/ Day 323
2) Investigating concomitant medications and concomitant therapy
3) Investigating adverse events
4) Height and body weight
   <Observation point>

Week 13/ Day 85, Week 25/ Day 169, Week 37/ Day 253, Week 48/ Day 330

5) Vital signs and clinical findings

If self-injection is performed, vital signs will be measured to the extent possible. Clinical findings will be checked by a method such as making a telephone call.

<Observation point>

Week 1/ Day 1 (pre-dose and 4 hours post-dose), Week 1/ Day 2, Week 2/ Day 8 (pre-dose and 4 hours post-dose), Week 3/ Day 15 (pre-dose and 4 hours post-dose), Week 4/ Day 22 (pre-dose and 4 hours post-dose), Week 5/ Day 29, Week 6/ Day 36, Week 7/ Day 43, Week 8/ Day 50, Week 9/ Day 57, Week 10/ Day 64, Week 11/ Day 71, Week 12/ Day 78, Week 13/ Day 85 (pre-dose and 4 hours post-dose), Week 14/ Day 92, Week 15/ Day 99, Week 16/ Day 106, Week 17/ Day 113, Week 18/ Day 120, Week 19/ Day 127, Week 20/ Day 134, Week 21/ Day 141, Week 22/ Day 148, Week 23/ Day 155, Week 24/ Day 162, Week 25/ Day 169 (pre-dose and 4 hours post-dose), Week 26/ Day 176, Week 27/ Day 183, Week 28/ Day 190, Week 29/ Day 197, Week 30/ Day 204, Week 31/ Day 211, Week 32/ Day 218, Week 33/ Day 225, Week 34/ Day 232, Week 35/ Day 239, Week 36/ Day 246, Week 37/ Day 253 (pre-dose and 4 hours post-dose), Week 38/ Day 260, Week 39/ Day 267, Week 40/ Day 274, Week 41/ Day 281, Week 42/ Day 288, Week 43/ Day 295, Week 44/ Day 302, Week 45/ Day 309, Week 46/ Day 316, Week 47/ Day 323, Week 48/ Day 330 (pre-dose and 4 hours post-dose), Week 48/ Day 331, Week 49/ Day 337, Week 52/ Day 358 (to be performed pre-dose on Week 2/ Day 8 to Week 12/ Day 78, Week 14/ Day 92 to Week 24/ Day 162, Week 26/ Day 176 to Week 36/ Day 246, and Week 38/ Day 260 to Week 47/ Day 323)

6) Blood tests

<Observation point>

Week 1/ Day 1, Week 1/ Day 2, Week 5/ Day 29, Week 9/ Day 57, Week 13/ Day 85, Week 17/ Day 113, Week 21/ Day 141, Week 25/ Day 169, Week 29/ Day 197, Week 33/ Day 225, Week 37/ Day 253, Week 41/ Day 281, Week 45/ Day 309, Week 48/ Day 330, Week 49/ Day 337, Week 52/ Day 358 (to be performed pre-dose on Week 1/ Day 1 and Week 5/ Day 29 to Week 48/ Day 330)

7) Urinalysis

<Observation point>

Week 1/ Day 1 (pre-dose,[*14] from 4 hours post-dose), Week 1/ Day 2,

Week 5/ Day 29, Week 9/ Day 57, Week 13/ Day 85 (pre-dose,*14 from 4 hours post-dose), Week 17/ Day 113, Week 21/ Day 141, Week 25/ Day 169 (pre-dose,*14 from 4 hours post-dose), Week 29/ Day 197, Week 33/ Day 225, Week 37/ Day 253 (pre-dose,*14 from 4 hours post-dose), Week 41/ Day 281, Week 45/ Day 309, Week 48/ Day 330 (pre-dose,*14 from 4 hours post-dose), Week 49/ Day 337, Week 52/ Day 358 (to be performed pre-dose on Week 5/ Day 29, Week 9/ Day 57, Week 17/ Day 113, Week 21/ Day 141, Week 29/ Day 197, Week 33/ Day 225, Week 41/ Day 281, Week 45/ Day 309)

8) 12-lead electrocardiogram
<Observation point>
See 6.2

9) CCI [redacted]
<Investigation point>
To be performed once each in the period from Week 4/ Day 22 to Week 6/ Day 36 and the period from Week 49/ Day 337 to Week 51/ Day 351.

10) MRI
<Location of imaging>
Upper arm: MRI or CT (to confirm the location of muscle biopsy)
Thigh: MRI
<Investigation point>
To be performed once in the period from Week 49/ Day 337 to Week 51/ Day 351.

11) Muscle biopsy
<Investigation point>
To be performed once in the period from Week 49/ Day 337 to Week 51/ Day 351.
To be performed after MRI or CT, motor function assessment, respiratory function assessment, cardiac function assessment, and quantitative muscle strength assessment.

12) Motor function assessment (lower limbs)
<Investigation point>
To be performed once each in the period from Week 12/ Day 84 to Week 13/ Day 85 (pre-dose), the period from Week 24/ Day 168 to Week 25/ Day 169 (pre-dose), and the period from Week 36/ Day 252 to Week 37/ Day 253 (pre-dose), and performed twice in the period from Week 49/ Day 337 to Week 51/ Day 351.

13) Motor function assessment (upper limbs)

<Investigation point>

To be performed once each in the period from Week 24/ Day 168 to Week 25/ Day 169 (pre-dose) and the period from Week 36/ Day 252 to Week 37/ Day 253 (pre-dose), and performed twice in the period from Week 49/ Day 337 to Week 51/ Day 351. Note that measurement will be started when possible, at a timing that suits the subject's schedule.

14) Respiratory function assessment

<Investigation point>

To be performed once each in the period from Week 12/ Day 84 to Week 13/ Day 85 (pre-dose), the period from Week 24/ Day 168 to Week 25/ Day 169 (pre-dose), the period from Week 36/ Day 252 to Week 37/ Day 253 (pre-dose), and the period from Week 49/ Day 337 to Week 51/ Day 351.

15) Cardiac function assessment

<Investigation point>

To be performed once each in the period from Week 12/ Day 84 to Week 13/ Day 85 (pre-dose), the period from Week 24/ Day 168 to Week 25/ Day 169 (pre-dose), the period from Week 36/ Day 252 to Week 37/ Day 253 (pre-dose), and the period from Week 49/ Day 337 to Week 51/ Day 351.

16) Quantitative muscle strength assessment

<Investigation point>

To be performed once each in the period from Week 12/ Day 84 to Week 13/ Day 85 (pre-dose), the period from Week 24/ Day 168 to Week 25/ Day 169 (pre-dose), and the period from Week 36/ Day 252 to Week 37/ Day 253 (pre-dose), and performed twice in the period from Week 49/ Day 337 to Week 51/ Day 351.

17) Blood collection

- Pharmacokinetics

  <Blood collection point>

  See 6.7

- Anti-dystrophin antibody

  <Blood collection point>

  Week 49/ Day 337

- Anti-DS-5141b antibody
  <Blood collection point>
  Week 49/ Day 337

18) Urine collection
- Urine protein
  <Urine collection point>
  Week 13/ Day 85, Week 25/ Day 169, Week 37/ Day 253, Week 49/ Day 337

19) Whether the subject can participate in the long-term extension study
  <Timing of confirmation>
  Week 49/ Day 337 to Week 51/ Day 351 (An explanation of the long-term extension study may be provided to subjects who complete 48 weeks of study drug administration in Part 2-Extension-2.)

*14: 24-hour urine pooling will be performed, starting on the previous day.

6.5 Test Items on Withdrawal from the Study and their Timing

Within 7 days from the date when the investigator or subinvestigator decides that the subject should be withdrawn from the study, the following investigations, examinations, and tests will be performed, as far as possible.

6.5.1 For Withdrawal in the Period from Day 1 to Day 15 of Any Dose Level in Part 1

1) Investigating concomitant medications and concomitant therapy
2) Investigating adverse events
3) Body weight
4) Vital signs and clinical findings
5) Blood tests and urinalysis
6) 12-lead electrocardiogram
7) Blood collection
- Pharmacokinetics
- Anti-dystrophin antibody
- Anti-DS-5141b antibody
- Blood cell dystrophin mRNA

8) Urine collection
- Urine protein

- Urine DS-5141b metabolites

6.5.2 For Withdrawal in the Period from Day 1 to Day 85 of Part 2

1) Investigating concomitant medications and concomitant therapy
2) Investigating adverse events
3) Body weight
4) Vital signs and clinical findings
5) Blood tests and urinalysis
6) 12-lead electrocardiogram
7) MRI or CT
   <Location of imaging>
   Upper arm: MRI or CT (to confirm the location of muscle biopsy)
   Thigh: MRI
8) Muscle biopsy
9) Motor function assessment
10) Respiratory function assessment
11) Cardiac function assessment
12) Quantitative muscle strength assessment
13) Blood collection
    - Pharmacokinetics
    - Anti-dystrophin antibody
    - Anti-DS-5141b antibody
    - Blood cell dystrophin mRNA
14) Urine collection
    - Urine protein

6.5.3 For Withdrawal in the Period from Week 1/ Day 1 to Week 49/ Day 337 of Part 2-Extension or from Week 1/ Day 1 to Week 49/ Day 337 of Part 2-Extension-2

1) Investigating concomitant medications and concomitant therapy
2) Investigating adverse events
3) Height and body weight
4) Vital signs and clinical findings
5) Blood tests
6) Urinalysis

7) 12-lead electrocardiogram
8) CCI [redacted] *15
9) MRI or CT
   <Location of imaging>
   Upper arm: MRI or CT (to confirm the location of muscle biopsy)
   Thigh: MRI
10) Muscle biopsy
11) Motor function assessment (lower limbs and upper limbs)*16
12) Respiratory function assessment
13) Cardiac function assessment
14) Quantitative muscle strength assessment
15) Blood collection
   - Pharmacokinetics
   - Anti-dystrophin antibody
   - Anti-DS-5141b antibody
16) Urine collection
   - Urine protein

*15: To be performed if the subject is withdrawn in the period from Week 1/ Day 1 to Week 49/ Day 337 of Part 2-Extension-2.
*16: Not necessary if motor function assessment (upper limbs) was not performed even once in the period from Week 24/ Day 168 to Week 37/ Day 253 (pre-dose) of Part 2-Extension-2.

6.5.4 For Withdrawal in the Period from Day 16 to Day 64 of Part 1, from Day 86 to Day 162 of Part 2, from Week 49/ Day 338 to Week 52/ Day 358 of Part 2-Extension, or from Week 49/ Day 338 to Week 52/ Day 358 of Part 2-Extension-2

1) Investigating concomitant medications and concomitant therapy
2) Investigating adverse events
3) Height and body weight
4) Vital signs and clinical findings
5) Blood tests and urinalysis
6) 12-lead electrocardiogram
7) CCI [redacted] *17

8) MRI or CT[*18]
<Location of imaging>
Upper arm: MRI or CT (to confirm the location of muscle biopsy)
Thigh: MRI
9) Muscle biopsy[*18]
10) Motor function assessment (lower limbs and upper limbs)[*18, 19]
11) Respiratory function assessment[*18]
12) Cardiac function assessment[*18]
13) Quantitative muscle strength assessment[*18]

*17: To be performed for subjects who participated in Part 2-Extension-2, but not necessary if performed on Week 49/ Day 337 of Part 2-Extension-2 in subjects withdrawn in the period from Week 49/ Day 338 to Week 52/ Day 358 of Part 2-Extension-2.
*18: Not necessary in subjects withdrawn in the period from Day 86 to Day 162 of Part 2 if performed on Day 85 of Part 2. Not necessary for subjects withdrawn in the period from Week 49/ Day 338 to Week 52/ Day 358 of Part 2-Extension if performed on Week 49/ Day 337 of Part 2-Extension, and not necessary for subjects withdrawn in the period from Week 49/ Day 338 to Week 52/ Day 358 of Part 2-Extension-2 if performed on Week 49/ Day 337 of Part 2-Extension-2.

*19: Not necessary if motor function assessment (upper limbs) was not performed even once in the period from Week 24/ Day 168 to Week 37/ Day 253 (pre-dose) of Part 2-Extension-2.

6.6 Follow-up After Withdrawal from the Study

At 28 days after the last dose of the study drug (acceptable limit: ±7 days), the following investigations, examinations, and tests will be performed, as far as possible. The contents of the tests will be the same as those during the study period.

1) Investigating concomitant medications and concomitant therapy
2) Investigating adverse events
3) Vital signs and clinical findings
4) Blood tests and urinalysis
5) 12-lead electrocardiogram

6.7 Pharmacokinetics (Blood Collection [Plasma])

At the time of blood collection for pharmacokinetics, 1 mL of blood will be collected in a blood collection tube prepared by the sponsor or central laboratory. After collection, the blood will be promptly mixed by inversion mixing. The plasma obtained by centrifugal separation will be stored frozen (set temperature: ≤−70°C) until it is submitted to the clinical specimen storage facility contracted by the sponsor. Details are specified in a separate procedure.

The investigator or subinvestigator will record whether blood was collected and the date/time of blood collection on the case report form.

<Blood collection point>

- Part 1 (each dose level)

  First dose:

  Day 1 (pre-dose and 0.5 hours, 1 hour, 2 hours, 4 hours, 6 hours, and 8 hours post-dose), Day 2 (24 hours post-dose), Day 4 (72 hours post-dose)

  Second dose:

  Day 8 (pre-dose), Day 9 (24 hours post-dose), Day 11 (72 hours post-dose), Day 15 (7 days post-dose), Day 36 (4 weeks post-dose), Day 64 (8 weeks post-dose)

- Part 2

  First dose:

  Day 1 (pre-dose and 0.5 hours, 1 hour, 2 hours, 4 hours, 6 hours, and 8 hours post-dose), Day 2 (24 hours post-dose)

  Second dose, fourth dose, sixth dose, eighth dose, 10th dose:

  Day 8 (pre-dose), Day 22 (pre-dose), Day 36 (pre-dose), Day 50 (pre-dose), Day 64 (pre-dose)

  12th dose:

  Day 78 (pre-dose, 0.5 hours, 1 hour, 2 hours, 4 hours, 6 hours, and 8 hours post-dose), Day 79 (24 hours post-dose), Day 85 (7 days post-dose), Day 106 (4 weeks post-dose), Day 134 (8 weeks post-dose), Day 162 (12 weeks post-dose)

- Part 2-Extension and Part 2-Extension-2 (subjects continuing participation from Part 2 and Part 2-Extension)

  First dose:

  Week 1/ Day 1 (pre-dose and 4 hours post-dose), Week 1/ Day 2 (24 hours post-dose)

  Second dose:

  Week 2/Day 8 (pre-dose)

Fifth dose, ninth dose, 13th dose, 17th dose, 21st dose, 25th dose, 29th dose, 33rd dose, 37th dose, 41st dose, 45th dose:

Week 5/ Day 29 (pre-dose), Week 9/ Day 57 (pre-dose), Week 13/ Day 85 (pre-dose), Week 17/ Day 113 (pre-dose), Week 21/ Day 141 (pre-dose), Week 25/ Day 169 (pre-dose), Week 29/ Day 197 (pre-dose), Week 33/ Day 225 (pre-dose), Week 37/ Day 253 (pre-dose), Week 41/ Day 281 (pre-dose), Week 45/ Day 309 (pre-dose)

48th dose:

Week 48/ Day 330 (pre-dose and 1 hour, 2 hours, 4 hours, 6 hours, and 8 hours post-dose), Week 48/ Day 331 (24 hours post-dose), Week 49/ Day 337 (7 days post-dose), Week 52/ Day 358 (4 weeks post-dose)

- Part 2-Extension and Part 2-Extension-2 (subjects participating from Part 2-Extension and Part 2-Extension-2)

First dose:

Week 1/ Day 1 (pre-dose and 0.5 hours, 1 hour, 2 hours, 4 hours, 6 hours, and 8 hours post-dose), Week 1/ Day 2 (24 hours post-dose)

Second dose:

Week 2/ Day 8 (pre-dose)

Fifth dose, ninth dose, 13th dose, 17th dose, 21st dose, 25th dose, 29th dose, 33rd dose, 37th dose, 41st dose, 45th dose:

Week 5/ Day 29 (pre-dose), Week 9/ Day 57 (pre-dose), Week 13/ Day 85 (pre-dose), Week 17/ Day 113 (pre-dose), Week 21/ Day 141 (pre-dose), Week 25/ Day 169 (pre-dose), Week 29/ Day 197 (pre-dose), Week 33/ Day 225 (pre-dose), Week 37/ Day 253 (pre-dose), Week 41/ Day 281 (pre-dose), Week 45/ Day 309 (pre-dose)

48th dose:

Week 48/ Day 330 (pre-dose and 1 hour, 2 hours, 4 hours, 6 hours, and 8 hours post-dose), Week 48/ Day 331 (24 hours post-dose), Week 49/ Day 337 (7 days post-dose), Week 52/ Day 358 (4 weeks post-dose)

<Acceptable limits>

- 0.5 hours, 1 hour post-dose : ±5 minutes
- 2 hours, 4 hours, 6 hours, 8 hours post-dose : ±10 minutes
- 24 hours post-dose : ±1 hour
- 72 hours post-dose : ±3 hours

<Rationale>
According to the result of a nonclinical study in which DS-5141b was administered to monkeys at 10 mg/kg, the Tmax of DS-5141b was 4.00 ± 2.00 (mean ± SD) and the terminal half-life, as a reference, was 296 hours. The terminal half-life of other AON was 29 days.[9] Based on these pharmacokinetics results and with reference to "Clinical Pharmacokinetic Studies of Pharmaceuticals,[10]" one blood collection point directly before administration, at least 1 point before reaching the predicted Cmax, at least 2 points close to Tmax, and at least 3 points in elimination phase as the time points were selected since these were considered necessary forpharmacokinetic assessment.

6.8 Checking the DNA Sequence of the Site of DS-5141b Double-Strand Formation (Blood Collection [Whole Blood])

To check the DNA sequence of the site of DS-5141b double-strand formation in the dystrophin gene, after informed consent and before registration, 2 mL of blood will be collected in a blood collection tube prepared by the sponsor or central laboratory. After collection, the blood will be promptly mixed by inversion, and then transferred to a storage container prepared by the sponsor, and stored frozen (set temperature: ≤−20°C) until it is submitted to the clinical specimen storage facility contracted by the sponsor. Details are specified in a separate procedure.
The investigator or subinvestigator will record whether blood was collected, the date of collection, and the result on the case report form.

6.9 Expression of Dystrophin Protein and Production of Exon 45-Skipped Dystrophin mRNA in Muscle Tissue (Muscle Biopsy)

To measure the dystrophin protein in muscle tissue and the dystrophin mRNA induced by exon 45 skipping, after registration, before the first dose of the study drug in each subject, after the last dose of the study drug (Day 85 to Day 99, or at withdrawal) in Part 2, after the last dose of the study drug (Week 49/ Day 337 to Week 51/ Day 351, or at withdrawal) in Part 2-Extension, and after the last dose of the study drug (Week 49/ Day 337 to Week 51/ Day 351, or at withdrawal) in Part 2-Extension-2, muscle tissue will be collected from, in principle, the biceps brachii muscle by open muscle biopsy. The location of collection will be decided after checking the condition of the muscle by MRI or CT performed in advance. After collection, the

specimen will be processed promptly, and stored frozen (set temperature: ≤−70°C) in a container prepared by the sponsor or central laboratory until it is submitted to the clinical specimen storage facility contracted by the sponsor. Details are specified in a separate procedure.
The investigator or subinvestigator will record whether a muscle biopsy was performed, the date of biopsy, and the region of the collected muscle on the case report form.

6.10 Measurement of Anti-Dystrophin Antibody (Blood Collection [Serum])

To measure anti-dystrophin antibody, 2.0 mL of blood will be collected in a blood collection tube prepared by the sponsor or central laboratory, before the first dose of the study drug and after the last dose of the study drug at each dose level (Day 15 or at withdrawal) in Part 1, before the first dose of the study drug and after the last dose of the study drug (Day 85 or at withdrawal) in Part 2, before the first dose of the study drug and after the last dose of the study drug (Week 49/ Day 337 or at withdrawal) in Part 2-Extension, and before the first dose of the study drug and after the last dose of the study drug (Week 49/ Day 337 or at withdrawal) in Part 2-Extension-2. After collection, the blood will be left for 30 minutes at room temperature and then centrifugal separation will be performed within 1 hour of collection, and the obtained serum will be divided into 3 storage containers. The obtained serum will be stored frozen (set temperature: ≤−70°C) until it is submitted to the clinical specimen storage facility contracted by the sponsor. Details are specified in a separate procedure.
The investigator or subinvestigator will record whether blood was collected and the blood collection day on the case report form.

6.11 Measurement of Anti-DS-5141b Antibody (Blood Collection [Plasma])

To measure anti-DS-5141b antibody, 1.0 mL of blood will be collected in a blood collection tube prepared by the sponsor or central laboratory, before the first dose of the study drug in Part 1 and after the last dose of the study drug at each dose level (Day 15 or at withdrawal) in Part 1, before the first dose of the study drug and after the last dose of the study drug (Day 85 or at withdrawal) in Part 2, after the last dose of the study drug (Week 49/ Day 337 or at withdrawal) in Part 2-Extension, and after the last dose of the study drug (Week 49/ Day 337 or at withdrawal) in Part 2-Extension-2.
For subjects participating from Part 2-Extension, blood will also be collected before the first dose of the study drug in Part 2-Extension, and for subjects participating from

Part 2-Extension-2, blood will also be collected before the first dose of the study drug in Part 2-Extension-2. After blood is collected, inversion mixing will promptly be performed and it will be cooled with ice. The plasma obtained from centrifugal separation will be stored frozen (set temperature: ≤−70°C) until it is submitted to the clinical specimen storage facility contracted by the sponsor. Details are specified in a separate procedure.
If anti-DS-5141b antibody is positive in the follow-up period (or at withdrawal), additional blood will be collected [redacted] to investigate anti-DS-5141b antibody. Additional blood collection will be performed [redacted], until anti-DS-5141b antibody is found to be negative, until the anti-DS-5141b antibody titer is found to have decreased below baseline (if anti-DS-5141b antibody was found at baseline), until the subject entered in a new study, or until the subject withdraws consent, whichever is earliest.
The investigator or subinvestigator will record whether blood was collected and the date of blood collection on the case report form.

6.12 Exploratory Biomarker Research

6.12.1 Imaging Analysis of skeletal muscle

To examine the disease progression and fat replacement in skeletal muscle, MRI will be performed in the thigh before the first dose of the study drug in each subject, before the first dose of the study drug and after the last dose of the study drug (Day 85 to Day 99, or at withdrawal) in Part 2, before the first dose of the study drug in Part 2-Extension, and before the first dose of the study drug and after the last dose of the study drug (Week 49/ Day 337 to Week 51/ Day 351, or at withdrawal) in Part 2-Extension-2, and the data will be submitted to the sponsor. Details of procedures and the data analysis facility will be specified separately. This exploratory biomarker research will only be performed for subjects in whom MRI can be performed appropriately.
The investigator or subinvestigator will record whether MRI was performed, the date of imaging, and the location of imaging on the case report form.

6.12.2 Measurement of In Vitro Dystrophin Protein and Dystrophin mRNA (Skin Biopsy)

To investigate the reactivity of the muscle cells of each subject to DS-5141b, in vitro studies using skin fibroblasts will be performed. For subjects participating in this

study from Part 1 or Part 2, a skin sample will be collected at the time of muscle biopsy before the first dose of the study drug and stored (set temperature: 4°C) in a storage container prepared by the sponsor or central laboratory until it is submitted to the central laboratory. Details are specified in a separate procedure.
The investigator or subinvestigator will record whether skin biopsy was performed and the date of biopsy on the case report form.

6.12.3 Measurement of Blood Cell Dystrophin mRNA (Blood Collection [Whole Blood])

To measure the dystrophin mRNA induced by exon 45 skipping in blood cells, before the first dose of the study drug and after the last dose of the study drug at each dose level (Day 15 or at withdrawal) in Part 1 and before the first dose of the study drug and after the last dose of the study drug (Day 85 or at withdrawal) in Part 2, 2.5 mL of blood will be collected in the blood collection tube prepared by the sponsor or central laboratory and stored frozen (set temperature: ≤−20°C) until it is submitted to the clinical specimen storage facility contracted by the sponsor. Details are specified in a separate procedure.
The investigator or subinvestigator will record whether blood was collected and the blood collection day on the case report form.

6.12.4 Measurement of Micro RNA (Blood Collection [Serum])

Micro RNA in blood (such as miR-1, miR-133, and miR-206) will be measured. Part of the serum obtained for measurement of anti-dystrophin antibody (see 6.10) will be used as the specimen. Details are specified in a separate procedure.

6.12.5 Measurement of Urine Protein (Urine Collection)

To measure urine protein (such as titin), which is an indicator of muscle decomposition, before the first dose of the study drug and after the last dose of the study drug at each dose level (Day 15 or at withdrawal) in Part 1, before the first dose of the study drug and after the last dose of the study drug (Day 85 or at withdrawal) in Part 2, before the first dose of the study drug, on Week 13/ Day 85, Week 25/ Day 169, and Week 37/ Day 253 in Part 2-Extension, and before the first dose of the study drug, on Week 13/ Day 85, Week 25/ Day 169, Week 37/ Day 253 and after the last dose of the study drug (Week 49/ Day 337 or at withdrawal) in Part 2-Extension-2, 10 mL of urine will be collected in the urine collection tube prepared by the sponsor or central

laboratory and stored frozen (set temperature: ≤−70°C) until it is submitted to the clinical specimen storage facility contracted by the sponsor. Details of the procedure and the measurement facility are specified separately.
The investigator or subinvestigator will record whether urine was collected and the urine collection day on the case report form.

6.12.6 Measurement of Blood DS-5141b Metabolites (Blood Collection [Plasma])

Unknown metabolites of DS-5141b will be exploratorily investigated. Part of the plasma obtained for pharmacokinetics (see 6.7) will be used as a specimen. Details are specified in a separate procedure.

6.12.7 Measurement of Urine DS-5141b Metabolites (Urine Collection)

To exploratorily investigate unknown metabolites of DS-5141b, before the first dose of the study drug in Part 1 and on the day after the last dose of the study drug at each dose level (Day 9 or at withdrawal), 5.0 mL of urine will be collected in a urine collection tube provided by the sponsor or central laboratory. The specimen will be stored frozen (set temperature: ≤−20°C) until it is submitted to the clinical specimen storage facility contracted by the sponsor. Details are specified in a separate procedure.
The investigator or subinvestigator will record whether urine was collected and the urine collection day on the case report form.

6.13 Storage and Disposal of Specimens for Genetic Analysis and Biomarker Research

6.13.1 Storage of Specimens

In view of the possibility that, based on newly obtained knowledge, additional examinations of the relationship between the efficacy or safety of the study drug and the biomarkers will be performed, and that the above biomarkers will be measured again, the submitted specimens will be stored at the respective measurement facilities for up to 10 years from the time of the notification of the study plan for this study.

6.13.2 Disposal of Specimens

All specimens that reach the end of their storage period will be disposed of by the biomarker measurement facility according to the instructions of the sponsor.
If a subject withdraws consent for biomarker research, specimens will be disposed of according to the following procedures, depending on the location of the specimens at

that time. If biomarker analysis was performed at the measurement facility before the subject withdrew consent, this data will not be disposed of.

1) If specimens are being temporarily stored at study site
   The investigator or subinvestigator will identify the specimens from the relevant subject and dispose of them.
2) If specimens are being stored at the clinical specimen storage facility
   The investigator or subinvestigator will inform the sponsor of the subject identification code of the relevant subject. The sponsor will instruct the clinical specimen storage facility to dispose of the relevant subject's specimens.

6.14 Long-Term Storage (Banking) of Clinical Specimens for Genomic and Genetic Analysis

Long-term storage (banking) of DNA specimens extracted from the subjects' blood will be performed, to enable genomic or genetic analysis relating to, for example, the efficacy or safety of DS-5141b. If research is performed using these DNA specimens, a research plan will be newly prepared.

6.14.1 Scope

At study sites where banking is approved, an explanation of banking will be provided, and samples obtained from subjects who provide informed consent based on this explanation will be included in the scope of banking. For subjects who provide informed consent for banking, the investigator or subinvestigator will record the date of informed consent on the case report form. If there is any information such as medical history that may affect genomic or genetic information (for example, allogeneic bone marrow transplantation), this will be recorded on the case report form.

6.14.2 Banking Specimens (DNA)

DNA will be extracted from some of the blood collected for checking the DNA sequence of the site of DS-5141b double-strand formation (see 6.8), and this will be used as the banking specimen.

6.14.3 Storage Period

The storage period of the banking specimens will be a maximum of 15 years from the date of submission of the notification of the study plan for this study.

6.14.4 Disclosure of the Result of Genomic and Genetic Analysis Using Banking Specimens

At present, the timing of pharmacogenomic investigation using banking specimens, the method of genomic or genetic analysis, and whether disclosure will be necessary are undetermined. Accordingly, we do not plan to disclose the result of genetic analysis to the investigator etc. and subjects.

6.14.5 Disposal of Banking Specimens

After the end of the storage period, or if a subject withdraws consent during the storage period, banking specimens will be promptly disposed of. However, if genetic analysis was performed before the end of the storage period or before consent was withdrawn, these data will not be disposed of.

7. PHARMACOKINETIC ENDPOINTS

The following pharmacokinetic parameters will be calculated from the plasma DS-5141a (the free form of DS-5141b) concentration in Part 1, Part 2, Part 2-Extension, and Part 2-Extension-2 using a non-compartment model. Details of pharmacokinetic analysis will be specified in the Statistical Analysis Plan.

<Pharmacokinetic parameters>

- Part 1 and Part 2 (first dose)
  Cmax, AUC168h, AUCinf, Tmax, Kel, t1/2, MRTinf, CL/F, Vz/F
- Part 2 (12th dose)
  Cmax, Cavg, AUCtau, Tmax, Kel, t1/2
- Part 2-Extension (48th dose) and Part 2-Extension-2 (48th dose)
  Cmax, Cavg, AUCtau, Tmax, Kel, t1/2, MRTinf, CLss/F, Vz/F, AR
- Part 2-Extension (first dose in subjects participating in the study from Part 2-Extension*) and Part 2-Extension-2 (first dose in subjects participating in the study from Part 2-Extension-2*)
  Cmax, AUC168h, AUCinf, Tmax, Kel, t1/2, MRTinf, CL/F, Vz/F
  *The 48th dose will be handled in the same way as for subjects continuing participation from Part 2
  Since administration of the study drug was temporarily discontinued in Part 2-Extension, pharmacokinetic parameters for the 48th dose will be calculated only in cases where calculation is possible.

<Rationale>

These pharmacokinetic parameters were specified to assess the pharmacokinetics of single doses and repeated doses of DS-5141b, with reference to "Clinical Pharmacokinetic Studies of Pharmaceuticals.[10]"

8. EFFICACY ENDPOINTS

8.1 Primary Endpoint

8.1.1 Expression of Dystrophin Protein in Muscle Tissue

Dystrophin protein will be measured by immunostaining, using frozen slices of muscle tissue. The expression of dystrophin protein will also be measured by the Western blot method using protein extracted from the muscle tissue.

8.2 Secondary Endpoint

8.2.1 Production of Exon 45-Skipped Dystrophin mRNA in Muscle Tissue

Using the total RNA extracted from muscle tissue, whether dystrophin mRNA induced by exon 45 skipping is produced will be measured with RT-PCR.

<Rationale and Appropriateness of Endpoint>
DMD is a serious disease that occurs as a result of loss of dystrophin protein due to mutation of the dystrophin gene. Becker muscular dystrophy (BMD), like DMD, occurs due to mutation of the dystrophin gene, but a shorter dystrophin protein thought likely to have partial function is expressed, and thus it is a disease type with milder symptoms and progression. DS-5141b is expected to bind to the target sequence of the pre-mRNA of the dystrophin gene, produce exon 45-skipped mRNA, causing the production of shorter, but functional dystrophin protein like BMD, and thus delay the progression of DMD. Thus, expression of dystrophin protein in muscle tissue is likely to lead to delay the progression of DMD. At the same time, detection of exon 45-skipped mRNA is likely to be a useful index showing that this drug is exerting an action.

9. SAFETY ENDPOINTS

The safety endpoints will be adverse events, laboratory data, body weight, vital signs, 12-lead electrocardiogram, and [redacted]

9.1 Definition of Adverse Event

An adverse event is any untoward or unintended sign (including abnormal changes in laboratory data and abnormal changes in vital signs), symptom or disease that occurs in a subject, whether or not they have a relationship with the study drug.
Symptoms or diseases that occur before administration of the study drug will be considered complications, and will not be handled as adverse events. However, if a complication worsens during administration of the study drug, it will be handled as an adverse event, and the date when worsening was observed will be considered the date of onset of the adverse event.

9.2 Definition of Serious Adverse Event

A serious adverse event is an adverse event that meets the following criteria.

- Results in death
- Is life-threatening
- Requires admission to a hospital or clinic or prolongation of the duration of the existing hospitalization
- Results in disability
- Is associated with a risk of disability
- Is medically significant in a way similar to the above
- Is a congenital anomaly or birth defect

9.3 Handling of Abnormal Changes in Laboratory Data

Laboratory test findings and test results that meet the following criteria (including blood tests, urinalysis, vital signs, and other test results) will be handled as adverse events.

- Suspension (or postponement of administration), or discontinuation of the study drug is necessary
- New medical or surgical intervention is necessary
- The investigator or subinvestigator determines that the finding is clinically significant for any other reason

9.4 Adverse Event Collection Period

The adverse event collection period will be as follows.

- From the first dose of the study drug at each dose level in Part 1 to the end of the follow-up period
- From the first dose of the study drug in Part 2 to the end of the follow-up period
- From the first dose of the study drug in Part 2-Extension to the end of the follow-up period in Part 2-Extension-2 (for subjects participating in the study from Part 2-Extension-2, from the first dose of the study drug in Part 2-Extension-2 to the end of the follow-up period in Part 2-Extension-2. For subjects participating in the long-term extension study, until the first dose of the study drug in the long-term extension study.)

All adverse events that occur during this period will be recorded on the case report form. Even outside the collection period, adverse events that the investigator or subinvestigator determines have a relationship with the study drug will be reported to the sponsor in the same way as during the collection period.

9.5 Items to Investigate for Adverse Events

If an adverse even occurs during the study, the items shown in Table 9.5-1 will be investigated and recorded on the case report form or another document.

Table 9.5-1 Items to Investigate When an Adverse Event Occurs

Item to investigate	Details of investigation	
Details of adverse event	Adverse event term, date of onset	
Action taken for adverse event	Details of study drug action taken, details of other action taken	
Outcome	Outcome classification, day of outcome assessment, stop date	
Outcome classification	Recovered/resolved	The adverse event disappears and the subject returns to the condition before the adverse event occurred
	Recovering/resolving	The adverse event almost disappears, and the subject returns to a condition close to that before the adverse event occurred
	Not recovered/not resolved	The adverse event does not disappear, and the subject remains in a condition similar to when the adverse event occurred (unchanged)
	Recovered/resolved with sequelae	The adverse event has disappeared, but the subject has sequelae
	Death	This indicates that the investigator etc. considers that the adverse event has a relationship with the death, or that a relationship cannot be ruled out, and in cases of death due to causes such as worsening of the underlying disease, this classification does not apply
	Unknown	There is no information, and the outcome is unknown
Severity	Mild	A tolerable level, with no impairment to activities of daily life
	Moderate	A level with some impairment of activities of daily life
	Severe	A level at which activities of daily life are impossible
Seriousness	Serious/nonserious	
Causality	Causality classification (as per the following causality classification), reason for judgment	
Causality classification	Related	• There is a reasonable temporal relationship between the occurrence of the adverse event and the administration of the study drug, it is not appropriate to determine that the adverse event is due the subject's condition or factors other than the study drug (such as the underlying disease, complications or concomitant medications), and an association with the study drug cannot be ruled out • There is a reasonable temporal relationship between the occurrence of the adverse event and the administration of the study drug, and the adverse event can be explained as a known reaction to the study drug or similar compounds, or based on its pharmacological action
	Unrelated	• There is no reasonable temporal relationship between the occurrence of the adverse event and administration of the study drug, or it is

Item to investigate	Details of investigation	
		appropriate to determine that the occurrence of the adverse event is due to the subject's condition or factors other than the study drug (such as the underlying disease, complications or concomitant medications), and an association with the study drug can be ruled out

9.6 Definition of Adverse Drug Reaction

Adverse events for which the relationship with the study drug is determined to be "related" will be handled as adverse drug reactions.

9.7 Action If an Adverse Event Occurs

9.7.1 Recommended Action for Adverse Events

If an adverse event occurs, the investigator or subinvestigator will take the necessary action, will report it to the sponsor if necessary, and, as far as possible, will observe the course of the adverse event until the subject recovers and the adverse event disappears or is relieved (even after the end of the specified observation period). However, even in a situation where the adverse event does not disappear and is not relieved, if it can be determined that the subject's condition is stable and his safety is ensured, the investigator or subinvestigator will end observation in the study, after providing an explanation to the subject and his legally acceptable representative (however, treatment of the relevant symptoms will continue).

In nonclinical toxicity studies, CCI [redacted] were observed in the toxic range in an intermittent subcutaneous administration toxicity study in mice. Therefore, CCI [redacted] will be kept in mind. In relation to CCI [redacted] will be cautiously observed. In particular, if symptoms such as CCI [redacted] observed, in addition to treatment of symptoms, diagnostic tests will be considered. Since DS-5141b is administered subcutaneously, reactions to the location of administration will be kept in mind. Also, in single-dose studies and intermittent administration studies in mice, CCI [redacted],

[redacted] were observed. In an intermittent administration study in mice, [redacted] was also observed. Based on these findings, we newly selected [redacted] as an important potential risk and [redacted] as another potential risk. [redacted]

If it is determined that detailed reporting of an adverse event is necessary, information including the observed signs and symptoms, the contents and results of tests, the treatment given, and the temporal course of these will be recorded on the case report form. Details of the above adverse events of [redacted] will be recorded on the case report form.

9.7.2 Action If a Serious Adverse Event Occurs

If a serious adverse event occurs, the investigator or subinvestigator will provide appropriate treatment, and also promptly report information about the adverse event to the sponsor, for example by telephone or fax. The investigator will also report the details in writing to the sponsor and the director of the study site. The written report to the director of the study site will be made according to the procedures and format of the relevant medical institution.

10. Other Endpoints

1) Motor function assessment items (lower limbs and upper limbs)

Motor function assessment will be performed before the first dose of the study drug in Part 1, before the first dose of the study drug and after the last dose of the study drug (Day 85 to Day 99, or at withdrawal) in Part 2, before the first dose of the study drug, after the 12th dose (Week 12/ Day 84 to Week 13/ Day 85 prior to study drug administration), after the 24th dose (Week 24/ Day 168 to Week 25/ Day 169 prior to study drug administration), after the 36th dose (Week 36/ Day 252 to Week 37/ Day 253 prior to study drug administration), and after the last dose of the study drug (Week 49/ Day 337 to Week 51/ Day 351, or at withdrawal) in Part 2-Extension, and before the first dose of the study drug, after the 12th dose (Week 12/ Day 84 to Week 13/ Day 85 prior to study drug administration), after the 24th dose (Week 24/ Day 168 to Week 25/ Day 169 prior to study drug administration), after the 36th dose (Week 36/ Day 252 to Week 37/ Day 253 prior to study drug administration), and after the last dose of the study drug (Week 49/ Day 337 to Week 51/ Day 351, or at withdrawal) in Part 2-Extension-2. Assessment will be performed twice at each planned time point before the first dose of the study drug and after the last dose of the study drug in Part 1, Part 2, Part 2-Extension, and Part 2-Extension-2, and recorded on the case report form. The maximum values will be used as data. At other planned time points, assessment will be performed once, and will be recorded on the case report form. The measurement procedure for each item will be specified in a separate procedure. Note that measurement of motor function assessment items (upper limbs) will be started when possible, at a timing that suits the subject's schedule.

- 6-minute walk test
  The distance a subject is able to walk in 6 minutes, walking as fast as possible, will be measured.
- Timed Floor to Stand
  The time a subject takes when getting out of floor and standing up as quickly as possible will be measured.
- Timed up and go test
  The time a subject takes to stand up from sitting on a platform (a stool), walk as quickly as possible to a cone 3 m ahead and sit back down on the same platform will be measured.

- Time to run/walk 10 m
  The time a subject takes to run or walk 10 m as quickly as possible will be measured.
- North Star Ambulatory Assessment
  Motor functions divided into 17 items, including standing position and walking, will be assessed. A score from 0 points to 2 points will be assigned for each item depending on the subject's function level, and the total point score will be used for assessment.
- Performance of Upper Limb
  Upper limb functions divided into 22 items, covering the regions of the shoulders, elbows and hands, will be assessed. A 3-stage score of 0, 1 or 2 will be assigned for each item, and the total point score will be used for assessment.

2) Respiratory function assessment items

Respiratory function assessment will be performed for subjects able to understand the instructions in the respiratory function test before the first dose of the study drug in Part 1, before the first dose of the study drug and after the last dose of the study drug (Day 85 to Day 99, or at withdrawal) in Part 2, before the first dose of the study drug, after the 12th dose (Week 12/ Day 84 to Week 13/ Day 85 prior to study drug administration), after the 24th dose (Week 24/ Day 168 to Week 25/ Day 169 prior to study drug administration), after the 36th dose (Week 36/ Day 252 to Week 37/ Day 253 prior to study drug administration), and after the last dose of the study drug (Week 49/ Day 337 to Week 51/ Day 351, or at withdrawal) in Part 2-Extension, and before the first dose of the study drug, after the 12th dose (Week 12/ Day 84 to Week 13/ Day 85 prior to study drug administration), after the 24th dose (Week 24/ Day 168 to Week 25/ Day 169 prior to study drug administration), after the 36th dose (Week 36/ Day 252 to Week 37/ Day 253 prior to study drug administration), and after the last dose of the study drug (Week 49/ Day 337 to Week 51/ Day 351, or at withdrawal) in Part 2-Extension-2. A respiratory function test (spirometry) will be performed, and forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), peak expiratory flow (PEF), and cough peak flow (CPF) will be measured. The measurement procedure for each item will be specified in a separate procedure.

3) Cardiac function assessment items

Cardiac function assessment will be performed before the first dose of the study drug in Part 1, before the first dose of the study drug and after the last dose of the study

drug (Day 85 to Day 99, or at withdrawal) in Part 2, before the first dose of the study drug, after the 12th dose (Week 12/ Day 84 to Week 13/ Day 85 prior to study drug administration), after the 24th dose (Week 24/ Day 168 to Week 25/ Day 169 prior to study drug administration), after the 36th dose (Week 36/ Day 252 to Week 37/ Day 253 prior to study drug administration), and after the last dose of the study drug (Week 49/ Day 337 to Week 51/ Day 351, or at withdrawal) in Part 2-Extension, and before the first dose of the study drug, after the 12th dose (Week 12/ Day 84 to Week 13/ Day 85 prior to study drug administration), after the 24th dose (Week 24/ Day 168 to Week 25/ Day 169 prior to study drug administration), after the 36th dose (Week 36/ Day 252 to Week 37/ Day 253 prior to study drug administration), and after the last dose of the study drug (Week 49/ Day 337 to Week 51/ Day 351, or at withdrawal) in Part 2-Extension-2. Cardiac ultrasonography (echocardiography) will be performed, and the left ventricular end-diastolic dimension, left ventricular fractional shortening, left ventricular ejection rate, E/A ratio, and E-wave deceleration rate will be measured. The measurement procedure for each item will be specified in a separate procedure.

4) Quantitative muscle strength assessment

Quantitative muscle strength assessment will be performed before the first dose of the study drug in Part 1, before the first dose of the study drug and after the last dose of the study drug (Day 85 to Day 99, or at withdrawal) in Part 2, before the first dose of the study drug, after the 12th dose (Week 12/ Day 84 to Week 13/ Day 85 prior to study drug administration), after the 24th dose (Week 24/ Day 168 to Week 25/ Day 169 prior to study drug administration), after the 36th dose (Week 36/ Day 252 to Week 37/ Day 253 prior to study drug administration), and after the last dose of the study drug (Week 49/ Day 337 to Week 51/ Day 351, or at withdrawal) in Part 2-Extension, and before the first dose of the study drug, after the 12th dose (Week 12/ Day 84 to Week 13/ Day 85 prior to study drug administration), after the 24th dose (Week 24/ Day 168 to Week 25/ Day 169 prior to study drug administration), after the 36th dose (Week 36/ Day 252 to Week 37/ Day 253 prior to study drug administration), and after the last dose of the study drug (Week 49/ Day 337 to Week 51/ Day 351, or at withdrawal) in Part 2-Extension-2. Using a handheld dynamometer, muscle strength in hip joint flexion and extension, in knee joint flexion and extension, and in ankle joint dorsal flexion and plantar flexion will be measured. Assessment will be performed twice at each planned time point before the first dose of the study drug and after the last dose of the study drug in Part 1, Part 2, and Part

2-Extension, and recorded on the case report form. The maximum values will be used as data. At other planned time points, assessment will be performed once, and will be recorded on the case report form. The measurement procedure for each item will be specified in a separate procedure.

5) Measurement of anti-dystrophin antibody
6) Measurement of anti-DS-5141b antibody

11. Statistical Analysis

This is a synopsis of statistical analysis and pharmacokinetic analysis. We will separately prepare a Statistical Analysis Plan to describe the analysis methods in more detail.

11.1 Objective of Analysis

The objective of this study is to exploratorily assess the safety, tolerability, efficacy, and pharmacokinetics of DS-5141b in DMD patients. Statistical power was not taken into account when the planned sample size of this study was selected. Thus, the statistical analysis in this study is descriptive, and statistical hypothesis testing will not be performed.

11.2 Analysis Sets

Before the database is locked, the sponsor will decide on the handling of each subject, holding discussions with the medical expert as necessary. In cases where the handling of subjects is not specified in the clinical study protocol, the sponsor will make a decision, after receiving advice from the medical expert.

11.2.1 Efficacy Analysis Population

The efficacy analysis population will be the population of subjects registered in the study, excluding the following subjects.

1) Subjects who do not meet the inclusion criteria
2) Subjects who did not receive at least 1 dose of the study drug
3) Subjects without any efficacy data after study drug administration

11.2.2 Pharmacokinetic Analysis Population

The pharmacokinetic analysis population will be the population of subjects registered in the study who were administered the investigational product and who meet the following criteria.

1) Subjects who have received the study drug at least once
2) Subjects with no major protocol deviations
3) Subjects whose plasma drug concentration data is available

11.2.3 Safety Analysis Population

The safety analysis population will be the population of subjects registered in this

study, excluding "subjects who were not administered the study drug at least once."

11.3 Data Handling

The sponsor will decide on the handling of all data, after discussion with the medical expert as necessary, and based on the data handling standard to be prepared separately, before locking the data.

11.3.1 Handling of Timing of Investigations and Measurements

The timing of investigations and measurements will be handled according to "6 STUDY PROCEDURES." Data not handled according to the data handling standards will be excluded from analysis. If no data meet the data handling standards, the relevant values will be handled as missing data.

11.3.2 Handling of Missing Data

Missing data will not be imputed.

11.4 Statistical Analysis Items and Methods of Analysis

11.4.1 Baseline Subject Characteristics

For baseline subject characteristics (demographic variables and baseline values), frequency tables will be prepared for categorical data, and summary statistics will be calculated for quantitative data.

11.4.2 Efficacy Analysis

Efficacy analysis will be performed in the efficacy analysis set.

11.4.2.1 Primary Endpoint

- Expression of the dystrophin protein in the muscle tissue

The dystrophin protein levels relative to the normal muscle, calculated by each assessment method (immunohistochemistry [IHC] and western blot [WB]) before the first dose of the study drug, after the last dose of the study drug in Part 2, and after the last dose of the study drug in Part 2-Extension-2, and their changes will be listed by subject, and their time course will be plotted.

11.4.2.2 Secondary Endpoint

- Production of exon 45-skipped dystrophin mRNA in the muscle tissue

A list by subject of whether exon 45-skipped dystrophin mRNA was present before the first dose of the study drug, after the last dose of the study drug in Part 2, and after the last dose of the study drug in Part 2-Extension-2 will be prepared.

11.4.3 Pharmacokinetic Analysis

Summary statistics will be calculated by treatment group for plasma concentration and pharmacokinetic parameters. The time course of plasma concentration will also be plotted. Additionally, the relationship between doses and pharmacokinetic parameters will be investigated.

To exploratorily assess the relationship between the pharmacokinetics of DS-5141b and response, modeling and simulation will be conducted using this study data or pooled data including other studies to be conducted in the future. These analyses will include a population pharmacokinetic analysis of DS-5141b and an exposure-response analysis for biomarkers, QTc interval, efficacy indicators or safety indicators. When modeling and simulation are conducted, the result will be reported separately.

11.4.4 Safety Analysis

This will be conducted in the safety analysis set. The Medical Dictionary for Regulatory Activities (MedDRA) will be used for coding adverse events, organ classification will be performed by MedDRA system organ class (SOC), and adverse event terms will be tabulated by preferred term (PT).

11.4.4.1 Adverse Event

The incidence of adverse events will be calculated. The frequencies of adverse events will also be tabulated by event and by severity. Adverse drug reactions will be analyzed in the same way. In tabulation by SOC (or PT), if multiple adverse events with the same SOC (or PT) occur in the same subject, they will be counted as a single event. SOCs will be displayed in the internationally agreed order, and PT will be displayed in the order of coding.

11.4.4.2 Laboratory Data

Summary statistics will be calculated for hematology tests, blood chemistry tests and urinalysis (quantitative values). The changes (time course) in each subject before and after administration will also be plotted. For urinalysis (qualitative values), the frequency of measurement indicators at each observation point will be tabulated, and

shift tables for each subject will be produced.

11.4.4.3 Height, Body Weight and Vital Signs

Summary statistics will be calculated, and the changes (time course) in each subject before and after administration will be plotted.

11.4.4.4 12-Lead Electrocardiogram

A frequency table for each observation point will be prepared for the physician's judgment on the standard 12-lead electrocardiogram.
Summary statistics for PR interval, QRS interval, QT interval, RR interval, and QTc will be calculated for each observation point, and time courses will be plotted. For QTc, the QT interval corrected by pulse rate, summary statistics will be calculated for each observation point and time courses will be plotted, using the following 2 methods of correction.
– Bazett's correction formula: $QTcB = QT/ (RR)^{1/2}$
– Fridericia's correction formula: $QTcF = QT/ (RR)^{1/3}$
Concentration-QT analysis will also be performed, to exploratorily investigate the relationship between the change in QTcF from baseline (ΔQTcF) and the blood concentration of DS-5141b.

11.4.4.5 CCI

[redacted]

11.4.5 Analysis Methods for Other Items

11.4.5.1 Motor Function Assessment Items (Lower Limbs and Upper Limbs)

For the following endpoints, summary statistics will be calculated for the measurement at each time point and the change from before the first dose of the study drug. A listing by subject and time course plot will also be prepared. For the 6-minute walk test, the ratios of measured values to expected values will be calculated and analyzed in the same way as measured values.

- 6-minute walk test
- Timed Floor to Stand
- Timed up and go test
- Time to run/walk 10 m

- North Star Ambulatory Assessment
- Performance of Upper Limb

11.4.5.2 Respiratory Function Assessment Items

For the following endpoints, summary statistics will be calculated for the measurement at each time point and the change from before the first dose of the study drug. A listing by subject and time course plot will also be prepared. For forced vital capacity, forced expiratory volume in 1 second, and peak expiratory flow, the ratios of measured values to expected values will be calculated and analyzed in the same way as measured values.

- Forced vital capacity (FVC)
- Forced expiratory volume in 1 second (FEV1)
- Peak expiratory flow (PEF)
- Cough peak flow (CPF)

11.4.5.3 Cardiac Function Assessment Items

For the following endpoints, summary statistics will be calculated for the measurement at each time point and the change from before the first dose of the study drug. A listing by subject and time course plot will also be prepared.

- Left ventricular end-diastolic dimension
- Left ventricular fractional shortening
- Left ventricular ejection rate
- E/A ratio
- E-wave deceleration rate

11.4.5.4 Quantitative Muscle Strength Assessment

For the following endpoints, summary statistics will be calculated for the measurement at each time point and the change from before the first dose of the study drug. A listing by subject and time course plot will also be prepared.

- Hip joint flexion and extension
- Knee joint flexion and extension
- Ankle joint dorsal flexion and plantar flexion

11.4.5.5 Measurement of Anti-Dystrophin Antibody

A list by subject of whether anti-dystrophin antibody was present at each time point

will be prepared.

11.4.5.6 Measurement of Anti-DS-5141b Antibody

A list by subject of whether anti-DS-5141b antibody was present at each time point will be prepared.

11.5 Changes to the Analysis Plan

If there are any changes to the analysis plan, for example due to change to the method of handling data or conversion of variables, the sponsor will consider the appropriateness of the contents of these changes and the effect on assessment in this study, and then make a decision on whether the change is possible. The sponsor will clearly record details including the contents of the discussion, whether the change was made and the reason for this in writing, and store these documents. If a change is made, the contents of this and the reason for it will be included in the clinical study report. Changes to the main analysis listed in the clinical study protocol will be made as per "15.7 Protocol Amendment."

11.6 Interim Analysis

After Part 1 has ended, interim assessment of the safety and pharmacokinetics in Part 1 will be performed, to decide on the doses to use in Part 2.

11.7 Planned Sample Size

Part 1: 3 subjects per cohort, for a total of 6 subjects
Part 2: 3 subjects each in the high-dose group and the low-dose group, for a total of 6 subjects
Part 2-Extension: 3 subjects each in the high-dose group and the low-dose group, for a total of 6 subjects
Part 2-Extension-2: 3 subjects each in the high-dose group and the low-dose group, for a total of 6 subjects

<Rationale>
The planned sample size was selected not from the perspective of statistical power but from the perspective of feasibility.
Because DMD is a rare disease, and there are several types of defects in the causative gene, the number of patients who can be targeted by a therapeutic drug that skips a

specific exon is limited. According to a patient registration site for neuromuscular disease patients (Remudy), the number of DMD patients registered as of the end of Jun 2015 was 1037, and of these, it is estimated that the number of patients treatable with the exon 45 skipping treatment of this study is approximately 9%[11, 12] (approximately 93 patients) of all DMD patients, and since it is possible to assess efficacy and safety appropriately in only some of these target patients, out of consideration for feasibility, we selected 6 subjects as the number of assessable subjects for the primary endpoint of this study.

12. Quality Control and Quality Assurance

The sponsor will assure that the conduct of the study and the preparation, recording and reporting of data comply with the following items, by following the quality assurance and quality control systems based on the standard operating procedures set down by the sponsor.

1) Clinical study protocol
2) The criteria specified in Article 14 Paragraph 3 and Article 80-2 of the Law on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (abbreviated name: Pharmaceuticals and Medical Devices Law)
3) The GCP Ordinance

To assure the reliability of all data relating to the study and to assure that data are processed properly, the sponsor will perform quality control at each stage when data are handled. The methods of quality control will be prepared in advance according to the standard operating procedures set down by the sponsor, and records of the quality control conducted will be kept.

The sponsor's responsible auditor will conduct GCP audits as part of quality assurance activities, to assess whether this study complies with GCP, the clinical study protocol, procedures and the like, independent and separately from usual monitoring and study quality control work.

13. Payment for Participation, Compensation for Study-Related Injuries and Insurance

13.1 Payment for Participation

Payments such as payments to relieve the financial burden on subjects will be made to subjects from the expenses paid by the sponsor to the study site, according to the rules set down separately by the study site.

13.2 Compensation for Study-Related Injuries

If a subject experiences any study-related injury caused by this study, the investigator or subinvestigator will provide treatment and take other necessary action. If a subject requests a response to a study-related injury, the investigator or subinvestigator will promptly contact the sponsor. The sponsor will set down procedures for compensating study-related injuries to the subject, and take measures such as purchasing insurance. The sponsor will bear the portion of the subject's copayment for the costs of treatment for the study-related injury, excluding the amount covered by payments such as health insurance. If any liability for damages arises, for example due to sequelae, compensation will be paid, using the payments under the Adverse Drug Reaction Relief System as guideline amounts. However, this does not necessarily apply if the cause of the study-related injury meets any of the following conditions.

1) It is proven that there is a clear relationship to another cause of the study-related injury
2) The temporal relationship between administration of the study drug and the study-related injury is implausible
3) There is a party who clearly caused harm, as in the case of a road traffic accident
4) The subject did not receive therapeutic benefits due to the study drug administration being ineffective
5) The subject or the subject's partner became pregnant during the study period
6) The subject failed to comply with the clinical study protocol, without a valid reason

If the study-related injury is determined to be due to the deliberate act or gross negligence of the study site or the subject, compensation may not apply, or the amount of compensation may be reduced.

13.3 Insurance

The sponsor will purchase the necessary insurance for payment of compensation for study-related injuries. The study site will purchase insurance or take other necessary measures in case study-related injury occurs due to medical error.

14. Publication Policy

1) The information obtained in this study must not be published, in part or in whole, without prior discussion with the sponsor. The sponsor will decide the method of publication. If information is published, the privacy of subjects will be protected.
2) The sponsor will use the information obtained in this study for purposes such as application for manufacturing and marketing approval for the investigational product. If the investigational product is approved, part of the contents of this study may be made public based on the "Act on Access to Information Held by Administrative Organs (Act No. 42 of 14 May 1999)," the "Act on Access to Information Held by Incorporated Administrative Agencies (Act No. 140 of 05 Dec 2001)" and "Publication of Information Relating to Approval Review of New Pharmaceuticals (Notification No. 0422001 of the Evaluation and Licensing Division, PFSB, dated 22 Apr 2005)." If information is made public, the privacy of subjects will be protected.

15. STUDY ADMINISTRATIVE INFORMATION

15.1 Ethics

15.1.1 Ethical Conduct of the Study

This study will be conducted in compliance with the standards set down in Article 14 Paragraph 3 and Article 80-2 of the Pharmaceuticals and Medical Devices Law and MHW Ordinance No. 28 dated 27 Mar 1997, "The Ministerial Ordinance on Good Clinical Practice" ("the GCP Ordinance"). It will be conducted in accordance with the ethical principles of the Declaration of Helsinki, and the human rights, welfare and safety of subjects will be ensured to the greatest extent possible.

In addition to the above, the genomic and genetic analysis performed during the study, and the banking of clinical specimens for genomic and genetic analysis and research using these samples will also be in accordance with the "Ethical Guidelines for Human Genome/Gene Analysis Research[13]" and the "Ethical Guidelines for Clinical Research.[14]"

15.1.2 Institutional Review Board

Before this study is conducted, it will be reviewed and approved by an Institutional Review Board (IRB) as set down in Article 27 of the GCP Ordinance. Once per year during the conduct of the study, or more frequently if requested by the IRB, the study will be reviewed to decide whether it can continue. A review to decide whether the study will continue will also be performed if information that may affect the safety of subjects or the conduct of the study is obtained.

15.2 Subject Confidentiality

To protect the confidentiality of individual subjects, documents submitted to an external party by the study site will identify subjects using subject identification codes, and will not use information such as names or medical record numbers that can be used to identify subjects. Persons who may learn confidential information about subject during their work will maintain the confidentiality of this information.

15.3 Obtaining Informed Consent

Before screening tests are performed, the investigator or subinvestigator will provide an easily understandable explanation of the following items to a legally acceptable representative who can act in the best interest of the subject, using the informed consent form, and will obtain written informed consent for the subject to participate in

the study, given of the legally acceptable representative's own free will. When informed consent is obtained, the legally acceptable representative will be given sufficient time to decide whether to allow the subject to participate in the study and the opportunity to ask questions, and will receive adequate answers to these questions.
The subject will also receive an explanation about information including the contents of the study using the informed consent or confirmation of intent form/assent form, as appropriate for his ability to understand, and efforts will be made to enable the subject to understand, and when possible, written confirmation of intent will be obtained.
The investigator or subinvestigator who provides the legally acceptable representative or the subject himself with an explanation about matters such as the contents of the study will add his/her name and seal to, or sign, the informed consent and confirmation of intent form, and each person will enter the date. If the study staff appointed by the director of the study site provides a supplementary explanation, in addition to the investigator or subinvestigator, the members of the study staff will also add their names and seals to, or sign, the informed consent and confirmation of intent form, and enter the date. The legally acceptable representative will write the subject's name and his/her relationship with the subject on the informed consent and confirmation of intent form, and then sign it and enter the date. If possible, the subject himself will also sign the informed consent and confirmation of intent form and enter the date.
The investigator or subinvestigator will give the legally acceptable representative a copy of the informed consent form and written explanation, a copy of the confirmation of intent form, and the assent form, and will store the original informed consent form and confirmation of intent form at the study site. The investigator or subinvestigator will make a written record (such as the original of the informed consent form or medical records) of having provided the legally acceptable representative with a copy of the informed consent form and written information, a copy of the confirmation of intent form, and the assent form.
Subjects from whom consent has been obtained by the above method will be recorded on the subject screening list and assigned subject identification codes.

[Items to be explained to subjects and their legally acceptable representatives]

1) That the study involves research
2) The study objectives
3) The study methods (the experimental aspects of the study and the inclusion criteria for subjects)

4) The planned duration of participation of subjects in the study
5) The planned number of subjects who will participate in the study
6) The expected benefits to the subject's mental and physical health from the study drug (or, if no benefits are expected, this fact) and the expected disadvantages to the subject
7) Whether other therapeutic approaches are available, and the expected significant benefits and risks of these therapeutic approaches
8) The compensation and treatment the subject can receive if he suffers any study-related injury
9) That the subject or his legally acceptable representative can decide whether to participate in the study of their own free will, and that the subject or his legally acceptable representative can refuse or withdraw consent for the subject to participate in the study at any time. Also, that the subject will not suffer any disadvantage for refusing or withdrawing consent, and will not lose any benefits he is entitled to if he does not participate in the study
10) That if any information that may affect the willingness of the subject or his legally acceptable representative to continue to participate in the study is obtained, the subject will promptly be informed of this information
11) The conditions or reasons for which the subject can be withdrawn from participation in the study
12) That the clinical research associate, responsible auditor, IRB, and regulatory authorities may view original medical records, and that when these records are viewed, the subject's confidentiality will be protected, and that by writing his name and adding his seal to, or signing, the informed consent form, the subject consents to these records being viewed
13) That even if the result of the study is published, the subject's confidentiality will be protected
14) If it is necessary for the subject to bear expenses, details of these
15) If any payment will be made to the subject, details of this
16) The name, position, and contact information of the investigator or subinvestigator
17) The office of the study site that should be contacted if the subject or his legally acceptable representative wants more information about the study and the subject's rights, or to make enquiries about a study-related injury
18) The rules that the subject should follow
19) The type of IRB performing reviews of the acceptability of the study, the items

reviewed by each IRB and other information relating to the IRB for the study

As a measure to prevent the spread of the novel coronavirus, self-administration will be allowed. Consent for self-administration will be obtained from the legally acceptable representative, and the guardian performing self-administration will be given training in the method of storing the study drug and the method of administering the study drug before self-administration starts.

15.4 Informed Consent for Pharmacogenomics and Biomarker Research

If genomic or genetic analysis will be performed during the study, or if there will be long-term storage of specimens (banking) for genomic or genetic analysis with no fixed timing, the investigator or subinvestigator will provide the subjects and legally acceptable representatives who have given consent for this study with an easily understandable explanation of the items shown below, and obtain written informed consent separate from the consent for this study, given of their own free will. This informed consent will be obtained before specimens are collected.

1) The characteristics and nature of genetic information
2) The objectives of this research
3) The methods of this research
4) The expected benefits and expected disadvantages to the subject's mental and physical health from this research
5) That the subject or his legally acceptable representative can decide whether to participate in the pharmacogenomic investigation of their own free will, and that the subject can refuse or withdraw consent to participate in this research at any time. Also, that the subject will not suffer any disadvantage for withdrawing consent, and that his participation in the study will not be affected if he does not participate in this research.
6) How specimens and data will be handled if consent is withdrawn
7) Information about how specimens will be handled and the storage period and disposal of specimens
8) The compensation that the subject can receive
9) The disclosure and ownership of the result of the research
10) If it is necessary for the subject to bear expenses, details of these
11) That the subject will not be receive remuneration for providing specimens
12) That the subject's confidentiality and other human rights will be protected

15.5 Provision of New Information Affecting the Conduct of the Study

If the investigator or subinvestigator obtains information that may affect the willingness of the subjects or their legally acceptable representatives to continue to participate in the study, he/she will promptly explain this information to the subjects and their legally acceptable representatives and confirm whether the subjects and their legally acceptable representatives are willing to continue to participate in the study. The investigator or subinvestigator will also record the date of explanation, the person providing the explanation, the contents of the explanation, the wishes of the subjects and legally acceptable representatives and the date of confirmation in documents such as medical records. In addition, if necessary, the investigator will promptly amend the informed consent form and written information, confirmation of intent form and assent form, submit it to the sponsor and report to the director of the study site and obtain approval from the IRB. Informed consent will not be obtained from new subjects until approval is received from the IRB. If the study is already being conducted in some subjects, informed consent for continuing to participate in the study will be obtained from these subjects again, by the same method of obtaining informed consent as above, using the amended informed consent form and written information, confirmation of intent form and assent form, and the legally acceptable representative will be provided with a copy of the informed consent form and written information, a copy of the confirmation of intent form and the assent form. The investigator or subinvestigator will make a written record (such as the original of the informed consent form or medical records) of having provided the legally acceptable representative with a copy of the informed consent form and written information, a copy of the confirmation of intent form and the assent form.

15.6 Planned Study Period

01 Oct 2015 to 31 Dec 2020

15.7 Protocol Amendment

If the sponsor amends the clinical study protocol after the start of the study, the sponsor will discuss the appropriateness of the changes and the effect on assessment in the study with persons such as the medical expert, as necessary, before making a decision on amendment. The sponsor will make a written record of the contents of the discussion, whether amendments were made and the reason for this, and store it.

The sponsor will promptly inform the investigator of the contents of the amendment to the clinical study protocol. If the version number of the clinical study protocol has been amended, the sponsor will obtain written agreement from the investigator again, and will carry out the procedures specified by the study site.

15.8 Termination and Temporary Discontinuation of the Study

If any of the following criteria is met, and the sponsor determines that it is not feasible to continue the study, the sponsor will temporarily discontinue a part or the whole of the study at that time. After this, the sponsor will decide whether to terminate a part or the whole of the study, and make a written record of this decision.

1) New safety information or serious adverse event information about the study drug has been obtained
2) There has been a major GCP violation and major deviation from the clinical study protocol by the sponsor, study site or investigator
3) Other information has been obtained during the conduct of the study

If the sponsor, in discussion with persons such as the medical expert, decides to terminate a part or the whole of the study, the sponsor will promptly inform the director of the study site in writing, including the reason for this. The director of the study site will promptly inform the investigator and IRB, including the reason.
If the study is terminated or temporarily discontinued for any reason, the investigator will promptly inform the subjects participating in the study and their legally acceptable representatives, take appropriate action and perform tests or other investigations to confirm the safety of subjects.

15.9 Procedures for Preparing the Case Report Form and Remarks

In this study, in addition to case report forms (prepared by the investigator), drug concentration measurement reports (prepared by the central laboratory) and electrocardiogram reports (prepared by the central laboratory), reports of the biomarker measurements in each of 6.8 to 6.12 (prepared by the central laboratory) will also be prepared. Details such as the method for preparing the measurement reports will be specified separately.

15.9.1 Style of the Case Report Form

In this study, case report forms will be filled out electronically, using a system for

electronically preparing case report forms (an EDC system, Table 15.9-1). A case report form (including an audit trail) will be prepared for each subject, and the case report form signed by the investigator will be handled as the original. An EDC system that has been validated will be used.

Table 15.9-1 EDC System

Name of EDC system	Medidata Rave®
Developer of the EDC system	Medidata Solutions, Inc.
Entry method	Web-based data entry
Entry terminals	Personal computers at the medical institution
Prohibited OS	None
Browser	Medidata Rave® supports browsers that handle HTML 5 and CSS2. The use of JavaScript must be enabled in browsers.
Recommended screen resolution	At least 1024 × 764
Recommended connection speed	≥128 kbps
Other requirements	Adobe Flash Player Ver. 10 or above

15.9.2 Preparing Case Report Forms

Before preparing case report forms, the investigator will receive training on electronic signatures, and the record of this training will take the place of the list of signatures and seals.

1) Case report forms will be prepared for subjects who have provided consent.
2) The investigator or subinvestigator will prepare case report forms according to the "Case Report Form Completion Guidelines" provided by the sponsor.
3) If members of the study staff assist with the preparation of case report forms, they will follow the directions of the investigator or subinvestigator.
4) The investigator will submit case report forms to the sponsor and store copies of them.
5) If there is any discrepancy between the data entered on the case report forms and the source documents, the investigator will separately prepare records explaining the reason for this and submit them to the sponsor, storing a copy.

15.9.3 Entering Names and Seals or Signatures on Case Report Forms

The investigator will check the case report forms prepared at the study site and sign them electronically.

15.9.4 Changes or Revisions to Case Report Forms

1) The investigator, subinvestigator or study staff will revise case report forms according to the "Case Report Form Completion Guidelines" provided by the sponsor.
2) The investigator will have responsibility for the contents entered on the case report forms, and will store copies of all records of changes and revisions to them.

15.10 Storage of Source Documents and Other Records

15.10.1 Definition of Source Documents

This refers to the original document, data and records, or certified copies of them specified by ICH-GCP 1.52, and includes the records (source data) necessary to reproduce and assess the narrative of the study. For example, hospital records, clinical charts, laboratory notes, memoranda, subject's diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial.

15.10.2 Record Keeping

15.10.2.1 Institutional Review Board

The person who established the IRB will store standard operating procedures, committee member lists, submitted documents, minutes of meetings and summaries of these, and letters, until whichever of the dates 1) and 2) below is later. However, if the sponsor decides that it is necessary to store these for a longer period, discussions will be held with the sponsor about the storage period and method of storage.

1) The date of approval of this drug (if development is terminated, the date 3 years after the day when notification of termination of development is received from the sponsor)
2) The date 3 years after the study is terminated or ends

15.10.2.2 Study Sites

The director of the study site or person responsible for storage of records will store the "study-related documents or records" that are to be stored at the study site until whichever of the dates 1) and 2) below is later. However, if the sponsor decides that

it is necessary to store these for a longer period, discussions will be held with the sponsor about the storage period and method of storage. For each record, a person responsible for storage will be specified, and this person will store these records. The director of the study site or person responsible for storage of records will take measure to ensure that these records are not lost or disposed of during the period for which they have a duty to store them, and that they can present the records if they are requested.

1) A date at least 15 years after the study ends, when there are no longer any marketing applications under review or investigation in the ICH region
2) A date at least 3 years after clinical development of the investigational product has been officially terminated

In the case of long-term storage of specimens for genomic and genetic analysis (banking), to handle withdrawal of consent by subjects who have ended the study, the study site will store the subject screening list for up to 20 years after the study has ended.

15.10.2.3 Sponsor

The sponsor will store the "study-related documents or records" that are to be stored until whichever of the dates 1) and 2) below is later.

1) A date at least 15 years after the study ends, when there are no longer any marketing applications under review or investigation in the ICH region
2) A date at least 3 years after clinical development of the investigational product has been officially terminated

15.11 Source Document Verification

At the time of monitoring or auditing by the sponsor or investigations by the regulatory authorities or IRB, the director of the study site and the investigator will provide direct access to all source documents and other study-related documents. To check that the study is being conducted appropriately and that the reliability of data is fully ensured, the sponsor will conduct monitoring and audits, and will directly access source documents and other study-related documents at the study site. The sponsor will discuss the method for directly accessing source documents with the investigator in advance.

15.12 Organization

The organization for the study is as follows. Each assigned person will perform work in accordance with the standard operating procedures of Daiichi Sankyo Co., Ltd.

15.12.1 Sponsor

Daiichi Sankyo Co., Ltd.
3-5-1 Nihonbashi Honcho, Chuo-ku, Tokyo 103-8426
Tel: PPD (main line)

PPD PPD PPD
PPD PPD Clinical Development Department III
PPD PPD PPD, Clinical Development Department III
1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140-8710
Tel: PPD (main line) Fax: PPD

PPD PPD CMC Department
PPD PPD Data Intelligence Division
PPD PPD Clinical Pharmacology Division
PPD PPD Clinical Pharmacology Division
PPD Biomarker Division
PPD PPD Clinical Pharmacology Division
PPD PPD Data Intelligence Division
PPD PPD RD/PV Reliability Assurance Division

PPD PPD Safety Management Division

3-5-1 Nihonbashi Honcho, Chuo-ku, Tokyo 103-8426
Tel: PPD Fax: PPD

PPD PPD Safety Management Division

PPD PPD Biomarker Division

PPD PPD Biomarker Division

Contact Office for Banking: Biomarker Division
1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140-8710
Tel: PPD Fax: PPD

15.12.2 Medical Expert

PPD, Development of Physical Therapy,
Faculty of Rehabilitation, Kobe Gakuin University
518 Arise, Ikawadanicho, Nishi-ku, Kobe-shi, Hyogo 651-2180
Tel: PPD
Contents of work:

Giving advice on the planning and conduct of the study and the preparation of the clinical study report from a medical perspective. As the approver of the clinical study report, signing the clinical study report if it is determined to be appropriate for approval.

15.12.3 EDC System Development

Medidata Solutions, Inc.
Person responsible: PPD
350 Hudson Street, 9th Floor, New York, New York 10014, USA
Tel: PPD (main line)
Contents of work:

Administering and maintaining the operation of the EDC system based on an outsourcing contract.

15.12.4 EDC System Support

Fujitsu Limited
Person responsible: PPD
Tokyu REIT Kamata Building, 5-13-2 Kamata, Ota-ku, Tokyo 144-0052
Tel: PPD
Contents of work:

Supporting the EDC system based on an outsourcing contract.

15.12.5 Study Site and Investigators

See Attachment 1 List of Study Sites and Investigators
Contents of work:

Based on discussions with the sponsor, agreeing on the clinical study protocol, preparing and amending the informed consent form and confirmation of intent form/assent form, selecting subjects and obtaining informed consent, instructing and overseeing subinvestigators and the study staff, providing documents and information, cooperating with monitoring and audits, reporting deviations from and changes to the clinical study protocol and adverse events, preparing case report forms, and storing “study-related documents or records.”

15.12.6 Central Laboratories

15.12.6.1 Electrocardiogram Analysis Site

Contractor
Suzuken Co., Ltd.
Person responsible: PPD
26 Himewaka-cho, Meito-ku, Nagoya-shi, Aichi 465-0045
Tel: PPD
Contents of work:

Performing work including project management, renting out and installing electrocardiographs, providing site training and transmitting data, based on an outsourcing contract.

Analysis site
BioClinica, Inc.
Person responsible: PPD
211 Carnegie Center, Princeton, NJ 08540

Tel: PPD

Contents of work:

Performing work such as analyzing electrocardiograms sent from study sites, data management and reporting results, based on an outsourcing contract.

15.12.6.2 Clinical Specimen Storage Facility

LSI Medience Corporation

Person responsible: PPD

3-30-1 Shimura, Itabashi-ku, Tokyo 174-8555

Tel: PPD

Contents of work:

Managing the recovery and storage clinical specimens such as blood and urine in this study, and their transportation to central laboratories, based on an outsourcing contract.

15.12.6.3 Contractor Storing and Managing Clinical Specimens for Checking the DNA Sequences of the DS-5141b Double-Strand Formation Site and Genomic/Genetic Analysis

LSI Medience Corporation

Managers: PPD

3-30-1 Shimura, Itabashi-ku, Tokyo 174-8555

Tel: PPD

Contents of work:

Measuring and storing samples sent from the study sites, based on an outsourcing contract.

Performing work such as storing (banking) and disposing of clinical specimens for genomic/genetic analysis (DNA specimens).

15.12.6.4 Drug Concentration Measurements

CMIC Pharma Science Co., Ltd.

17-18 Nakahata-cho, Nishiwaki-shi, Hyogo 677-0032

Contents of work:

Measuring and storing samples sent from study sites, based on an outsourcing contract.

15.12.6.5 Measurement of Muscle Tissue Dystrophin Protein and Dystrophin mRNA, Measurement of Blood Cell Dystrophin mRNA

GeneticLab Co., Ltd.
Sapporo IT Front Building Third Floor, 28-196, Nishi 15, Kita 9 Jo, Chuo-ku, Sapporo-shi, Hokkaido 060-0009
Contents of work:

Measuring and storing samples sent from study sites, based on an outsourcing contract.

BioAgilytix Labs, LLC.
2300 Englert Dr, Durham, NC 27713 USA
Contents of work:

Measuring and storing samples sent from study sites, based on an outsourcing contract.

AGADA Biosciences Inc.
1344 Summer Street, Halifax, NS B3H 0A8, Canada
Contents of work:

Measuring and storing samples sent from study sites, based on an outsourcing contract.

15.12.6.6 Measurement of Anti-DS-5141b Antibody

Shin Nippon Biomedical Laboratories, Ltd.
2438 Miyanoura-cho, Kagoshima-shi, Kagoshima 891-1394
Contents of work:

Measuring and storing samples sent from study sites, based on an outsourcing contract.

15.12.6.7 Measurement of Anti-Dystrophin Antibody

Sumika Chemical Analysis Service, Ltd.
3-1-135 Kasugadenaka, Konohana-ku, Osaka-shi, Osaka 554-0022
Contents of work:

Measuring and storing samples sent from study sites, based on an outsourcing contract.

15.12.6.8 Measurement of In Vitro Dystrophin Protein and Dystrophin mRNA

ACEL, Inc.
Person responsible: PPD
Room 2506, Sagamihara Incubation Center SIC-2, 5-4-30 Nishihashimoto, Midori-ku, Sagamihara-shi, Kanagawa 252-0131
Tel: PPD
Contents of work:

Measuring and storing samples sent from study sites, based on an outsourcing contract.

Takara Bio Inc.
Nojihigashi 7-4-38, Kusatsu-shi, Shiga 525-0058
Contents of work:

Measuring and storing samples sent from ACEL, Inc., based on an outsourcing contract.

15.12.6.9 Measurement of Micro-RNA

Takara Bio Inc.
Nojihigashi 7-4-38, Kusatsu-shi, Shiga 525-0058
Contents of work:

Measuring and storing samples sent from study sites, based on an outsourcing contract.

15.12.6.10 Measurement of Blood and Urine DS-5141b Metabolites

Drug Metabolism & Pharmacokinetics Research Laboratories, Daiichi Sankyo Company, Limited
1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140-8710

15.12.6.11 Musculoskeletal Image Analysis

Micron, Inc.
Person responsible: PPD
Nihonbashi Nishikawa Building, 1-5-3 Nihonbashi, Chuo-ku, Tokyo 103-0027
Tel: PPD
Contents of work:

Analysis of images sent from study sites, based on an outsourcing contract.

15.12.6.12 Measurement of Urine Protein

LSI Medience Corporation
3-30-1 Shimura, Itabashi-ku, Tokyo 174-8555
Contents of work:

Measuring and storing samples sent from study sites, based on an outsourcing contract.

15.12.7 Safety Assessment Committee Member

PPD , Pharmaspur Inc.
Toyo Building, 1-2-10 Nihonbashi, Chuo-ku, Tokyo 103-0027
Contents of work:

Assessing safety data as a neutral third party independent of the sponsor and the investigator, and providing advice to the sponsor on matters such as whether to continue, change or terminate the study.

15.13 Department Responsible for Audit

Person responsible: PPD
, Daiichi Sankyo Company, Limited
1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140-8710
Tel: PPD , Fax: PPD
Contents of work:

Conducting GCP audits.

15.14 Emergency Contact Information

1) Contact information for evenings (18:00 to 9:00) and Saturdays, Sundays and holidays (all day)
   Emergency contact desk
   Tel: PPD

2) Contact information for daytime (9:00 to 18:00) Mondays to Fridays (except holidays)
   PPD , Daiichi Sankyo Company, Limited
   Tel: PPD (main line), PPD

15.15 Company Conducting Joint Development

Orphan Disease Treatment Institute Co., Ltd.
1-2-58 Hiromachi, Shinagawa-ku, Tokyo 140-8710

16. References

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14. Ministry of Health, Labour and Welfare. Ethical Guidelines for Clinical Research (created on 30 Jul 2003, comprehensively revised on 28 Dec 2004, comprehensively revised on 31 Jul 2008) [In Japanese].

17. Appendices

Appendix 1 Subject Registration Form

Appendix 2 Standards for Classification of Serious Adverse Drug Reactions
(Notification No. 80 of the Safety Division, PMSB dated 29 Jun 1992)

Appendix 3 Timing of Examinations, Observations and Tests

Attachments

Attachment 1 List of Study Sites and Investigators