Report on the Deliberation Results

November 13, 2015

Pharmaceutical Safety and Environmental Health Bureau
Medical Device and Regenerative Medicine Product Evaluation Division

[Classification]	Instrument & Apparatus 58, Orthopedic Instrument & Apparatus
[Generic name]	Biosignal-responsive motor function improvement device
[Brand name]	HAL for Medical Use (Lower Limb Type)
[Applicant]	Cyberdyne Inc.
[Date of application]	March 25, 2015 (Marketing Authorization Application)

[Results of deliberation]

In the meeting held on November 10, 2015, the Committee on Medical Devices and *In-vitro* Diagnostics reached the following conclusion and decided that this conclusion should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs Council.

The product should be approved on condition that it be subject to a use-results survey. This product is classified as a controlled medical device and a specially designated maintenance-and-management-required medical device. The product is not classified as a biological product or a specified biological product.

Review Report

October 23, 2015
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following medical device product submitted for registration are as follows.

[Classification]	Instrument & Apparatus 58, Orthopedic Instrument & Apparatus
[Generic Name]	Biosignal-responsive motor function improvement device (new generic name)
[Brand name]	HAL for Medical Use (Lower Limb Type)
[Applicant]	Cyberdyne Inc.
[Date of application]	March 25, 2015
[Items warranting special mention]	Orphan medical devices
[Reviewing office]	Office of Medical Devices I

The scope of blacked out information is subject to change in the future.

Review Results

October 23, 2015

[Classification]	Instrument & Apparatus 58, Orthopedic Instrument & Apparatus
[Generic Name]	Biosignal-responsive motor function improvement device (new generic name)
[Brand name]	HAL for Medical Use (Lower Limb Type)
[Applicant]	Cyberdyne Inc.
[Date of application]	March 25, 2015

[Results of review]

HAL for Medical Use (Lower Limb Type) ("HAL") consists of the base component (with a controller etc.), a battery pack, upper and lower leg cuffs, sensor shoes, and other components. HAL assists lower limb movements during gait training therapy by driving the hip and knee power units according to bio-electric signals measured at the body surface, joint angles, plantar force, and trunk absolute angles.

The submitted non-clinical trial data regarding the electrical safety, electromagnetic compatibility, and performance of HAL demonstrated no particular problems.

The results of an investigator-initiated clinical trial (the clinical trial) conducted in Japan were submitted as clinical trial data. The efficacy of HAL was evaluated by 2-minute walking tests performed before and after 9 sessions of treatment. The results showed that the walk distance following HAL therapy was approximately >10% higher than that following treatment with a dedicated hoist (the control) ($P = 0.037$, t-test). The safety of HAL was evaluated based on adverse events and malfunctions. Adverse events reported during the use of HAL for which a causal relationship to the device could not be ruled out were myalgia (10.0%), back pain (6.7%), pain in extremities (3.3%), excoriation (6.7%), dermatitis contact (6.7%), skin exfoliation (3.3%), and contusion (3.3%).

PMDA conducted an overall evaluation of the submitted data based on comments from the Expert Discussion. The current clinical data alone are insufficient for a complete (long-term) evaluation of HAL, partly because HAL is an orphan medical device. However, HAL is considered to have a certain level of efficacy with acceptable safety. PMDA has concluded that the efficacy and safety of HAL should be further evaluated after marketing approval. The efficacy and safety data should be provided to healthcare professionals. A treatment manual, etc. should be prepared to help them use HAL effectively and identify eligible patients appropriately based on the data.

As a result of its regulatory review, PMDA has concluded that HAL may be approved for the intended use as described below and that the application should be deliberated by the Committee on Medical Devices and *In-vitro* Diagnostics.

[Intended use]

1. Intended use

HAL is used to improve gait function in patients with slowly progressive neuromuscular disease. HAL improves gait function by assisting the movement of lower limbs according to bio-electric signals during gait training. Patients wear HAL intermittently to repeat the training.

2. Eligible patients

HAL is indicated for patients with impaired gait function due to slowly progressive neuromuscular disease. Patients are eligible for HAL therapy if they (1) have a diagnosis of slowly progressive neuromuscular disease, namely spinal muscular atrophy (SMA), spinal and bulbar muscular atrophy (SBMA), amyotrophic lateral sclerosis (ALS), Charcot-Marie-Tooth (CMT) disease, distal myopathy, inclusion body myositis (IBM), congenital myopathy, or muscular dystrophy; (2) need human assistance with walking or a walking aid; and (3) meet all the criteria below:

(a) Patients weighing 40 to 100 kg

(b) Patients approximately 150 to 190 cm tall or with an appropriate body size (e.g., upper/lower leg length, hip width) who are able to wear HAL

Review Report

October 23, 2015

I. Product for Review

[Classification]	Instrument & Apparatus 58, Orthopedic Instrument & Apparatus
[Generic Name]	Biosignal-responsive motor function improvement device (new generic name)
[Brand name]	HAL for Medical Use (Lower Limb Type)
[Applicant]	Cyberdyne Inc.
[Date of application]	March 25, 2015
[Proposed intended use]	1. Intended use HAL suppresses the progression of muscle atrophy and weakness by assisting muscle contraction in patients with slowly or chronically progressive intractable neuromuscular disease. Patients wear HAL regularly, intermittently, and therapeutically to receive assistance in muscle contraction. 2. Eligible patients HAL is indicated for patients with unsteady gait who receive treatment to suppress the progression of intractable rare neuromuscular disease. Patients with target disease, namely slowly or chronically progressive neuromuscular disease, are eligible for HAL therapy if they (1) have symptoms attributable to spinal muscular atrophy (SMA), spinal and bulbar muscular atrophy (SBMA), amyotrophic lateral sclerosis (ALS), Charcot-Marie-Tooth (CMT) disease, distal myopathy, inclusion body myositis (IBM), congenital myopathy, or muscular dystrophy, and (2) meet all the criteria below: (a) Patients weighing 40 to 100 kg (b) Patients approximately 150 to 190 cm tall who are able to wear HAL. Patients shorter or taller than this height range but able to wear HAL with an appropriate body size (e.g., upper/lower leg length, hip width).
[Items warranting special mention]	Orphan medical devices

II. Product Overview

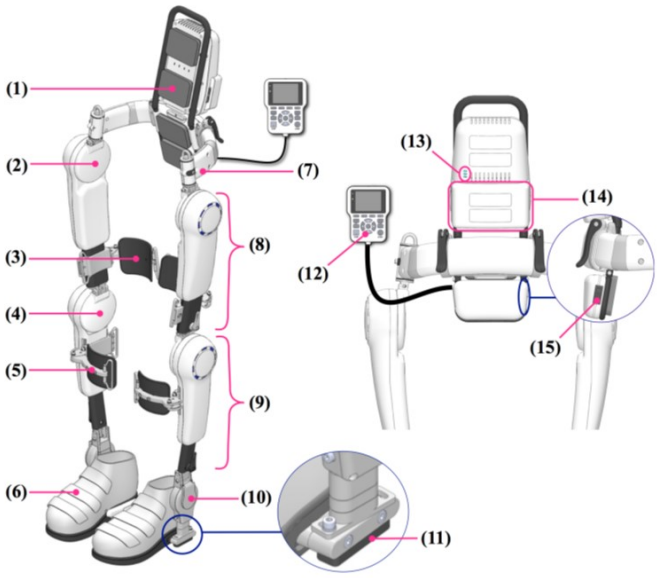
HAL for Medical Use—Lower Limb Type ("HAL" or "HAL for Medical Use") consists of the base component worn by the patient (with a controller etc.), a battery pack, upper and lower leg cuffs, sensor shoes, and other components (Figure 1). When a patient attempts to move muscles, bio-electric signals (BES) (i.e., compound muscle action potentials measured by surface electrodes) appear on the skin surface. (The compound muscle action potentials are produced by the excitation of each motor unit consisting of a motor neuron and the muscle fibers innervated by the neuron.) HAL assists the motions of the lower limb joints, as necessary, by driving the hip and knee power units according to BES measured by electrodes on the body surface and data from joint angle sensors, plantar force sensors (floor reaction force sensors), and trunk absolute angle sensors (acceleration and angular velocity sensors). The electrodes are attached directly to the skin covering the hip flexors (rectus femoris), hip extensors (gluteus maximus), knee flexors (biceps femoris or semitendinosus), and knee extensors (lateral great muscle or medial great muscle), as shown in Figure 2. The electrodes are attached to areas where muscle contraction is judged to be strong by palpation. The positions of the electrodes should be adjusted as necessary so that BES can be detected when the patient extends or bends his/her hip and knees. Each of the hip and knee power units has a joint angle sensor. Each sensor shoe (right and left) has 2 plantar force sensors under the insole. The absolute angle sensor is incorporated into the power control panel in the back module.

The power units can be operated in 3 control modes. Different modes can be selected for each power unit.

(a) CVC (Cybernic Voluntary Control) Mode: This mode controls assist torque based on the strength of BES. Assist force is adjusted according to sensitivity level of BES, torque tuner, and balance tuner.

(b) CAC (Cybernic Autonomous Control) Mode: This mode generates torque assist that corresponds to pre-programmed leg trajectories (motion pattern).

(c) CIC (Cybernic Impedance Control) Mode: This mode reduces difficulty in moving caused by the weight and frictional resistance of the components of HAL.



(1) Back module
(2) Hip power unit
(3) Upper leg cuff
(4) Knee power unit
(5) Lower leg cuff
(6) Sensor shoes
(7) Hip frame
(8) Upper leg frame
(9) Lower leg frame
(10) Ankle joint
(11) Stabilizer
(12) Controller
(13) Battery level indicator
(14) Battery pack
(15) Power switch

Figure 1. Product overview

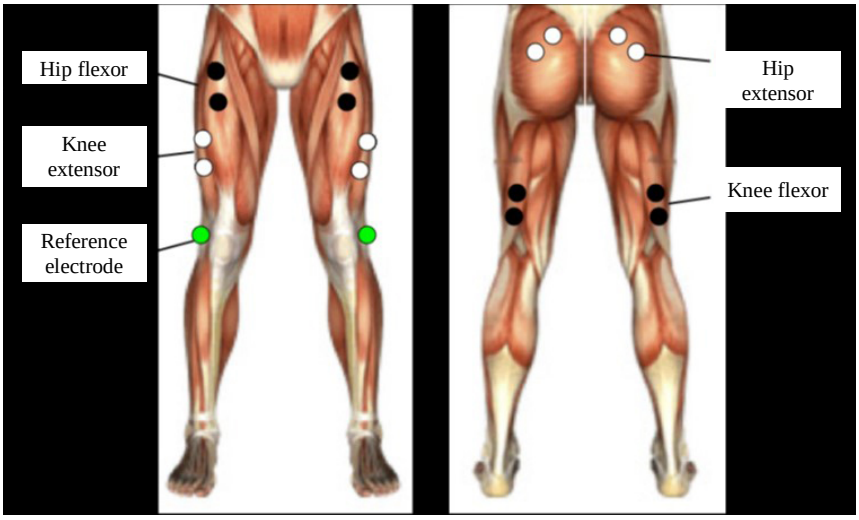


Figure 2. Examples of electrode attachment

III. Summary of the Submitted Data and Outline of the Review by PMDA

The data submitted for the application and the applicant's response to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below:

The expert advisors who participated in the Expert Discussion on HAL declared that they did not fall under the provisions of Item 5 of the "Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008) ("the Rules"). Some expert advisors, however, fell under the provisions of Item 4 (5) of the Rules, but were nominated based on their declarations, etc., regarding HAL, in accordance with the provision of Item 6 of the Rules.

1. History of development, use in foreign countries, and other information

1.(i) History of Development

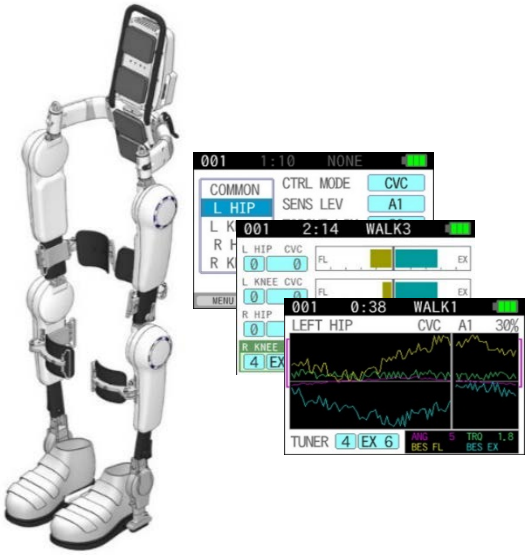
1.(i). A Summary of the submitted data

The applicant launched the HAL for Living Support in 2009. Unlike HAL for Medical Use, HAL for Living Support is not a medical device. HAL for Living Support is not intended to achieve a therapeutic effect but to support the lower limb motion of users. The 2 types of HAL are also different in the appearance and functions, such as the ability to measure and process BES and fitting adjustment points (Figure 3 and Table 1) because of different target users and operators.

Approximately a total of [redacted] HAL for Living Support were sold in Japan by the end of September 2015. There have been no reports of malfunctions or adverse events associated with the use of the device.

Unlike HAL for Living Support, HAL for Medical Use was developed as a medical device to produce a therapeutic effect. In order to demonstrate the therapeutic effect of HAL for Medical Use based on objective data, a Japanese clinical trial was initiated by an investigator (hereinafter referred to as the clinical trial) to evaluate the therapeutic effect of HAL for Medical Use in improvement of the gait function in patients with any of 8 intractable neuromuscular diseases. In the clinical trial, patients repeated gait training wearing HAL for Medical Use, then underwent tests without wearing HAL for Medical Use, to evaluate improvements in their gait function. Since no radical treatment has been established for these 8 diseases, patients with the diseases currently have no therapeutic options other than symptomatic treatment (e.g., exercise therapy) to improve their QOL.

HAL for Medical Use was designated as an orphan medical device (Device Designation No. 26 of 2014 [*26 ki*]) in December 2014 for patients with neuromuscular diseases (SMA, SBMA, ALS, CMT, distal myopathy, IBM, congenital myopathy, muscular dystrophy, and HTLV-1-associated myelopathy). In this application for marketing approval, HAL targeted the said 8 diseases except HTLV-1-associated myelopathy.



HAL for Living Support	HAL for Medical Use

Figure 3. Differences between HAL for Living Support and HAL for Medical Use

Table 1. Main differences between HAL for Living Support and HAL for Medical Use

	HAL for Living Support	HAL for Medical Use
BES processing	[redacted]	Detects and processes BES in neuromuscular diseases (amplification factor, approximately [redacted]-fold)
BES level indication (reference information for level setting)	Levels	Waveforms in chronological order
Setting interface	An external PC and the base component	Integrated in the base component
Adjustment of leg length	Multistep adjustment with a dedicated tool	Single step adjustment without using a tool
Ankle joint mechanism	Free joint	A spring mechanism to suppress plantarflexion

1.(ii) Status of use in foreign countries

1.(ii). A Summary of the submitted data

The European model of HAL for Medical Use, developed by the applicant, was granted a CE marking in June 2013. The European model has similar characteristics as the Japanese model under review for marketing approval in Japan. As of the end of September 2015, as many as [redacted] units of the European model had been used in Germany among patients with spinal cord injury or stroke, and no malfunction were reported. The European model has the same hardware operation principles and basic functions as the Japanese model, but includes the single leg version in contrast to the Japanese model. In the US, the applicant filed a *de novo* application for the same specifications as the European model in November 2014. (The application was changed to a 510(k) application in June 2015.)

1.(iii) Information on the device

1.(iii).A Summary of the submitted data

The specifications for performance of HAL included performance in BES measurement, joint angle measurement, plantar force measurement, trunk absolute angle measurement, torque control, and Programmable Electrical Medical System (PEMS). The specifications for safety included the international standards that stipulate the electrical safety of medical electrical equipment (IEC 60601-1:2005) and electromagnetic compatibility (IEC 60601-1-2:2007), joint torque limit, angular velocity limit, and strength testing for the protection mechanism for joint angles. The applicant submitted data that explain the appropriateness of all these specifications.

1.(iii).B Outline of the review by PMDA

PMDA requested the applicant to take the following actions because they were considered necessary to ensure the performance and safety of HAL, based on the Guidance on the Evaluation of Devices for Physical Function Recovery.[1]

(1) HAL assists limb movement according to the wearer's own will. The lag time between a torque command and torque generation should be within an appropriate range. Therefore, specifications for the response time between signal (BSE and various sensor signals) input and assistance should be defined.
(2) The torque level of each power unit and coordination between the power units are controlled by software. Therefore, specifications for the main control functions should be clearly defined.

The applicant responded accordingly.

PMDA reviewed the additional specifications and the data presented in "2. Data on design and development" (see below). PMDA concluded that the specifications had no particular problems.

2. Data on design and development

2.(i) Physical and Chemical Properties

2.(i).A Summary of the submitted data

The properties of HAL were verified based on its mechanical properties. The data on its physical and chemical properties were omitted, because the properties of components of the raw materials are not related to the nature of the device.

2.(i).B Outline of the review by PMDA

PMDA concluded that there was no particular problem with the omission of the data on physical and chemical properties.

2.(ii) Electrical safety and electromagnetic compatibility

2.(ii).A Summary of the submitted data

The safety and performance specifications for HAL were developed in accordance with the international standards that stipulate the safety of medical electrical equipment (IEC 60601-1:2005) and electromagnetic compatibility (IEC 60601-1-2:2007). The applicant submitted data on the electrical safety and electromagnetic compatibility of HAL, namely the results of tests performed based on IEC 60601-1 and IEC 60601-1-2. The safety and performance specifications for HAL were shown to meet both IEC 60601-1 and IEC 60601-1-2, demonstrating the electrical safety and electromagnetic compatibility.

2.(ii).B Outline of the review by PMDA

PMDA reviewed the data on electrical safety and electromagnetic compatibility, and concluded that there was no particular problem.

2.(iii) Biological Safety

2.(iii).A Summary of the submitted data

Biological safety data was omitted because HAL is not supposed to come into direct contact with body fluids or tissue directly.

2.(iii).B Outline of the review by PMDA

PMDA concluded that there was no particular problem with the omission of biological safety data.

2.(iv) Radiation Safety

2.(iv).A Summary of the submitted data

Radiation safety data was omitted because HAL does not emit radiation.

2.(iv).B Outline of the review by PMDA

PMDA concluded that there was no particular problem with the omission of radiation safety data.

2.(v) Mechanical safety

2.(v).A Summary of the submitted data

Mechanical safety data were omitted, because mechanical safety was verified in mechanical property and electrical safety tests and an additional verification was considered unnecessary.

2.(v).B Outline of the review by PMDA

PMDA asked the applicant to elucidate abnormal behavior of HAL from the safety viewpoint.

The applicant explained that HAL does not keep the joints fixed in the same position in case of power failure, and added the description of the abnormal behavior to the application documents.

PMDA asked the applicant to explain the following points in terms of the risks associated with mechanical forces imposed by HAL on users: (1) the adequacy of the motion range of HAL in comparison with the normal motion ranges of human joints; (2) torque and angular velocity settings; and (3) safety measures to prevent the motion range, angular velocity, and joint torque from exceeding the limits allowed for individual patients.

The applicant's explanation:
HAL is equipped with an actuator and a mechanical stopper designed according to inherently safe design principles. Even at the maximum torque, the actuator generates mechanical motion that does not exceed the tolerable level for the human body, and the mechanical stopper prevents the joints from moving outside the normal range of human motions. HAL has additional safety measures, namely (1) the torque limit function and (2) a mechanism to restrict the angular velocity of a joint when the joint moves beyond the assist angle range preset by a physician. Given this, the risks in question are acceptable. In a patient with a limited range of motion, presetting a range of assist angle inhibits a behavioral change (velocity)

of the joint tending to exceed the preset range. Therefore, HAL is not designed to actively assist the wearer's motion outside the preset range.

PMDA also asked the applicant to elucidate differences between HAL for Medical Use and HAL for Living Support. HAL for Medical Use has key modifications from HAL for Living Support: the mechanisms to minimize knee buckling and plantar flexion and prevent the wearer's hair and clothes from being caught in the device. PMDA asked the applicant to explain the details of these mechanisms in particular.

The applicant's explanation:
The torque control mechanism prevents knee buckling, and the spring-loaded free joints of the ankles restrain planter flexion. Each actuator is enclosed with a housing to prevent hair and clothes from being caught in it. In particular, the power units are designed to keep the rotors protected from contact with external objects. The rotors rotate more than one way and the torque control mechanism prevents the generation of torque greater than a prespecified level. This prevents objects hair, clothes, and other objects from getting caught excessively in the actuators.

PMDA's view on the mechanical safety of HAL:
The power units of HAL have no controller or mechanism to lock the joints; HAL thus will not limit the patient's posture or motion against his/her intention. Therefore, HAL is unlikely to force patients to keep a certain posture or move unstably by a motion mode that does not harmonize with his/her wills. The risk of falls can be eliminated by requiring patients to use a hoist or other supporting tools (that prevent falls without requiring any efforts by the patient) when they wear HAL [see "6.B. (5) Treatment program and usage"].

HAL for Medical Use has been designed to prevent abnormal behaviors of the device, reduce the risks caused by mechanical forces acting on patients, and incorporate measures to prevent objects from being caught in the actuators. PMDA concluded that these risks are acceptable. Based on the applicant's explanation and actions taken, PMDA concluded that there was no particular problem with the mechanical safety of HAL.

2.(vi) Stability and durability

2.(vi).A Summary of the submitted data

The life span of HAL for Medical Use was determined to be 5 years (self-warranted), based on post-marketing data on HAL for Living Support and the fact that HAL for Medical Use requires special maintenance and inspection. Stability testing data was omitted from this application in accordance with PFSB/ELD/OMDE Notification No. 1227-5 dated December 27, 2012, by Office of Medical Devices Evaluation (OMDE), Evaluation and Licensing Division (ELD), Pharmaceutical and Food Safety Bureau (PFSB), Ministry of Health, Labour and Welfare (MHLW).

2.(vi).B Outline of the review by PMDA

PMDA concluded that there was no particular problem with the omission of stability and durability data.

2.(vii) Performance

2.(vii).A Summary of the submitted data

The applicant submitted data on tests performed on HAL. The tests verified the performance and safety specifications for HAL: performance in BES measurement, joint angle measurement, plantar force measurement, trunk absolute angle measurement, joint torque limits, torque control, PEMS, and joint angle protection mechanism. A test article slightly different from HAL was subjected to verification of the limit of joint angular velocity, a performance and safety specification for HAL; the verification results were also submitted. HAL and the test article had different exterior parts, different EMC shielding parts, and different software including a test mode for performance verification. These differences, however, were judged to have no effects on the evaluation of the joint angular velocity limit. In addition, all the tests showed that HAL met all the predefined specifications.

2.(vii).B Outline of the review by PMDA

PMDA asked the applicant to explain how to ensure that HAL users receive timely assistance based on BES detected by HAL, as described in "1.(iii).B Outline of the review by PMDA."

The applicant's explanation:

Timely assistance based on BES is ensured by specifying drive system response time in performance specifications. Specifically, "response time between torque command input and driving current input into the power unit," is specified, because it primarily influences the lag time between signal measurement and torque generation.

Based on the applicant's explanation, PMDA concluded that there was no particular problem with the torque response time.

PMDA also requested the applicant to explain the rationale for the specifications for BES at the measurement sites.

The applicant's explanation:

BES, which are to be detected to control HAL, are measured on the skin surface. These signals, originating from muscle and nerve cells, are produced by a common mechanism. The signals measured on the skin surface are those from muscle and nerve cells. In healthy persons, however, most signals measured on the skin surface come from muscle cells, because muscle cells overwhelmingly outnumber nerve cells that control muscles. If the number of muscle cells decreases because of a disease or for other reasons, the ratio of muscle cells to nerve cells gradually changes with a declining proportion of muscle cell-derived BES. Nevertheless, muscle cells are still considered to outnumber nerve cells in patients eligible for HAL therapy. In any case, HAL measures and uses signals sent by both nerve and muscle

cells without distinction. HAL is designed based on the feature of electromyography, taking into account that signals originating from both muscle and nerve cells are measured on the skin surface. [redacted]

Needle electromyography may show long-duration and high-amplitude waveforms in patients with neurogenic disease, and short-duration and low-amplitude waveforms in patients with myogenic disease. [redacted] Therefore, there are no problems because the magnitude of torque generated in response to long-duration and low-amplitude noises is small.

PMDA reviewed the applicant's explanation and considered that developing BES specifications based on the specifications for electromyography was acceptable. PMDA concluded that there was no particular problem with the specifications for BES detection, because the specifications for the response to BES (amplification, input impedance, and common mode rejection ratio [CMRR]) were considered at least equivalent to the specifications for conventional electromyography.

PMDA asked the applicant to elucidate the behavior of HAL in case of a BES measurement error, due to, for example, a detached electrode.

The applicant's explanation:
When a BES measurement error (due to a detached electrode or other causes) is detected during assistance in CVC mode, the input signal level is regarded as "0" and the joint motion is controlled accordingly (in a mode equivalent to CIC mode). At the same time, the error is indicated on the controller with a beep. While an error is being indicated on the controller, the only available option for operation is "stop assisting." Therefore, BES measurement errors (due to a detached electrode or other causes) are unlikely to force the wearer to move his/her limbs excessively. CAC and CIC modes are free of this risk because HAL do not use BES in these modes.

PMDA's view:
When HAL turns into CIC mode unexpectedly, BES-based torque assistance is discontinued. This may prevent the wearer from achieving appropriate gait movement. However, the risk of forcing an unintended posture or movement is low. The risk of falls can be eliminated by using a hoist or other supporting tools during HAL therapy, as mentioned in "6.B.(5) Treatment program and usage." Given this, PMDA concluded that there was no particular problem on this issue.

PMDA asked the applicant to elucidate quantitative relationships between inputs and outputs, including BES from the extensor and flexor muscles and data from the sensors of joint angles, plantar force, and

trunk absolute angle in each mode (CVC, CAC, or CIC) and in each task (Stand, Walk, Auto, or Manual), as described in "1.(iii).B Outline of the review by PMDA."

The applicant's explanation:
The submitted application data clearly describe how flexor and extensor muscle-derived BES and sensor data are controlled and translated into torque response for each task in each mode. The applicant also verified the knee joint control by the planter sensor that prevents knee buckling of the supporting leg and the behavioral control that allows HAL to move while its center of gravity shifts within specified ranges.

PMDA concluded that there was no particular problem with the explanation by the applicant, considering that the outputs in response to various inputs were properly specified and verified.

2.(viii) Usage

2.(viii).A Summary of the submitted data

Data on usage of HAL were omitted because verification testing of usage was considered unnecessary.

2.(viii).B Outline of the review by PMDA

PMDA considers that the usage of HAL is an important element related to its efficacy and safety, but there is no appropriate non-clinical model. PMDA therefore assessed whether the specified usage of HAL was appropriate based on clinical trial results [see "6.B.(5) Treatment program and usage"].

3. Data on conformity to the requirements specified in Paragraph 3 of Article 41 of the Pharmaceutical Affairs Law

3.A Summary of the submitted data

The applicant submitted a Declaration of Conformity, which states that HAL meets the requirements for medical devices, as stipulated by the Minister of Health, Labour, and Welfare (MHLW Ministerial Announcement No. 122, 2005; hereinafter referred to as "the Essential Principles"), in accordance with Paragraph 3 of Article 41 of the Pharmaceutical Affairs Law.

3.B Outline of the review by PMDA

PMDA reviewed the conformity of HAL to the Essential Principles. In relation to requirements specified in Article 3 for the performance and functions intended by the medical device, PMDA concluded that the set of tests initially selected by the applicant were not sufficient to evaluate time between signal input and assistance, as stated in "2.(vii).B Outline of the review by PMDA" in "2.(vii) Performance." In response, the applicant performed additional tests on the response of the driving system. In terms of performance in BES measurement (a specification for the performance and safety of HAL), PMDA concluded that the verification tests were not sufficient to demonstrate the conformity of HAL to the performance specifications set by the applicant. The applicant then performed additional tests on

common-mode rejection ratio (CMRR), input impedance, and frequency characteristics. PMDA reviewed the results of the additional tests and concluded that there was no particular problem.

PMDA concluded that the set of tests initially selected by the applicant were not sufficient to demonstrate the conformity to the requirements specified in Article 2-4 (regarding the disclosure of the remaining risks) and Article 6 (regarding the efficacy of medical equipment), as stated below in "6.B Outline of the review by PMDA." PMDA asked the applicant to disclose data on the efficacy and safety obtained in the clinical trial, including limitations of the clinical trial, and to ensure that the label for HAL (the label) includes information that calls for appropriate patient selection and use of HAL in consideration of its risks and benefits. The applicant agreed.

Furthermore, PMDA considers that the evaluation items initially set by the applicant were not sufficient to demonstrate conformity to the requirements specified in Article 1 as preconditions for designing medical devices (particularly, qualifications for HAL users: [1] the level of technical knowledge and experience HAL users are expected to have; and [2] the level of education and training expected to be provided to HAL users), as stated below in "6.B Outline of the review by PMDA." PMDA then asked the applicant to prepare a HAL therapy manual describing how to use HAL properly. The applicant agreed.

4. Data on risk management

4.A Summary of the submitted data

The applicant submitted a summary of risk management, the risk management system, and its implementation status in reference to ISO 14971 "Medical devices—Application of risk management to medical devices."

4.B Outline of the review by PMDA

PMDA reviewed the documents on risk management and concluded that there was no particular problem.

5. Manufacturing process

5.A Summary of the submitted data

The applicant submitted quality control data for the evaluation of manufacturing process of HAL. Data on the sterilization method was omitted because HAL does not require sterilization.

5.B Outline of the review by PMDA

PMDA reviewed the data on the manufacturing process and considered that there was no particular problem.

6. Clinical data or other data accepted by the MHLW as a substitute for clinical data

6.A Summary of the submitted data

The applicant submitted the results of a clinical trial initiated by a Japanese clinical investigator. This randomized, controlled, 2-phase crossover study was conducted at 9 study centers in Japan from March 6, 2013 (the date of receiving the first informed consent) through August 8, 2014 (the date of completing the last follow-up). The purpose of the trial was to show the efficacy and safety of HAL therapy by demonstrating gait improvement in patients who wore HAL intermittently for a short period and then repeated gait training.

The trial enrolled patients with deteriorated gait function due to lower limb dysfunction associated with intractable rare neuromuscular diseases (spinal muscular atrophy, spinal and bulbar muscular atrophy, amyotrophic lateral sclerosis with slowly progressive lower-limb symptoms, Charcot-Marie-Tooth disease, distal myopathy, inclusion body myositis, congenital myopathy, muscular dystrophy, and conditions not yet definitely diagnosed as, but equivalent to, these diseases). Table 2 summarizes key inclusion and exclusion criteria.

Table 2. Summary of key inclusion and exclusion criteria

Inclusion criteria	• Patients aged ≥18 years • Patients without rapid changes in gait symptoms during the previous 3 months • Patients incapable of walking 10 m independently and safely without a cane, walker, or handrail due to unstable gait caused by lower limb dysfunction but capable of walking ≥10 m with minor assistance, a handrail, walker, or movable hoist (assistive device may be placed on the lower limb when necessary) • Patients weighing 40 to 100 kg and 150 to 190 cm tall who were able to wear HAL
Exclusion criteria	• Patients on a mechanical ventilator, a respiratory assistance device, or oxygen therapy or those considered to require such interventions • Patients considered unable to receive gait training because of exertional dyspnea or cardiac failure • Patients considered unable to receive gait training because of severe skeletal deformation, such as osteoarthritis of the hip, knee, or spine and scoliosis • Patients who had gait disturbance due to diseases of the brain, spinal cord, peripheral nerves, and muscles other than neuromuscular diseases relevant to this study • Patients with a condition (e.g., bleeding tendency, osteoporosis) that would interfere with the conduct of gait training • Patients with serious hepatic disorder, renal disorder, or cardiovascular disease • Patients with malignant tumor that has not been completely cured • Patients who initiated or discontinued the following treatments within 2 months of the beginning of the run-in period: New gait rehabilitation program for lower limbs; steroid therapy (excluding steroids inhaled, applied to the skin, or administered locally); administration of riluzole, sodium valproate, or any drug intended to inhibit progression of diseases to be treated by HAL therapy

	• Patients who had bone fracture, bruise, trauma, or other conditions requiring hospitalization for treatment within 3 months of the beginning of the run-in period • Pregnant or possibly pregnant women and women who wish to become pregnant during the study period • Patients unable to have the bioelectrodes attached to the body due to a skin disease • Patients incapable of moving the hip or knee with assistance in the CVC mode during the run-in period and patients for whom the floor reaction force sensor does not react • Patients who underwent gait training with the HAL for Living Support within 1 year

The subjects were divided into Groups A and B and underwent gait training therapy in Treatment Periods 1 and 2. In Treatment Period 1, the subjects did not wear HAL and used only a dedicated hoist (Figure 4). In Treatment Period 2, the subjects wore HAL and used the dedicated hoist. The subjects in Group A first underwent Treatment Period 1 and then Treatment Period 2, whereas the subjects in Group B first underwent Treatment Period 2 and then Treatment Period 1. Figure 5 summarizes the clinical trial schedule.

The dedicated movable hoist with belts to lift the patient's body served as the control for evaluation. It was also used to ensure the safety of the treatment by preventing the patient from falling. The hoist was used throughout the treatment and during the function evaluation regardless of whether HAL was used. The hoist belts were loosened enough to protect the patient's body in case of falling, but were allowed to be tightened as necessary when non-weight or partial-weight bearing gait training was considered to increase the efficacy of HAL.

Figure 4. Dedicated hoist

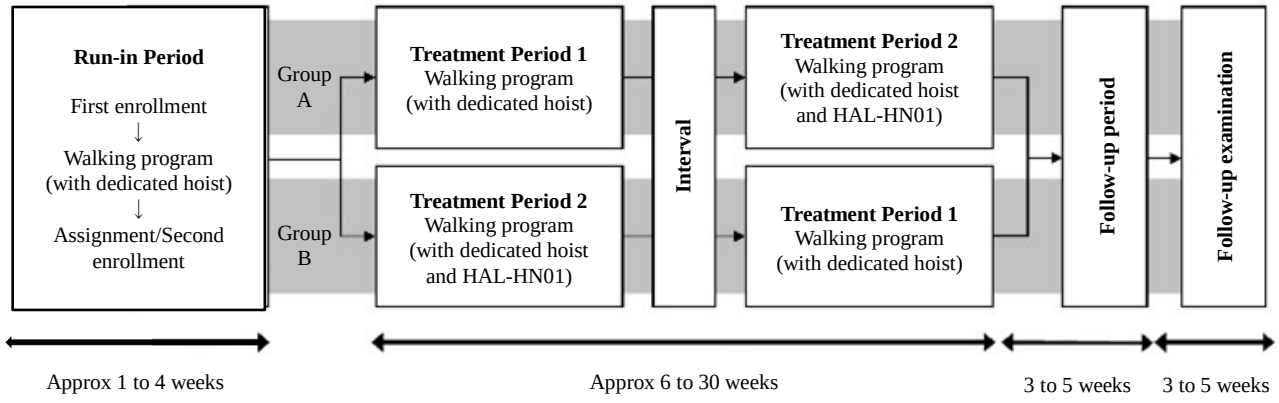


Figure 5. Outline of clinical trial schedule

Details of the walking program in each treatment period:

- A 40-minute training once daily. The training program consists of a 5-minute warming-up exercise, gait training, cooling down (stretching of the extremities and trunk), and rest (for ≤20 minutes)
- Patients underwent the program for a total of 9 times within 13 weeks: Patients were allowed to receive the training program up to 3 times in Week 1 (not on 2 consecutive days) and up to 4 times in Week 2 and subsequent weeks (not on 3 consecutive days). Thus, each treatment period was completed in 3 weeks (the shortest) to 13 weeks (the longest).
- A 1- to 3-week interval between treatment periods

Gait function was evaluated at the following points: before the beginning of treatment on the first treatment day of each treatment period; 1 to 3 days after the last treatment day of each treatment period; and 4 weeks (± 1 week) after the last treatment day (i.e., the last day of Treatment Period 2 for Group A; the last day of Treatment Period 1 for Group B). At 4 weeks (± 1 week) after the last evaluation of gait function, patients underwent a follow-up examination for adverse events, etc.

The primary efficacy endpoint was 2-minute walk distance (the distance to the toe after 2 minutes walking). The difference obtained by subtracting the improvement rate in walk distance after Treatment Period 2 (HAL and a hoist) from that after Treatment Period 1 (a hoist) in Group A was defined as d_1. The difference obtained by subtracting the improvement rate in walk distance after Treatment Period 1 (a hoist) from that after Treatment Period 2 (HAL and a hoist) in Group B was defined as d_2. Treatment effect was defined as $(d_1–d_2)/2$. The null hypothesis that there is no difference in treatment efficacy between $d_1/2$ and $d_2/2$ was tested (two-sided significance level of 5%). If a significant difference was detected and if treatment effect $(d_1–d_2)/2$ was negative, the change in walk distance after Treatment Period 2 was considered larger than that after Treatment Period 1 in Groups A and B combined; this means HAL has therapeutic efficacy.

Secondary efficacy endpoints were (a) 10-meter walk test (walking speed and the number of steps measured when patients walk as fast as possible between the 2-meter point and 8-meter point), (b) gait assessment by patients (Table 3), (c) gait assessment by healthcare professionals (Table 4), (d) manual

muscle test (Table 5), and (e) assessment of activities of daily living (ADL) (Table 6). The secondary endpoints, as with the primary endpoint, were used to analyze treatment effect $(d_1–d_2)/2$. (f) assessment by operators (Table 7) and time taken to wear HAL were also measured.

Table 3. Gait assessment by patients (visual analogue scale)

Fatigue during walking	100 = most extreme fatigue imaginable
Light tread during walking	100 = lightest tread imaginable
Stability during walking	100 = most stable walking imaginable
Sense of security during walking	100 = highest sense of security imaginable
Pleasure during walking	100 = most pleasant walking imaginable

Table 4. Gait assessment by healthcare professionals:

Stance phase	Anterior or posterior trunk flexion	For each item: -3, Significantly worse -2, Moderately worse -1, Slightly worse 0, No change +1, Slightly improved +2, Moderately improved +3, Significantly improved
	Lateral trunk flexion	
	Lateral trunk/pelvis displacement	
	Pelvic drop to the opposite side	
	Reduced hip extension	
	Excess knee flexion	
	Excess ankle plantar flexion or dorsiflexion	
	Clubfoot severity	
	Reduced ankle plantar flexion when the sole leaves the ground	
Swing phase	Trunk flexion	
	Lateral trunk flexion	
	Pelvis lift	
	Lateral pelvis rotation	
	Degree of hip flexion	
	Degree of knee flexion	
	Excess ankle plantar flexion	

Table 5. Manual muscle test

Hip flexion	Right	For each item: 0, No muscle contraction 1, Presence of muscle contraction but no joint movement 2, Able to move but not against gravity 3, Able to move through full range of motion against gravity 4, Able to move through full range of motion against gravity and slight resistance 5, Normal
	Left	
Hip extension	Right	
	Left	
Knee flexion	Right	
	Left	
Knee extension	Right	
	Left	
Ankle dorsiflexion	Right	
	Left	
Ankle plantar flexion	Right	
	Left	

Table 6. ADL evaluation (Barthel index)

Feeding	10	Independent, able to wear a self-help device, able to finish a meal in a reasonable period of time
	5	Partially dependent (e.g. needs help cutting food)
	0	Totally dependent
Transfer from wheelchair to bed	15	Independent, able to operate the brake and foot rest (including being independent without the need to use a wheelchair)
	10	Needs minor help or supervision
	5	Able to sit, almost dependent
	0	Totally dependent or unable
Grooming	5	Independent (face/hair/teeth/shaving)
	0	Partially dependent or unable
Toilet use	10	Independent, able to undress and dress, clean self, and clean the portable toilet (if used) without help
	5	Partially dependent, needs help in supporting the body, undressing and dressing, and cleaning self
	0	Totally dependent or unable
Bathing	5	Independent
	0	Partially dependent or unable
Walking	15	Able to walk ≥45 m with or without an assistive device (excluding wheelchairs and walkers)
	10	Needs help (e.g., a walker) in walking ≥45 m
	5	Unable to walk but able to operate a wheelchair to move ≥45 m
	0	Other than the above
Stairs	10	Independent with or without using a handrail
	5	Needs help or supervision
	0	Unable
Dressing	10	Independent, able to wear and remove shoes or orthoses, zip and unzip clothing etc.
	5	Partially dependent, needs help but able to do more than half unaided, able to do in a reasonable period of time
	0	Other than the above
Bowel control	10	Continent, able to use enemas or suppositories independently
	5	Occasional accident, needs help in handling enemas and suppositories
	0	Other than the above
Bladder control	10	Continent, able to handle a urine bottle independently
	5	Occasional accident, needs help in handling a urine bottle
	0	Other than the above

Table 7. Evaluation of HAL by operators

Overall evaluation of device operability	For each item: 1, Easy 2, Fair 3, Not easy
Preparation before use	
Attaching the device to a patient	
During gait training	
Removing the device	
Clearing the device after use	

The safety of HAL was evaluated based on adverse events, malfunctions, the occurrence of errors in behavior monitoring data, blood pressures, pulse rate, electrocardiogram (ECG), and abnormalities (systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or systolic blood pressure <90 mmHg; pulse rates ≥110 bpm or <50 bpm; abnormal ECG waveforms with reference to Classification of the Severity of Adverse Drug Reactions [PAB/SD Notification No. 80 dated June 29, 1992, by the Safety Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare]).

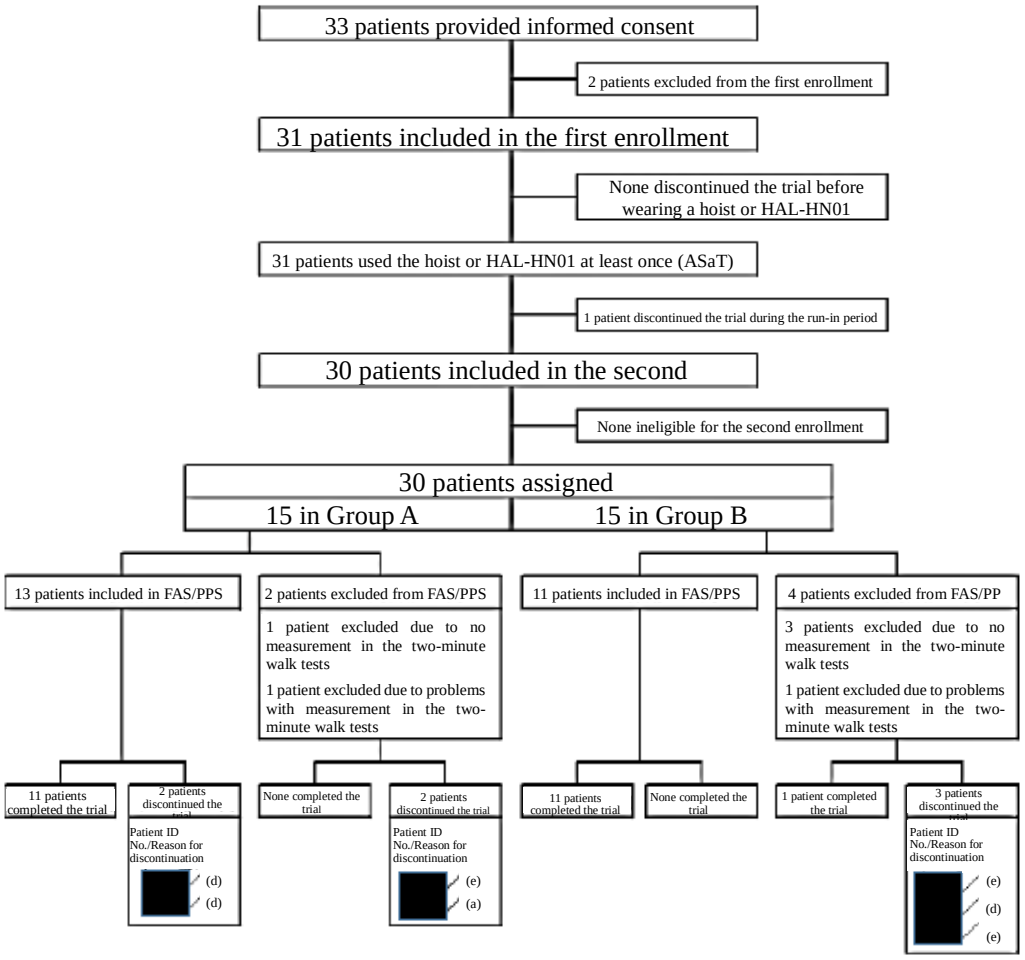
During the trial, the administration of steroids, riluzole, sodium valproate, and any drug intended to inhibit the progression of the diseases targeted in this trial was allowed as long as the daily dose in the run-in period (1 to 4 weeks before the treatment period) was maintained throughout the study period. Patients were allowed to receive any rehabilitation (except for new gait training for the lower limbs), rehabilitation to maintain the physical activity of inpatients, and pain relief rehabilitation.

The target sample size was 30 patients (15 each in Groups A and B), which was determined on the basis of the improvement rate in individuals who used HAL for Living Support and other devices at the study centers. A total of 33 patients actually provided informed consent, and 31 patients met the inclusion criteria without meeting the exclusion criteria for the first enrollment; and 30 (15 each in Groups A and B) were eligible for the second enrollment to undergo behavior verification. The safety analysis set consisted of the 31 patients included in the first enrollment, who had worn the hoist or HAL at least once. A total of 24 patients (13 in Group A and 11 in Group B) were included in the efficacy analysis set. Table 8 below shows the underlying diseases of the patients included in the efficacy analysis set. In total, 22 patients (11 each in Groups A and B) completed the trial. Figure 6 shows the change in the number of patients from the receipt of informed consent and the reasons for discontinuation of the trial. A patient discontinued the trial during the run-in period because the patient's weight did not meet the inclusion criteria. In Groups A and B combined, 6 patients were excluded from the efficacy analysis set. In 4 of the 6 patients, 2-minute walk tests were not conducted. (Patient [redacted] [Group A] requested the discontinuation of the test because the floor reaction force sensor did not work; Patient [redacted] [Group B] was not able to visit the study center because of a buttock bruise, resulting in an interval exceeding "3 weeks between treatments," a discontinuation criterion; Patient [redacted] [Group B] was admitted to another hospital for pneumonia; and Patient [redacted] [Group B] discontinued the test because of knee osteoarthritis.) In the remaining 2 patients, accurate measurements were not obtained in the 2-minute walk test. (In Patient [redacted] [Group A], the measurements of the 2-minute walk test at Visit 4 [fourth

visit] were more than double those at Visit 3 [third visit] and were considered to be erroneous data [although the patient completing 24 visits]. Patient [redacted] [Group B] had viral gastroenteritis-induced decline in physical strength considered to affect the efficacy evaluation, although the patient completed the trial). Of the patients in the efficacy analysis set, 2 discontinued the trial: Patient [redacted] (Group A) was unable to undergo the walk test at Visit 24 (the follow-up period) because of a right patella fracture; and Patient [redacted] (Group A) died from cerebral infarction (after the follow-up period).

Table 8. Underlying diseases of the patients in the efficacy analysis set

Diseases	Group A (number of patients)	Group B (number of patients)	Total (number of patients)
Spinal muscular atrophy	3	2	5
Bulbospinal muscular atrophy	2	0	2
Amyotrophic lateral sclerosis	1	0	1
Charcot-Marie-Tooth disease	1	2	3
Distal myopathy	2	3	5
Inclusion body myositis	1	0	1
Congenital myopathy	0	0	0
Muscular dystrophy	3	4	7
Total	13	11	24



Reasons for discontinuation of the trial
(a) At the request of the patient
(b) Events falling under the exclusion criteria 1, 2, 3, 4, 5, 6, 7, 10, or 11 occurred during the study period.
(c) Patients became unable to undergo the walking program for ≥3 weeks.
(d) The trial could not be continued because of an adverse event.
(e) An investigator decided that the trial should be discontinued to ensure appropriate efficacy evaluation and the safety of the patient.
(f) The patient was later found to be ineligible for the trial.
(g) The patient did not follow the instructions of an investigator.

Figure 6. Changes in the number of patients during the trial and reasons for discontinuation

6.A.(1) Primary efficacy endpoint

The improvement rates in the 2-minute walk test were as follows: Group A, 9.30% after Treatment Period 1 (a hoist) and 9.99% after Treatment Period 2 (HAL and a hoist); Group B, 5.44% after Treatment Period 1 and 24.87% after Treatment Period 2 (Treatment Period 2 preceded Treatment Period 1 in Group B). The treatment efficacy $(d_1–d_2)/2$ was -10.07 ± [redacted]% (P = 0.037, t-test), meaning that the primary endpoint was achieved with a significant difference between $d_1/2$ and $d_2/2$. Table 9 below summarizes the results from the 2-minute walk tests.

Table 9. Results from 2-minute walk tests (mean ± SD)

	Group A	Group B
Baseline (m)	[redacted]	[redacted]
Immediately after First Treatment Phase[*1] (m)	[redacted]	[redacted]
Change in walk distance after First Treatment Phase[*1] (m)	[redacted]	[redacted]
Improvement rate after First Treatment Phase[*1] (%)	9.30 ± [redacted] (Treatment Period 1)	24.87 ± [redacted] (Treatment Period 2)
Immediately before Second Treatment Phase[*2] (m)	[redacted]	[redacted]
Immediately after Second Treatment Phase[*1] (m)	[redacted]	[redacted]
Change in walk distance after Second Treatment Phase[*2] (m)	[redacted]	[redacted]
Improvement rate after First Treatment Phase[*2] (%)	9.99 ± [redacted] (Treatment Period 2)	5.44 ± [redacted] (Treatment Period 1)
Improvement rate after the entire treatment period[*3] (%)	16.81 ± [redacted]	41.94 ± [redacted]
4 weeks later (m)	[redacted]	[redacted]
Change in walk distance 4 weeks later[*4] (m)	[redacted]	[redacted]
Improvement rate 4 weeks later[*4] (%)	[redacted]	[redacted]

[*1] First Treatment Phase: Treatment Period 1 (a hoist) for Group A and Treatment Period 2 (HAL and a hoist) for Group B
[*2] Second Treatment Phase: Treatment Period 2 (HAL and a hoist) for Group A and Treatment Period 1 (a hoist) for Group B
[*3] The entire treatment period: From baseline until the end of Second Treatment Phase
[*4] Change from the end of Second Treatment Phase

6.A.(2) Secondary efficacy endpoints

Table 10 shows (a) the walking speed in patients undergoing the 10-meter walk test. The treatment efficacy $(d_1–d_2)/2$ was -9.14 ± [redacted]% (P = [redacted], t-test) with no significant difference between $d_1/2$ and $d_2/2$. Table 11 shows the number of steps in patients undergoing the 10-meter walk test. The treatment efficacy $(d_1–d_2)/2$ was 1.1 ± [redacted]% (P = [redacted], t-test) with no significant difference between $d_1/2$ and $d_2/2$.

Table 10. Walking speed in the 10-meter walk test (mean ± SD)

Improvement rate	Group A	Group B
After First Treatment Phase[*1](%)	[redacted]	[redacted]
After Second Treatment Phase[*2] (%)	[redacted]	[redacted]
After the entire treatment period[*3] (%)	[redacted]	[redacted]

[*1] First Treatment Phase: Treatment Period 1 (a hoist) for Group A and Treatment Period 2 (HAL and a hoist) for Group B
[*2] Second Treatment Phase: Treatment Period 2 (HAL and a hoist) for Group A and Treatment Period 1 (a hoist) for Group B
[*3] The entire treatment period: From baseline to the end of Second Treatment Phase

Table 11. The number of steps in the 10-meter walk test (mean ± SD)

Improvement rate	Group A	Group B
After First Treatment Phase[*1] (%)	[redacted]	[redacted]
After Second Treatment Phase[*2] (%)	[redacted]	[redacted]
After the entire treatment period[*3] (%)	[redacted]	[redacted]

[*1] First Treatment Phase: Treatment Period 1 (a hoist) for Group A and Treatment Period 2 (HAL and a hoist) for Group B

[*2] Second Treatment Phase: Treatment Period 2 (HAL and a hoist) for Group A and Treatment Period 1 (a hoist) for Group B

[*3] The entire treatment period: From baseline to the end of Second Treatment Phase

A statistically significant efficacy of HAL was not demonstrated by (b) gait assessment by patients, (c) gait assessment by healthcare professionals, or (e) the evaluation of activities of daily living. However, (d) manual muscle test showed statistically significant efficacy at (left) hip flexion ([redacted] ± [redacted]%, P = [redacted], Mann-Whitney U test) but not at the other 11 test sites with P values of ≥[redacted] (Mann-Whitney U test).

(f) User-friendliness of HAL was evaluated by operators following the first through ninth use. The total scores of the degree of difficulty in operation were[redacted], respectively. [redacted] The mean time required to wear HAL, excluding the attachment of the electrodes, was [redacted] minutes and [redacted] seconds in the fifth use, [redacted] minutes and [redacted] seconds in the seventh use, and [redacted] minutes and [redacted] seconds in the ninth use.

6.A.(3) Safety evaluation

6.A.(3).1) All adverse events

A total of 42 adverse events occurred in 13 of 15 patients (86.7%) in Group A, and 59 adverse events occurred in 14 of 15 patients (93.3%) in Group B (Table 12).

Table 12. All adverse events

	Group A (N = 15)			Group B (N = 15)		
	Number of patients	Number of events	%	Number of patients	Number of events	%
All	13	42	86.7	14	59	93.3
Gastroenteritis	1	1	6.7	0	0	0.0
Gastroenteritis viral	0	0	0.0	1	1	6.7
Genital herpes	0	0	0.0	1	1	6.7
Influenza	0	0	0.0	1	1	6.7
Nasopharyngitis	4	6	26.7	5	6	33.3
Pharyngitis	1	1	6.7	0	0	0.0
Pneumonia	2	2	13.3	1	1	6.7
Tinea pedis	1	1	6.7	0	0	0.0
Respiratory tract infection	1	1	6.7	0	0	0.0
Decreased appetite	1	1	6.7	0	0	0.0
Insomnia	0	0	0.0	1	1	6.7
Cerebral infarction	1	1	6.7	0	0	0.0
Hypoesthesia	0	0	0.0	1	3	6.7
Supraventricular extrasystoles	0	0	0.0	1	1	6.7
Hypertension	0	0	0.0	1	1	6.7
Thrombosis vena cava inferior	0	0	0.0	1	1	6.7
Laryngeal oedema	0	0	0.0	1	1	6.7
Upper respiratory tract inflammation	0	0	0.0	1	1	6.7
Abdominal pain upper	1	1	6.7	0	0	0.0
Constipation	0	0	0.0	1	1	6.7
Dental caries	1	1	6.7	0	0	0.0
Gastritis	0	0	0.0	1	1	6.7
Stomatitis	1	1	6.7	0	0	0.0
Toothache	2	2	13.3	0	0	0.0
Large intestine polyp	0	0	0.0	1	1	6.7
Cholecystitis	0	0	0.0	2	2	13.3
Cold urticaria	0	0	0.0	1	1	6.7
Dermatitis contact	2	2	13.3	3	3	20.0
Erythema	0	0	0.0	1	1	6.7
Hyperkeratosis	1	1	6.7	0	0	0.0
Rash	1	1	6.7	0	0	0.0
Seborrhoeic dermatitis	1	1	6.7	0	0	0.0
Skin exfoliation	0	0	0.0	1	1	6.7
Arthralgia	1	1	6.7	4	4	26.7
Back pain	3	3	20.0	4	4	26.7
Musculoskeletal pain	1	1	6.7	0	0	0.0

Myalgia	4	4	26.7	6	6	40.0
Neck pain	0	0	0.0	2	2	13.3
Osteoarthritis	0	0	0.0	1	1	6.7
Osteoporosis	0	0	0.0	1	1	6.7
Pain in extremity	1	1	6.7	0	0	0.0
Developmental hip dysplasia	1	1	6.7	0	0	0.0
Fatigue	0	0	0.0	1	1	6.7
Pain	0	0	0.0	2	3	13.3
Fall	2	2	13.3	2	2	13.3
Ligament sprain	0	0	0.0	1	1	6.7
Patella fracture	1	1	6.7	0	0	0
Excoriation	0	0	0.0	2	2	13.3
Contusion	3	4	20.0	2	2	13.3
Total	39*	42	—	55*	59	—

* The value is the sum of the number of patients in each event and thus does not correspond to the total number of patients.

A total of 31 events occurred in 16 patients (52.2%) during Treatment Period 1 (a hoist) and 42 events in 24 patients (80.0%) during Treatment Period 2 (HAL and a hoist) (see Table 13). Meanwhile, 28 events occurred during off-treatment periods (i.e., the events listed in Table 13 but not in Table 12): myalgia (4 events), back pain (3 events), arthralgia (2 events), fall (1 event), ligament sprain (1 event), patella fracture (1 event), contusion (1 event), hyperkeratosis (1 event), and rash (1 event).

Table 13. Adverse events occurring during treatment periods

	Treatment Period 1 (N = 29)			Treatment Period 2 (N = 30)		
	Number of patients	Number of events	%	Number of patients	Number of events	%
All	16	31	55.2	24	42	80.0
Gastroenteritis viral	0	0	0.0	1	1	3.3
Genital herpes	1	1	3.4	0	0	0.0
Influenza	0	0	0.0	1	1	3.3
Nasopharyngitis	7	7	24.1	3	3	10.0
Pneumonia	0	0	0.0	2	2	6.7
Tinea pedis	1	1	3.4	0	0	0.0
Respiratory tract infection	0	0	0.0	1	1	3.3
Insomnia	0	0	0.0	1	1	3.3
Hypoaesthesia	1	2	3.4	1	1	3.3
Supraventricular extrasystoles	1	1	3.4	0	0	0.0
Hypertension	1	1	3.4	0	0	0.0
Laryngeal oedema	0	0	0.0	1	1	3.3
Upper respiratory tract inflammation	0	0	0.0	1	1	3.3
Abdominal pain upper	0	0	0.0	1	1	3.3
Constipation	1	1	3.4	0	0	0.0
Dental caries	1	1	3.4	0	0	0.0
Gastritis	0	0	0.0	1	1	3.3
Toothache	0	0	0.0	2	2	6.7

Dermatitis contact	1	1	3.4	4	4	13.3
Erythema	0	0	0.0	1	1	3.3
Seborrhoeic dermatitis	1	1	3.4	0	0	0.0
Skin exfoliation	0	0	0.0	1	1	3.3
Arthralgia	3	3	10.3	0	0	0.0
Back pain	2	2	6.9	2	2	6.7
Musculoskeletal pain	0	0	0.0	1	1	3.3
Myalgia	1	1	3.4	5	5	16.7
Neck pain	1	1	3.4	1	1	3.3
Osteoarthritis	0	0	0.0	1	1	3.3
Osteoporosis	1	1	3.4	0	0	0.0
Pain in extremity	0	0	0.0	1	1	3.3
Developmental hip dysplasia	1	1	3.4	0	0	0.0
Fatigue	0	0	0.0	1	1	3.3
Pain	1	2	3.4	1	1	3.3
Fall	2	2	6.9	1	1	3.3
Excoriation	0	0	0.0	2	2	6.7
Contusion	1	1	3.4	4	4	13.3
Total	29*	31	—	42*	42	—

* These values are the sum of the number of patients in each event and thus do not correspond to the total number of patients.

6.A.(3).2) Death

A death was reported (Patient [redacted]). The patient was treated in Treatment Periods 1 and 2 and died of stroke approximately a month after the completion of follow-up period. Any causal relationship between the death and the HAL was ruled out, because the death occurred approximately 7 weeks after the last use of HAL, approximately 4 weeks after the last walk test.

6.A.(3).3) Serious adverse events

A total of 5 serious adverse events (resulting in death, requiring hospitalization or prolongation of hospitalization, resulting in persistent or significant disability or incapacity, being a congenital anomaly or birth defect, or other medically important condition) were reported in 4 patients including the death mentioned earlier, but a causal relationship with HAL therapy was ruled out for all these events (see Table 14).

Table 14. Serious adverse events

Event	Summary
Cerebral infarction (Patient [redacted])	See "6.A.(3).2) Death"
Right patella fracture (Patient [redacted])	After completing Treatment Periods 1 and 2, the patient fell from an electric lift chair at home, having forgotten to lock the safety catch before standing up. Having his knees buckled, the patient fell knee-first. Approximately a month later, the patient was discharged from the hospital with the fracture improving.
Pneumonia (Patient [redacted])	The patient completed Treatment Period 1. During Treatment Period 2, the patient experienced pneumonia and recovered approximately 10 days later.
Pneumonia and laryngeal oedema (Patient [redacted])	During Treatment Period 2, the patient experienced pneumonia secondary to influenza. A tracheostomy was performed due to laryngeal oedema and excessive sputum production. Approximately a month later, the patient recovered, being transferred from ICU to a general ward.

6.A.(3).4) Adverse events for which a causal relationship to HAL could not be ruled out

A causal relationship to HAL could not be ruled out for 6 adverse events in 4 of 15 patients (26.7%) in Group A and 13 events in 10 of 15 patients (66.7%) in Group B (in total, 19 events in 14 of 30 patients [46.7%]) (see Table 15). All the events were considered mild (i.e., not affecting normal daily activities).

Table 15. Adverse events for which a causal relationship to HAL could not be ruled out

	Group A (N = 15)			Group B (N = 15)		
	Number of patients	Number of events	%	Number of patients	Number of events	%
All	4	6	26.7	10	13	66.7
Dermatitis contact	1	1	6.7	2	2	13.3
Erythema	0	0	0.0	1	1	6.7
Skin exfoliation	0	0	0.0	1	1	6.7
Arthralgia	0	0	0.0	1	1	6.7
Back pain	1	1	6.7	1	1	6.7
Myalgia	1	1	6.7	3	3	20.0
Osteoarthritis	0	0	0.0	1	1	6.7
Pain in extremity	1	1	6.7	0	0	0.0
Pain	0	0	0.0	1	1	6.7
Fall	1	1	6.7	0	0	0.0
Excoriation	0	0	0.0	2	2	13.3
Contusion	1	1	6.7	0	0	0.0
Total	6*	6	—	13*	13	—

* The values are the sum of the number of subjects in each event and thus do not correspond to the total number of patients.

A causal relationship to HAL could not be ruled out for 2 events occurring in 2 of 29 patients (6.9%) during Treatment Period 1 (a hoist) and 15 events occurring in 12 of 30 patients (40.0%) during Treatment Period 2 (see Table 16). Myalgia, pain, and skin disorder tended to occur more frequently in Treatment Period 2. The causality of adverse events occurring in Treatment Period 1 was also evaluated in association with HAL (not with the hoist). In off-treatment periods, 2 events for which a causal relationship to HAL could not be ruled out occurred: myalgia (1 event) and fall (1 event).

Table 16. Adverse events, occurring in treatment periods, for which a causal relationship to HAL could not be ruled out

	Treatment Period 1 (N = 29)			Treatment Period 2 (N = 30)		
	Number of patients	Number of events	%	Number of patients	Number of events	%
All	2	2	6.9	12	15	40.0
Dermatitis contact	1	1	3.4	2	2	6.7
Erythema	0	0	0.0	1	1	3.3
Skin exfoliation	0	0	0.0	1	1	3.3
Arthralgia	1	1	3.4	0	0	0.0
Back pain	0	0	0.0	2	2	6.7
Myalgia	0	0	0.0	3	3	10.0

Osteoarthritis	0	0	0.0	1	1	3.3
Pain in extremity	0	0	0.0	1	1	3.3
Pain	0	0	0.0	1	1	3.3
Excoriation	0	0	0.0	2	2	6.7
Contusion	0	0	0.0	1	1	3.3
Total	2*	2	—	15*	15	—

* The values are the sum of the number of patients in each event and thus do not correspond to the total number of patients.

6.A.(3).5) Malfunctions

A total of 22 cases of malfunctions were reported, but there was no adverse event associated with the malfunctions: The shutdown of HAL due to a defect in the back module or controller in 1 patient (1 case); 1 patient could not use HAL because of a defect in the back module or controller (1 case); abnormal noise at joints in 1 patient (1 case); abnormal stop of the base component and control panel in 1 patient (1 case); tight screw at a lower cuff in 1 patient (1 case); the shutdown of HAL due to an error in 1 patient (4 cases); a slide plate falling off in 1 patient (1 case); battery depletion with no alarm in 1 patient (1 case); a broken banding band in 1 patient (1 case); slippage of the hip frame in 1 patient (7 cases); the part to open and close the cuff falling off in 1 patient (1 case); loosening of the lock lever to support the thigh in 1 patient (1 case); and the screen display going blank in 1 patient (1 case).

6.A.(3).6) Operation monitoring data (error history)

A total of 202 errors were reported in the operation monitoring data (see Table 17). Among them, 170 errors were caused by abnormal BES.

Table 17. Number of patients who experienced an error and number of errors occurred (N = 30)

Error	Number of patients	Number of errors	%
Back module or controller error	2	4	6.7
Power unit error (right hip)	2	2	6.7
Power unit error (left hip)	2	2	6.7
Power unit error (right knee)	4	8	13.3
Power unit error (left knee)	1	1	3.3
Sensor shoe connection error (right)	5	6	16.7
Sensor shoe connection error (left)	4	5	13.3
Sensor shoe failure (right)	1	3	3.3
BES error (right hip)	12	26	40.0
BES error (left hip)	12	25	40.0
BES error (right knee)	17	74	56.7
BES error (left knee)	13	45	43.3
Run out of battery	1	1	3.3

6.A.(3).7) Others

The blood pressure and pulse rate did not change markedly before and after the treatment and did not differ significantly between the treatment periods. Moderate hypertension (that would affect some daily activities) occurred in 1 patient, but a causal relationship to HAL was ruled out for the event. The patient was treated with medication and recovered. Abnormal ECG findings were observed in 14 patients during the clinical trial, but none of the findings was considered to pose any problem. The frequency of "abnormality" before or after treatment did not differ between the treatment periods.

6.A.(4) Test articles

The test article used in the clinical trial is different from the product under application, because the test article was modified to correct the malfunctions and for other reasons (see Table 18). The applicant reported that these modifications did not affect the results of the clinical trial and that the latest version of HAL passed the safety test.

Table 18. Modifications to the test article for the clinical trial

Modified area	Details
Substrates	The accuracy of signaling related to inter-substrate communication was increased to reduce communication errors caused by noise during operation.
Substrates	The shape of BES cable connectors in the base component was modified so that the connectors in knee parts have a different shape from those in hip parts, to ensure foolproof assembly of HAL.
Substrates	Some electronic parts were replaced with new ones because of the discontinuation of production and for compliance within electromagnetic compatibility (EMC) regulations.
Software	Software was upgraded to accommodate the upgraded substrates.
Software	Bug fixing was performed. The fixed bug has not reappeared.
Software	Software was upgraded to add the remote support function that allows maintenance data to be uploaded to the server. This modification does not affect normal operation of HAL.
Software	Software was upgraded to support the new display system that allows the external monitor to display the operating state of HAL. This modification does not affect the normal operation of HAL.
Ankle	The finely adjusted ends and improved processing accuracy reduced clearance between parts and noise.
Cuff	A standardized method for screw hole processing reduced variations due to different processing method and prevented the deformation of holes.
Cuff	The fixing structure for the shafts that open and close the cuffs was adjusted to prevent the shafts from misalignment.
Back module	The slide plate for battery pack mounting was integrally molded to prevent it from falling off.
Back module	The position of the holes to pass the banding band securing the back module was adjusted to prevent the band from being broken.
Hip frame	The hip width adjustment mechanism was modified for better fitting.

Hip frame	The hip frame was redesigned to reduce the loosening of screws.
Controller	The cable fixing structure of the controller case was redesigned to increase resistance to tension.
Controller	The substrate and controller case were modified in response to the discontinuation of the production of the liquid crystal panel.
Controller	The controller cable was extended while an additional cable clip was provided on the case, to respond to 2 different types of requests by users: a longer cable and a shorter cable.
Leg frames	Wear-resistance of wear-prone parts (bearings, and abduction and adduction adjustment parts) was improved because they are likely to wear in the long-term use.
Leg frames	The shape of the leg frames was modified to alleviate the problem that aligned lower leg frames become out of alignment during use.
Belts	Belt strength was enhanced and the fastening method was modified to better secure the wearer to HAL.
Sensor shoes	Sensor shoes were modified to accommodate the hot-pluggable connectors connecting to the body.
Battery charger	Full charge criteria were modified by slightly adjusting the voltage level indicating the completion of full charge, to allow the battery pack to fully exert its autonomous cell balancing ability.

6.B Outline of the review by PMDA

The review by PMDA focused on the following points based on comments from the Expert Discussion.

Of note, PMDA had no choice but to evaluate HAL in an experimental manner, because (1) HAL has a novel structure and mechanism; (2) sufficient clinical trial data could not be collected because HAL is intended for patients with rare diseases; and (3) there is no standard evaluation method. The efficacy and safety of HAL thus cannot be fully evaluated based solely on the available clinical trial data. Nevertheless, PMDA has decided to conduct an approval review of HAL based on a comprehensive evaluation of risk-to-benefit balance. The risk-to-benefit balance evaluation is to be performed in light of clinical benefits for rare diseases, while making clear what have been evaluated and what have not been evaluated. PMDA performed the review on the assumption that the treatment program will be optimized according to data including those from a post-approval use-results survey.

6.B.(1) Appropriateness of evaluating the target patients collectively

In the clinical trial, the efficacy of HAL was evaluated in patients with various diseases. A total of 8 diseases were subject to the evaluation, but analyses by disease were not performed. The trial enrolled no patient with congenital myopathy, 1 patient with inclusion body myositis, 1 patient with amyotrophic lateral sclerosis, and only 7 patients with muscular dystrophy, the most frequent underlying disease among the enrolled patients (Table 8). PMDA, given the difficulty enrolling a sufficient number of patients due to the rareness of target disease, examined whether it was appropriate to evaluate the 8 diseases collectively from the following perspectives:

1) A common mechanism of therapeutic effect
2) The progression of gait impairment

3) Measurement of BES used in CVC mode (the main mode of HAL)

6.B.(1).1) A common mechanism of effect

PMDA asked the applicant to explain the applicability of HAL to these 8 diseases in terms of the causes of impaired gait function and the characteristics and similarity of symptoms.

The applicant's explanation:

The target diseases are primarily of impaired lower motor neurons and muscle fibers that constitute motor units. In these patients, gait function is gradually deteriorated while muscle atrophy and weakness slowly progress. The absence of significant leg spasm or cerebellar or extrapyramidal symptoms is also common to these diseases. The importance of existing therapies for these diseases is mentioned in the Manual for the Treatment of Spinal Muscular Atrophy,[2] the Practice Guidelines for the Treatment of Amyotrophic Lateral Sclerosis,[3] the Manual for the Treatment of Charcot-Marie-Tooth Disease,[4] and the Practice Guidelines for Duchenne Muscular Dystrophy.[5] HAL generates assist torque using BES representing motor unit potentials to assist the lower limb motion of patients with impaired gait function due to the diseases. HAL is expected to have more pronounced gait improvement effect than the existing therapies.

PMDA's view:

The 8 diseases, except for amyotrophic lateral sclerosis, have a common feature that they do not cause upper motor neuron impairment but result in deteriorated walking ability associated with muscular weakness due to impaired lower motor neurons or muscles. The diseases are also assumed to respond to the existing therapies by the same mechanisms: muscle strength recovery from disuse syndrome and relearning of gait motion. The existing therapies have been shown to be important for impaired walking ability due to these diseases, as mentioned in the current guidelines; HAL therapy is also expected to be effective in patients with the diseases. From this viewpoint, PMDA considers it possible to evaluate the efficacy of HAL in gait function based on the combined data of the 8 diseases. HAL is not designed to act on the causes of the diseases but is expected to provide better effect on the recovery of gait function in patients with the diseases than conventional therapies, by providing BES-based assistance during repeated gait training.

Amyotrophic lateral sclerosis generally involves upper motor neuron impairment (muscle spasms, etc.) as well. Patients with amyotrophic lateral sclerosis were enrolled in the trial only if they had slowly progressing symptoms of lower limbs, and those with upper motor neuron-dominant symptoms were excluded. Therefore, PMDA concluded that the "Important Precautions" section of the proposed label should note that the efficacy and safety of HAL have not been demonstrated in patients with upper motor neuron-dominant amyotrophic lateral sclerosis. The applicant agreed.

6.B.(1).2) Progression of gait impairment

The 8 diseases progress through various stages, and in some stages, HAL may be ineffective or even increase risks. Given this situation, PMDA asked the applicant whether HAL therapy should be limited to patients in disease stages, for example, that correspond to the gait impairment criteria used in the clinical trial (i.e., unable to walk 10 meters independently but able to walk ≥10 meters with human assistance or a walker, etc.)

The applicant's response:
The clinical trial enrolled patients who had difficulty walking 10 meters independently but were able to walk ≥10 meters by holding on to something or with a stick, etc. The efficacy of HAL was evaluated in these patients with an appropriate degree of impaired gait function. HAL may be effective in patients in earlier or later disease stages as well, but no clinical trial data on such patients are available.

PMDA's view:
No data are available for patients having less or more impaired gait function than the patients enrolled in the clinical trial did. Therefore the "Intended use or efficacy" section of the label should clearly state that HAL is indicated for patients requiring assistive devices or human assistance while walking, as stated in ["6.B.(4) Intended Use or Efficacy"]. Further, the "Precautions for intended use or efficacy" section of the label should state that the efficacy and safety data originated only from patients who had difficulty walking 10 meters independently but were able to walk ≥10 meters by holding something or with assistance of a stick, etc. PMDA requested the applicant to modify the descriptions in these sections as such. The applicant agreed. PMDA considers that patients with any of the 8 diseases are expected to respond to HAL therapy in a similar manner as long as their gait impairment are similar in severity, and that the efficacy of HAL for the 8 diseases can be evaluated collectively.

6.B.(1).3) Measurement of BES used in CVC mode (the main mode of HAL)
PMDA asked the applicant whether HAL has adequate capacity to measure BES in target patients (i.e., abilities to measure signals weaker than those in healthy persons, to measure BES in patients with either neurogenic or myogenic diseases, and to properly function in the presence of involuntary active potentials commonly observed in amyotrophic lateral sclerosis or myotonic discharges observed in myotonic dystrophy).

The applicant's response:
Among the target diseases of HAL, myogenic diseases (distal myopathy, inclusion body myositis, congenital myopathy, and muscular dystrophy) are characterized by smaller motor unit potentials. Neurogenic diseases (spinal muscular atrophy, spinal and bulbar muscular atrophy, amyotrophic lateral sclerosis, Charcot-Marie-Tooth disease) may exhibit sparse motor unit potentials. Action potentials in patients with the neurogenic diseases become smaller when measured by surface electrodes or if they have advanced atrophy. BES in patients with target diseases vary in amplitudes and densities. HAL is capable of detecting BES (which represent motor unit potential) in different amplitudes and densities by adjusting the amplitudes and densities with an appropriate filter and sensitivity levels selected. In the

run-in period of the clinical trial, HAL successfully detected BES and was shown to be operable in CVC mode in all patients (31 patients) with either myogenic or neurogenic disease who met the inclusion criteria. BES generated by involuntary muscle contraction, etc. are converted into assist torque of reduced magnitude by the torque tuner and torque limit so that the torque is not perceived as a malfunction. The filter also has an optional function to eliminate BES generated by involuntary muscle contraction. In the clinical trial, HAL detected BES generated by voluntary contraction in 2 patients with myotonic dystrophy so that they were able to receive HAL therapy.

PMDA's view:
Based on the applicant's response, PMDA considers that measuring BES in patients with any of the 8 diseases are basically feasible. Patients who meet the inclusion criteria mentioned in 6.B.(1).2) (unable to walk 10 meters independently but able to walk ≥10 m with human assistance or a walker, etc.) should have muscles that retain their functions and are able to produce reasonable active potentials. This also supports the feasibility of BES measurement.

From the viewpoints mentioned in 6.B.(1).1) to 6.B.(1).3), PMDA considers that the improvement of gait function following HAL therapy in patients with any of the 8 diseases can be evaluated collectively. However, as the clinical trial provided extremely limited data on each disease, additional data should be collected after the approval of HAL, to ensure that there is no trend toward inconsistency in the efficacy of HAL among the diseases, as stated later in "7. Data on planning of post-marketing surveillance, etc. specified in Article 2-1 of the Ministerial Ordinance on Good Postmarketing Study Practice for Medical Devices."

Muscular dystrophy is one of the target diseases of HAL. No patients with Duchenne muscular dystrophy were enrolled in the clinical trial, but HAL is expected to be effective in patients with the disease from the viewpoint of 6.B.(1).1) to 6.B.(1).3) above. Duchenne muscular dystrophy is known to be more common in children. Some children may meet the criteria for the degree of gait impairment and the physical requirements for wearing HAL (patients weighing 40 to 100 kg and 150 to 190 cm tall) as mentioned in 6.B.(1).2). Unlike the efficacy in patients in the clinical trial who were ≥18 years old (an inclusion criterion), the efficacy of HAL in children is assumed to vary with growth, scoliosis, equinus foot, or contracture, and heart failure associated with aggressive gait training may become evident in children. These effects remain unknown from the clinical trial data. Given this, PMDA asked the applicant's view on whether HAL can be used in children and, if so, what precautions are needed.

The applicant's explanation:
The required height of ≥150 cm for the use of HAL corresponds to the average height of 12-year-old boys and girls. The body weight of 40 kg corresponds to the average weight of boys and girls 11.5 years old. The clinical trial did not provide data for children <18 years old, but HAL is expected to have efficacy even in children <18 years old who meet the inclusion criteria other than the age. In children with Duchenne muscular dystrophy, however, ankle contracture, spinal deformation, respiratory failure

symptoms, and heart failure symptoms worsen with age. These symptoms must be carefully monitored and controlled during HAL therapy. The clinical trial enrolled patients with slowly progressive nerve and muscular diseases who had once gained walking ability before it was impaired. However, there has been no clinical trial to evaluate the development of walking ability after HAL therapy in patients with spinal muscular atrophy type 2, congenital myotonic dystrophy, or congenital or childhood-onset myopathy who have never been able to walk independently. Therefore, the "Use for pregnant, parturient and nursing women, and children" section of the label will highlight (1) the lack of data on children, (2) need for close attention to disease-specific complications, and (3) the lack of clinical trial evaluating the development of walking ability in patients who have never been able to walk independently. The guidance for the proper use of HAL and other information materials will also advise healthcare professionals to pay attention to cardiopulmonary insufficiency, ankle contracture, spinal deformation, and other symptoms that are assumed to manifest in pediatric myotonic dystrophy.

PMDA's view:
The current lack of data on HAL therapy in children does not necessarily mean that the device should be contraindicated even for children with a body size appropriate for the device. The applicant's intention to provide precautionary advice is thus appropriate. However, data on unknown adverse events (including those related to cardiopulmonary insufficiency) should be collected through the use-results survey. When any new trend becomes evident, it should be communicated to healthcare professionals or any other appropriate action should be taken for the trend.

6.B.(2) Efficacy evaluation

PMDA reviewed the clinical trial results on the efficacy of HAL from the following viewpoints:

1) Appropriateness of endpoints
2) Results of the primary endpoint
3) Results of the secondary endpoints

6.B.(2).1) Appropriateness of endpoints

The applicant's explanation on the primary and secondary endpoints of the clinical trial:
The 2-minute walk test, the primary endpoint, assesses walking endurance (resistance to fatigue). A 6-minute walk test also assesses walking endurance but was considered unsuitable for the primary endpoint, because HAL is indicated for patients with nerve and muscular diseases who have difficulty walking 10 meters independently and therefore would not be able to walk for 6 minutes. Furthermore, some reports have shown a correlation between the 2-minute walk test and the 6-minute walk test.[6,7,8]

The following are the details of secondary endpoints: (a) A 10-meter walk test does not evaluate endurance but is useful for gait function analysis. (b) Gait assessment by patients was intended to assess gait-related symptoms reported by patients and the degree of satisfaction of patients; visual analog scales were used to assess the level of fatigue, lightness of tread, the feeling of stability, sense of security, and pleasantness during walking. (c) Gait assessment by healthcare professionals was intended to assess

changes before and after HAL therapy in gait parameters in the stance and swing phases defined in the Rivermead Visual Gait Assessment.[9] Specifically, the central review committee on visual gait assessment evaluated the gait parameters recorded on video during the 2-minute walk test and the 10-meter walk test. (d) Manual muscle test, a useful tool to assess muscle strength of patients with nerve and muscular diseases, was performed to assess the flexion and extension of hip, knee, and ankle joints, which are directly involved in gait. (e) ADL assessment (Barthel index) consisted of 10 assessment items representing daily activities to evaluate the degree of independence in daily life. (f) Assessment by operators focused on usability when wearing HAL and walking with HAL and time to wear (excluding time to attach the electrodes), which are considered critical in the clinical use of HAL.

PMDA's view:
Because HAL is expected to improve the wearer's gait function, gait function should be evaluated to assess the efficacy of HAL. Walking ability, an index mentioned in the Guidance on the Evaluation of Devices for Physical Function Recovery,[1] is thus an appropriate endpoint. The guidance recommends a 6-minute walk test. The use of a 2-minute walk test, however, is reasonable in the clinical trial of HAL because of the patients' difficulty walking for a long time due to their underlying diseases. In the clinical trial of HAL, the primary endpoint was a 2-minute walk test, and the secondary endpoints were 10-meter walk test, ADL assessment (Barthel index), gait assessment by patients, gait assessment by healthcare professionals, manual muscle test, and the operator's assessments of usability and time to wear HAL. Despite the lack of a QOL-related endpoint, the selected endpoints are generally sufficient to evaluate gait function.

6.B.(2).2) Results of the primary endpoint
PMDA reviewed the results of primary efficacy endpoint from the following viewpoints:
(A) Appropriateness of crossover evaluation
(B) Effects of patient characteristics and usage of the device, etc.
(C) Difference in the results between Groups A and B

6.B.(2).2). (A) Appropriateness of crossover evaluation
According to the applicant, the clinical trial was conducted in a crossover fashion because of a small number of eligible patients with the rare target diseases.

According to the submitted clinical trial data, the mean walk distance at baseline, immediately after First Treatment Phase, and immediately before Second Treatment Phase were [redacted] meters, [redacted] meters, and [redacted] meters, respectively, in Group A, and [redacted] meters, [redacted] meters, and [redacted] meters, respectively, in Group B [see Table 9]. PMDA assumes that, at the beginning of Second Treatment Phase, in both Groups A and B, the effects of the first intervention was not washed out. In other words, the walk distance after First Treatment Phase did not return to baseline. (The patients maintained the improved gait function achieved through the first intervention). Conducting a crossover trial was inevitable considering a limited number of patients with the target diseases and relatively stable symptoms of the

patients enrolled. However, it is undeniable that the improvement in gait function achieved in First Treatment Phase remained during Second Treatment Phase. PMDA thus compared the results of interventions in First Treatment Phase, namely Treatment Period 1 (a hoist) of Group A and Treatment Period 2 (HAL and a hoist) of Group B, to avoid influence of prior intervention. In Group A, the mean improvement rate after Treatment Period 1 was 9.30%; in Group B, the mean improvement rate after Treatment Period 2 was 24.87% (*P* = [redacted], t-test). This shows significant additional effect of HAL. In Second Treatment Phase, on the other hand, the mean improvement rate after Treatment Period 1 (a hoist) was 5.44% in Group B; and the mean improvement rate after Treatment Period 2 (HAL and a hoist) was 9.99% in Group A. In Group B, the effect of intervention (the improvement rate) after Treatment Period 1 (Second Treatment Phase) tended to be lower than that after Treatment Period 2 (First Treatment Phase); the improvement rate after Second Treatment Phase is assumed to have been influenced by the residual effects of intervention (i.e., improved gait function) in First Treatment Phase. PMDA further asked the applicant to discuss not only the mean walk distance but also changes in walk distance in individual patients and trends in improvement.

The applicant's response:
Figure 7 shows changes in 2-minute walk test measurements of each patient: 13 patients in Group A and 11 patients in Group B. In total, 76.9% of patients in Group A and 100% of patients in Group B showed improvement after First Treatment Phase (Treatment Period 1 [a hoist] in Group A; Treatment Period 2 [HAL and a hoist] in Group B). The improvement rates after Treatment Period 2 in 72.7% of patients in Group B were higher than the mean improvement rate after Treatment Period 1 in Group A. When First and Second Treatment Phases are combined, 70.8% of patients showed improvement in 2-minute walk test after Treatment Period 1 and 75.0% of patients after Treatment Period 2.

PMDA's conclusion:
The overall trend showed that HAL was superior in efficacy to a hoist alone, in light of the comparison between Groups A and B after First Treatment Phase. Influential factors and other factors in each patient are described in "6.B.(2).2).(B) Effects of patient characteristics and usage, etc. of HAL."

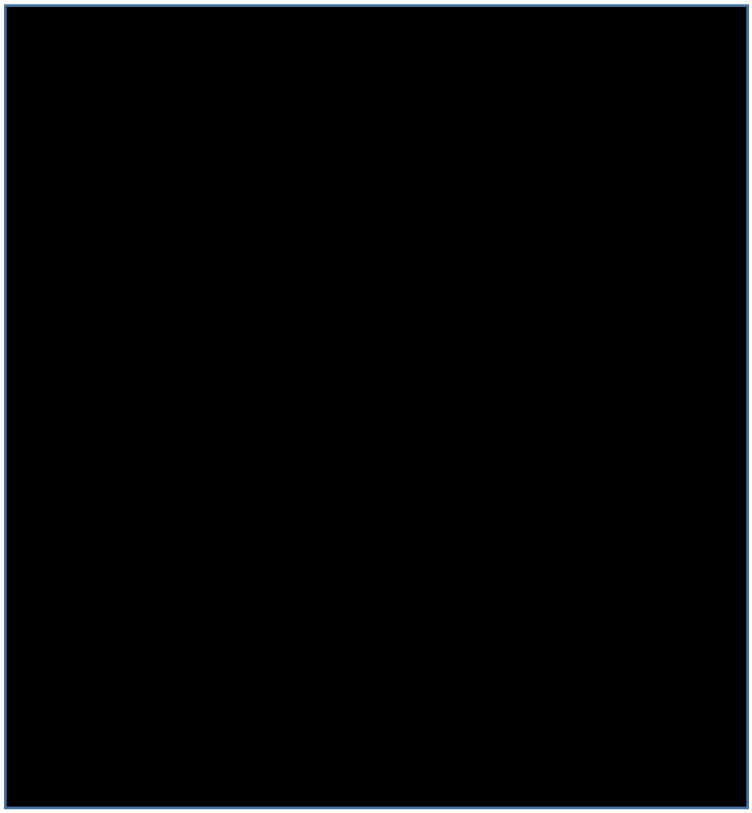


Figure 7. Changes in primary endpoint (2-minute walk test) in each patient
Horizontal axis, number of tests (visits); vertical axis, distance (meter)

- - - - Treatment Period 1 (a hoist)

——— Treatment Period 2 (HAL and a hoist)

PMDA asked the applicant to explain the rationale for defining the baseline as "2-minute walk distance at Visit 3 (third visit) or at Visit 4 (fourth visit), whichever is longer."

The applicant's response:

The baseline was initially 2-minute walk distance at Visit 4 but was changed to "2-minute walk distance at Visit 3 or Visit 4, whichever is longer" after data were collected. This was because, as explained in the minute of a case review meeting, there was no intervention between Visits 3 and 4, and thus the levels of gait function of subjects were considered similar at both visits. On the other hand, in 9 of 30 subjects, the 2-minute walk distance at Visit 4 was shorter than at Visit 3. In order to evaluate the maximal gait function of subjects, the longer distance was selected as baseline. This change was made in the appendix attached to the statistical analysis plan, with the provision that any radical change in 2-minute walk distance at the Visit 4 as compared with Visit 3 should be reviewed in a case review meeting (a standard for handling of clinical cases and data). Treatment efficacy in the crossover treatment and in First Treatment Phase was estimated for comparison among the following baselines (2-minute walk distance): (a) Visit 4, (b) Visit 3 or Visit 4, whichever is longer, (c) the mean of Visit 3 and Visit 4, or (d) Visit 3 [see Table 19]. The results of estimation showed a similar trend among these different baseline values, demonstrating consistency with the primary analysis results.

Table 19. Treatment efficacy (mean ± SD) by different baselines (2-minute walk distance): (a) Visit 4, (b) Visit 3 or Visit 4, whichever is longer, (c) mean of Visit 3 and Visit 4, or (d) Visit 3

Baseline	Crossover		First Treatment Phase (Treatment Period 1 in Group A, Treatment Period 2 in Group B)	
	Treatment efficacy (Mean)	P-value (two-sided)	Treatment efficacy (Mean)	P-value (two-sided)
(a)	[redacted] ± [redacted]%	*P* = [redacted]	[redacted] ± [redacted]%	*P* = [redacted]
(b)	-10.07 ± [redacted]%	*P* = 0.037	[redacted] ± [redacted]%	*P* = [redacted]
(c)	[redacted] ± [redacted]%	*P* = [redacted]	[redacted] ± [redacted]%	*P* = [redacted]
(d)	[redacted] ± [redacted]%	*P* = [redacted]	[redacted] ± [redacted]%	*P* = [redacted]

PMDA's view:

The change of baseline during the clinical trial was somewhat inappropriate. Nevertheless, it would be difficult to identify the most appropriate baseline from various candidate baselines. The submitted analysis results based on the baseline (b) was not inappropriate. All candidate baselines were shown to produce significant difference in treatment efficacy between "HAL and a hoist" and "a hoist" or a trend toward improvement after HAL therapy. HAL targets rare diseases with no curable treatment available, and the number of patients with the diseases is limited. PMDA therefore decided to evaluate the efficacy of HAL comprehensively by reviewing the submitted results based on the baseline (b) and the details of individual clinical cases.

6.B.(2).2).(B) Effects of patient characteristics and usage, etc. of HAL.

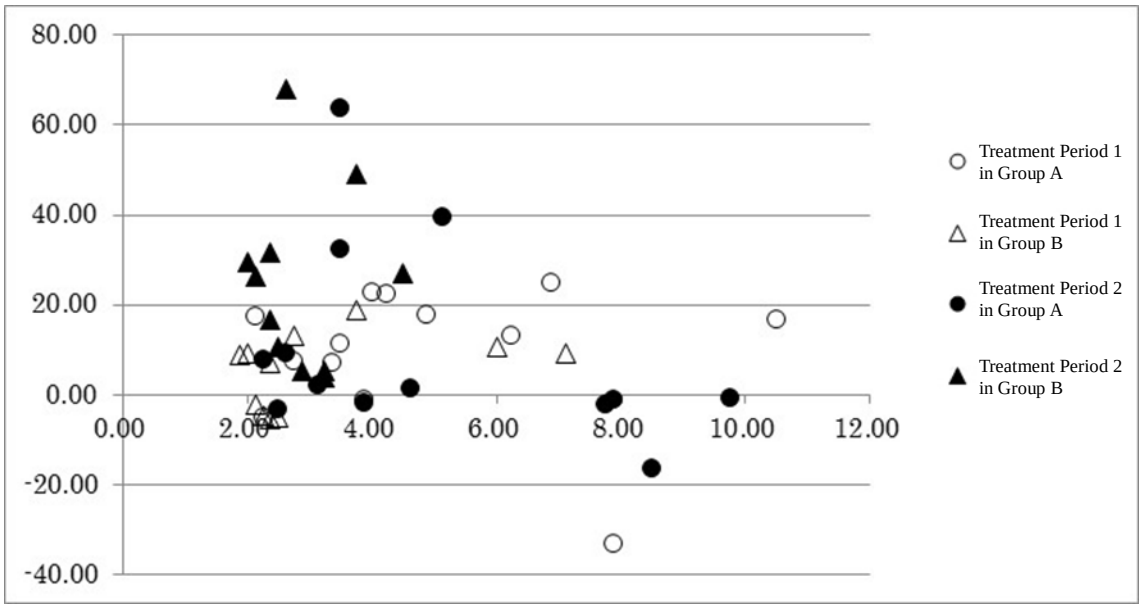
PMDA asked the applicant to explain effects of biases in patient characteristics and usage of HAL during Treatment Periods 1 and 2.

The applicant's explanation:

Figure 8 and Table 20 show the correlation between influential factors and treatment efficacy (improvement rates) in Treatment Periods 1 and 2.

(a) Age at enrollment (horizontal axis, years of age) and improvement rate (longitudinal axis, %)

(b) Baseline 2-minute walk distance (horizontal axis, meter)
and improvement rate (longitudinal axis, %)



(c) Treatment interval (horizontal axis, days)
and improvement rate (longitudinal axis, %)

Figure 8. Influential factors and improvement rates

○ Treatment Period 1 (a hoist) in Group A; ● Treatment Period 2 (HAL and a hoist) in Group A

△ Treatment Period 1(a hoist) in Group B; ▲ Treatment Period 2 (HAL and a hoist) in Group B

Table 20. Mean improvement rate by influential factor

(a) Disease

Group	Influential factors	Treatment Period 1 (%)	Treatment Period 2 (%)
Group A	Spinal muscular atrophy (n = [redacted])	[redacted]	[redacted]
	Bulbospinal muscular atrophy (n = [redacted])	[redacted]	[redacted]
	Amyotrophic lateral sclerosis (n = [redacted])	[redacted]	[redacted]
	Charcot-Marie-Tooth (CMT) disease (n = [redacted])	[redacted]	[redacted]
	Distal myopathy with rimmed vacuoles (DMRV) (n = [redacted])	[redacted]	[redacted]
	Miyoshi myopathy (n = [redacted])	[redacted]	[redacted]
	Inclusion body myositis (n = [redacted])	[redacted]	[redacted]
	Muscular dystrophy (n = [redacted])	[redacted]	[redacted]
Group B	Spinal muscular atrophy (n = [redacted])	[redacted]	[redacted]
	Bulbospinal muscular atrophy (n = [redacted])	[redacted]	[redacted]
	Amyotrophic lateral sclerosis (n = [redacted])	[redacted]	[redacted]
	CMT disease (n = [redacted])	[redacted]	[redacted]
	DMRV (n = [redacted])	[redacted]	[redacted]
	Miyoshi myopathy (n = [redacted])	[redacted]	[redacted]
	Inclusion body myositis (n = [redacted])	[redacted]	[redacted]
	Muscular dystrophy (n = [redacted])	[redacted]	[redacted]
Total	Spinal muscular atrophy (n = [redacted])	[redacted]	[redacted]
	Bulbospinal muscular atrophy (n = [redacted])	[redacted]	[redacted]
	Amyotrophic lateral sclerosis (n = [redacted])	[redacted]	[redacted]
	CMT disease (n = [redacted])	[redacted]	[redacted]
	DMRV (n = [redacted])	[redacted]	[redacted]
	Miyoshi myopathy (n = [redacted])	[redacted]	[redacted]
	Inclusion body myositis (n = [redacted])	[redacted]	[redacted]
	Muscular dystrophy (n = [redacted])	[redacted]	[redacted]

(b) Origin (myogenic or neurogenic)

Group	Influential factors	Treatment Period 1 (%)	Treatment Period 2 (%)
Group A	Myogenic (n = [redacted])	[redacted]	[redacted]
	Neurogenic (n = [redacted])	[redacted]	[redacted]
Group B	Myogenic (n = [redacted])	[redacted]	[redacted]
	Neurogenic (n = [redacted])	[redacted]	[redacted]
Total	Myogenic (n = [redacted])	[redacted]	[redacted]
	Neurogenic (n = [redacted])	[redacted]	[redacted]

(c) Prior rehabilitation (rehabilitation continued for ≥2 months before Visit 1)

Group	Influential factors	Treatment Period 1 (%)	Treatment Period 2 (%)
Group A	Not performed (n =)		
	Performed (n =)		
Group B	Not performed (n =)		
	Performed (n =)		
Total	Not performed (n =)		
	Performed (n =)		

(d) Inpatients/outpatients

Group	Influential factors	Treatment Period 1 (%)	Treatment Period 2 (%)
Group A	Inpatients (n =)		
	Outpatients (n =)		
Group B	Inpatients (n =)		
	Outpatients (n =)		
Total	Inpatients (n =)		
	Outpatients (n =)		

(e) Concurrent rehabilitation (including lower limb motions)

Group	Influential factors	Treatment Period 1 (%)	Treatment Period 2 (%)
Group A	Not performed (n =)		
	Performed (n =)		
Group B	Not performed (n =)		
	Performed (n =)		
Total	Not performed (n =)		
	Performed (n =)		

(f) Malfunction

Group	Influential factors	Treatment Period 1 (%)	Treatment Period 2 (%)
Group A	Not occurred (n =)		
	Occurred (n =)		
Group B	Not occurred (n =)		
	Occurred (n =)		
Total	Not occurred (n =)		
	Occurred (n =)		

The improvement rates by disease are shown in Table 20 (a). Improvement rates after Treatment Period 2 (HAL and a hoist) were generally higher than those after Treatment Period 1 (a hoist). However, the number of enrolled patients was insufficient to characterize the influence of the individual diseases. The improvement rates may also be affected by treatment frequency (intervals) or inpatient/outpatient status of the patient, and therefore data should be collected further. When the target diseases are grouped into myogenic and neurogenic diseases [Table 20 (b)], both groups tended to show greater improvement after

Treatment Period 2 in Group B than after Treatment Period 1 in Group A. Patients with neurogenic disorders tended to show higher efficacy. (The mean additional effect of HAL on improvement rate was [redacted]% in the neurogenic group [n = 13] and [redacted]% in the myogenic group [n = 11].)

Figure 8 and Table 20 show that the improvement rates after Treatment Period 2 tended to be higher than those after Treatment Period 1, although the data on individual influential factors were obtained from a small number of patients. The same tendency was revealed by a comparison of the First Treatment Phase between Groups A and B (Treatment Period 1 in Group A vs. Treatment Period 2 in Group B).

Meanwhile, Figure 8 (c) shows a correlation between the treatment frequency (interval) and the improvement rates; the shorter the interval, the higher the improvement rate. Treatment intervals were shorter in inpatients and longer in outpatients. The mean treatment frequency in inpatients was [redacted] sessions weekly in Treatment Period 1 and [redacted] sessions weekly in Treatment Period 2. The mean treatment frequency in outpatients was [redacted] sessions weekly in both Treatment Periods 1 and 2. Table 20 (d) shows higher improvement rates in inpatients than in outpatients. Group B had more inpatients and more patients receiving treatment at short intervals than Group A. In inpatients and patients with shorter treatment intervals, improvement rates after Treatment Period 2 were higher than those after Treatment Period 1. It was difficult to determine whether the higher improvement rate in inpatients was attributable to shorter treatment intervals or to more flexible scheduling, better physical condition control, or easier fitting and precise setting adjustment of the device, than in outpatients. Nevertheless, this result indicates the importance of an appropriate treatment program to achieve the effect of HAL.

Patients undergoing prior rehabilitation showed lower treatment efficacy after Treatment Period 1, but did not show a trend toward a greater additional treatment effect of HAL after Treatment Period 2 [Table 20 (c)]. Patients in Group A who did not undergo concurrent rehabilitation showed lower improvement rate after Treatment Period 2 [Table 20 (e)], and 4 of these 5 patients were outpatients. In patients undergoing concurrent rehabilitation, overall improvement rates after Treatment Period 2 did not tend to be clearly higher than those after Treatment Period 1. Patients in Group A who experienced malfunction of HAL showed lower improvement rates after Treatment Period 2, but this trend was not seen in Group B or the combined group (i.e., Group A plus Group B) [Table 20 (f)].

PMDA's view:
In patients with shorter treatment intervals, improvement rates after Treatment Period 2 in Group B was higher than those after Treatment Period 1 in Group A, although a bias was seen in treatment frequency (intervals) in Groups A and B. Also in inpatients, improvement rates after Treatment Period 2 in Group B was higher than those after Treatment Period 1 in Group A, although there may have been a bias in admission rates. As stated in "6.B.(5) Treatment program and usage," HAL is expected to be highly effective if used according to an appropriate program based on knowledge obtained in the clinical trial. However, given the limited number of patients enrolled in the clinical trial, more knowledge about influential factors needs to be accumulated [see "7. Data on planning of post-marketing surveillance,

etc. specified in Article 2-1 of the Ministerial Ordinance on Good Postmarketing Study Practice for Medical Devices]. The effect of concurrent rehabilitation on the efficacy of HAL cannot be determined because of limited data available, but such effect was probably not strong enough to affect the efficacy evaluation of HAL.

6.B.(2).2).(C) Difference in treatment efficacy between Groups A and B

PMDA asked the applicant to discuss reasons for (1) higher improvement rate in Group B receiving HAL therapy in First Treatment Phase than in Group A and (2) lower improvement rate in Group A receiving HAL therapy in Second Treatment Phase.

The applicant's response:

Differences between Groups A and B are, as mentioned earlier, shorter treatment intervals and higher admission rates in Group B [Figure 8 (c) and Table 20 (d)]. The mean treatment interval was [redacted] days in Group A and [redacted] days in Group B. Most patients who had shorter treatment intervals were inpatients, while most patients who had longer treatment intervals were outpatients. The lower improvement rate after Treatment Period 2 (Second Treatment Phase) in Group A was probably due the higher proportion of outpatients who usually receive treatment at longer intervals. Group A underwent Treatment Period 2 after Treatment Period 1, and a long time passed since a behavioral check performed on HAL during the run-in period. No additional behavioral check test was planned before the start of Treatment Period 2, and this may have been another reason for inadequate treatment efficacy in Group A. Therefore, in order to increase efficacy in outpatients, fine tuning on a daily basis and an appropriate treatment program are necessary. The transition period between First and Second Treatment Phases was [redacted] days in Group A and [redacted] days in Group B, showing no significant difference.

PMDA's view:

The applicant's explanation is generally acceptable. An up to 16-week delay may occur in intervention with HAL according to the clinical trial protocol, but no major change is likely to occur in clinical conditions during the delay. In Group A, active treatment in Treatment Period 1 (a hoist) demonstrated a certain effect, and this effect remained throughout the transition period. This residual effect may have tended to reduce the potential margin of improvement, resulting in lower efficacy of Treatment Period 2. On the basis of the applicant's response presented in 6.B.(2).2). (B) and (C), PMDA considers that treatment intervals may affect treatment efficacy of HAL. PMDA asked the applicant to disseminate information regarding treatment intervals based on knowledge from the clinical trial. The applicant agreed to specify the recommended treatment interval in the label. PMDA considers that patients can obtain additional effects of HAL if the device is used properly.

Based on the discussions in 6.B.(2).2). (A), (B), and (C), PMDA considers that the primary endpoint analysis of HAL demonstrated its greater efficacy than the treatment with a hoist alone. As stated in "6.B.(1).1) A common mechanism of effect," HAL improved gait function more effectively, than conventional therapies, by assisting the wearer's gait motion according to BES in repetitive gait training.

At present, however, it is unclear whether the effect of HAL therapy is attributable to any novel mechanism not possessed by the conventional therapies. The additional effect of HAL therapy is assumed to be approximately 10% throughout the entire treatment period and approximately 16% based on a comparison between both First Treatment Phases (Treatment Period 1 in Group A vs. Treatment Period 2 in Group B). The improvement in gait function was evaluated by the ability to walk using a hoist. (Patients used a hoist in the 2-minute walk test.) This precludes adequate verification of benefits of HAL to patients' daily lives. Nevertheless, the additional benefit by HAL has clinical significance in patients with gradually deteriorating gait function. The label should contain the clinical trial data, restrictions on use, and the frequency of adverse events, to facilitate the proper use of HAL with consideration given to possible risks and benefits. The applicant agreed to do so. The usage of HAL and its treatment program should be optimized to ensure the effective use of HAL. PMDA therefore discussed the usage and treatment program of HAL, as presented in "6.B.(5) Treatment program and usage."

PMDA understands that sufficient effort was made to ensure the objective evaluation of clinical trial data. However, the way the hoist was operated and the open label design of clinical trial should also have influenced the trial results. These biases may not have been completely eliminated, but PMDA evaluated the clinical trial data in a comprehensive manner, in light of the rareness of the target diseases and the clinical significance of HAL as a treatment option. As stated later in "7. Data on planning of post-marketing surveillance, etc. specified in Article 2-1 of the Ministerial Ordinance on Good Postmarketing Study Practice for Medical Devices," further data should be collected.

6.B.(2).3) Results of secondary endpoints

The secondary endpoints (A) through (E), except some manual muscle test data, failed to show statistically significant differences in efficacy between "HAL and a hoist" and "a hoist alone." PMDA asked the applicant's view on the obtained data.

The applicant's response:

The results of (A) the 10-meter walk test did not show statistically significant differences in the crossover analysis and in comparison between Treatment Period 1 (a hoist) in Group A and Treatment Period 2 (HAL and a hoist) in Group B. However, the 10-meter walk test results showed greater improvement rates after Treatment Period 2 in Group B, thus being consistent with the results of the 2-minute walk test (Table 10). This support the improvement in gait function by HAL. Figure 9 shows changes in walking speed in 13 patients in Group A and 11 patients in Group B. Walking speed improved in 69.2% of patients in Group A after Treatment Period 1 (First Treatment Phase) and 100% of patients in Group B after Treatment Period 2 (First Treatment Phase). In 81.8% of patients in Group B, improvement rates after Treatment Period 2 were higher than the mean improvement rate after Treatment Period 1 in Group A. When First and Second Treatment Phases are combined, walking speed improved in 66.7% of patients after Treatment Period 1 and 91.7% of patients after Treatment Period 2.

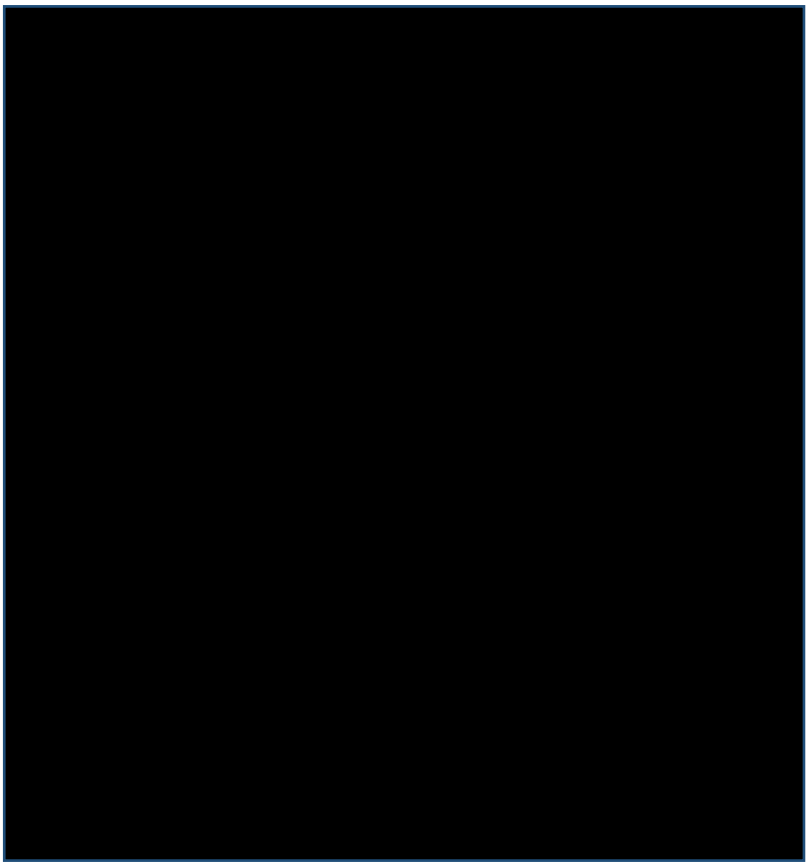


Figure 9. Changes in 10-meter walk test results (speed) in each patient

Horizontal axis, number of tests (Visits); vertical axis, speed (m/sec.)

- - - - Treatment Period 1 (a hoist)

——— Treatment Period 2 (HAL and a hoist)

Tables 21 to 24 show the percentages of patients with improvement in (B) gait assessment by patients, (C) gait assessment by healthcare professionals, (D) manual muscle test, and (E) ADL assessment.

Table 21. Percentages of patients with improvement in gait assessment by patients

	100—Fatigue during walking	Light tread during walking	Stability during walking	Sense of security during walking	Pleasure during walking
After Treatment Period 1 in Group A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
After Treatment Period 2 in Group B	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
After Treatment Period 1 in Groups A and B	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
After Treatment Period 2 in Groups A and B	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 22. Percentages of patients with improvement in gait assessment by healthcare professionals

	Stance phase	Swing phase
After Treatment Period 1 in Group A	[redacted]	[redacted]
After Treatment Period 2 in Group B	[redacted]	[redacted]
After Treatment Period 1 in Groups A and B	[redacted]	[redacted]
After Treatment Period 2 in Groups A and B	[redacted]	[redacted]

Table 23. Percentages of patients with improvement in manual muscle test

	Hip flexion, Right	Hip flexion, Left	Hip extension, Right	Hip extension, Left	Knee flexion, Right	Knee flexion, Left	Knee extension, Right	Knee extension, Left	Ankle dorsiflexion, Right	Ankle dorsiflexion, Left	Ankle plantar flexion, Right	Ankle plantar flexion, Left
After Treatment Period 1 in Group A	[redacted]											
After Treatment Period 2 in Group B	[redacted]											
After Treatment Period 1 in Groups A and B	[redacted]											
After Treatment Period 2 in Groups A and B	[redacted]											

Table 24. Percentages of patients with improvement in ADL assessment (Barthel Index)

	Feeding	Transfer from wheelchair to bed	Grooming	Toilet use	Bathing	Walking	Stairs	Dressing	Bowel control	Bladder control
After Treatment Period 1 in Group A	[redacted]									
After Treatment Period 2 in Group B	[redacted]									
After Treatment Period 1 in Groups A and B	[redacted]									
After Treatment Period 2 in Groups A and B	[redacted]									

In (B) gait assessment by patients, the percentage of patients showing improvement after Treatment Period 2 tended to be slightly higher than that after Treatment Period 1, except for fatigue during walking, but the tendency was not obvious. In (C) gait assessment by healthcare professionals, no notable tendency was observed. In (D) the manual muscle test, the percentage of patients showing improvement after Treatment Period 2 tended to be slightly higher than that after Treatment Period 1, except for some test items. The crossover analysis shows a statistically significant improvement in the scores for left hip flexion after Treatment Period 2 (HAL and a hoist), but there was no obvious tendency in other test items except for left hip flexion. In (E) ADL assessment, there was no difference before and after treatment in most assessment items. In ADL assessment, the percentage of patients showing improved walking after Treatment Period 1 tended to be higher than that after Treatment Period 2. In total, [redacted] patients showed a 1-grade improvement in their walking score after Treatment Period 1, and [redacted] patients after Treatment Period 2. The other patients showed no change (without worsening in walking score) before and after treatment.

These secondary endpoints did not show a significant difference between “HAL and a hoist” and “a hoist” in the planned analysis, but were consistent with the results from the 2-minute walk test, supporting the improvement in gait function by HAL therapy.

PMDA understands that the secondary endpoints had to be evaluated in a limited number of patients. This limited evaluation has suggested that HAL tends to provide greater therapeutic effect, with some exceptions, than treatment with a hoist alone. The significant improvement in the left hip flexion score in the manual muscle test may be related to improved gait function, the primary endpoint; but, at present, the relationship is still not clear. The benefits of HAL to patients’ daily lives including QOL, which were not evaluated for this application, should be investigated through the use-results survey of HAL [see “7. Data on planning of post-marketing surveillance, etc. specified in Article 2-1 of the Ministerial Ordinance on Good Postmarketing Study Practice for Medical Devices”]. The benefits identified through the survey should be communicated to healthcare professionals.

The applicant’s explanation on (F) assessment by operators:
In the clinical trial, it took patients approximately 5 minutes to wear HAL at Visit 5 and subsequent visits (time for electrode positioning not included). Time to wear HAL should be ≤5 minutes on average in a single treatment session so that patients do not get tired. HAL for Medical Use detects BES more accurately than HAL for Living Support. Therefore, the positions to attach electrodes can be determined according to the patient’s body size and by locating muscle contraction sites by palpation. The method for electrode positioning will be described in the label. Once the positions of electrodes have been determined, the positions should be marked on the wearer’s skin or recorded in a dedicated form, or the electrodes attached on the skin should be photographed. This will allow the use of the same electrode positions in subsequent HAL therapies.

PMDA’s view
The applicant should continue to improve the usage of HAL, for example, by informing healthcare professionals of the optimum wearing procedure, based on future findings on this matter.

The applicant agreed.

6.B.(3) Safety evaluation

6.B.(3).1) Adverse events

PMDA discussed adverse events from the following viewpoints:

(A) Possible muscle impairment
(B) Risk of falls
(C) Serious adverse events
(D) Other adverse events

6.B.(3).1). (A) Possible muscle disorders

PMDA considers that the effects of overloaded muscles associated with HAL should be investigated because patients with the target diseases may have muscle disorders. PMDA asked the applicant to analyze adverse events probably associated with muscle disorders, etc.

The applicant's response:

In gait training therapy, muscles or joints may be overloaded and suffer myalgia or arthritis. In order to avoid such muscle injury, load must be controlled within an appropriate range during gait training therapy. In the clinical trial, HAL therapy was conducted under the proper control of physicians and physiotherapists because some of the target myogenic diseases make muscles vulnerable to load.

In Treatment Period 2 (HAL and a hoist), 12 of 30 patients experienced 15 events of myalgia or other types of pain (arthralgia, back pain, musculoskeletal pain, neck pain, osteoarthritis, pain in extremity, and pain). In Treatment Period l (a hoist), 7 of 29 patients experienced 10 such events. These events thus tended to occur slightly more frequently in Treatment Period 2 than in Treatment Period 1. (Events occurring in the transition period or other non-treatment periods were categorized into Treatment Period 1 or 2, whichever is related to the events). Table 25 shows correlation between myalgia and other pain and the efficacy of HAL therapy (mean improvement rate).

Table 25. Correlation between myalgia and other pain and treatment efficacy (mean improvement rate)

	Treatment Period 1	Treatment Period 2
With myalgia and other pain	11.3% (n = 4)	19.8% (n = 9)
Without myalgia or other pain	6.8% (n = 20)	15.0% (n = 15)
With myalgia	22.5% (n = 1)	24.0% (n = 2)
Without myalgia	6.9% (n = 23)	16.2% (n = 22)

The incidences of myalgia and other pain tended to increase with increasing improvement rates in the 2-minute walk test both in Treatment Periods 1 and 2. Treatment Period 2, which produced higher improvement rates, may have caused more frequent pain events. In Treatment Period 2, pain events occurred in 10 of 14 patients with an improvement in manual muscle test scores. In Treatment Period 1, pain events occurred in 2 of 8 patients with improved manual muscle test scores.

On the other hand, 7 patients showed decreased gait function in the 2-minute walk test after Treatment Period 2. Two of the 7 patients had a pain event associated with treatment in the period. One patient experienced knee osteoarthritis but had improved manual muscle test scores. The other patient had upper extremity myalgia (resulting from holding the hoist too tightly), and this event was unlikely to be related to the function of lower extremities. Of 4 patients with decreased manual muscle test scores, only one experienced upper extremity myalgia (the same patient mentioned earlier) and the other 3 patients did not experience any pain events.

Four patients experienced myalgia for which a causal relationship with HAL cannot be ruled out.

- Mild myalgia in the anterior thigh caused by awkward motion of HAL and the use of muscles that are seldom used in normal daily activities (Patient [redacted], SMA, inpatient)
- Myalgia in the forearm due to holding on to the hoist firmly to keep balance during unaccustomed gait training with HAL (Patient [redacted], distal myopathy, inpatient)
- Myalgia in the hamstrings and triceps of both lower extremities caused by treatment with HAL (Patient [redacted], SBMA, outpatient)
- Myalgia due to the heavy weight of HAL during behavior checking (Patient [redacted], distal myopathy, outpatient)

These patients recovered in a few days. None of the reported myalgia persisted for a long time. This suggests that none of the enrolled patients vulnerable to high load experienced any events resulting in severe muscle tissue injury. Risks of overload on muscles and muscle injury due to HAL were properly controlled in the clinical trial. A causal relationship with HAL cannot be ruled out for the following adverse events (other than myalgia): back pain due to the vertebrae hit by HAL in 1 patient; pain of unknown cause in the anterior lower leg to the ankle in 1 patient; knee osteoarthritis assumed to have occurred after walking a longer distance (as a result of increased walking capacity) in 1 patient; and back pain, pain in extremities, and arthralgia in 1 patient each due to walking for longer distances (as a result of increased walking capacity). Close attention should be paid to similar cases of knee osteoarthritis. Patients should be screened for knee osteoarthritis before starting HAL therapy and examined for eligibility for continuing the therapy.

Careful efforts are required to avoid the risk of muscle disorders associated with HAL therapy. In the clinical trial, however, HAL did not show a significantly higher risk than the treatment with a hoist alone, because HAL was used under proper management by physicians and physiotherapists. This indicates that the risk of muscle injury associated with HAL is controllable with proper supervision and an appropriate treatment program. The risk can be reduced by ensuring that the intensity of treatment (the frequency and amount of training) do not exceed the levels used in the clinical trial; that each patient are examined for the effects of fatigue and muscle pain and other changes so that the settings and alignment of the device are properly adjusted for each patient.

Because no long-term clinical trial has been performed to evaluate HAL, HAL should not be used over a prolonged period aimlessly. Whether to continue the treatment should be discussed when short-term treatment is found no longer effective. This should be mentioned in the standards for the proper use of HAL or other reference materials. The “Important Precautions” section of the label should state that the long-term safety or efficacy has not been confirmed because of the lack of data on long-term HAL therapy (i.e., >9 sessions).

PMDA’s views are summarized in the discussion on safety in the latter part of Section 6.B.(3).1).(D).

6.B.(3).1).(B) Risk of fall

During HAL therapy, a hoist is used to prevent the patient from falling. On the other hand, patients who have adapted themselves to wearing HAL may have the sense of strangeness when walking without wearing the device and fall or lose their balance. PMDA asked for the applicant's view on such risks. In addition, 4 events of falls occurred in 4 patients (Patient ID [redacted], [redacted], [redacted], and [redacted] including Patient ID [redacted] with an event for which a causal relationship with HAL cannot be ruled out), and other events related to falls were observed during the clinical trial. PMDA asked the applicant to discuss the occurrence of fall-related adverse events.

The applicant response:

HAL is intended for patients with impaired gait function due to neuromuscular diseases. Thus the users of the device are at high risk of falls from the beginning, and treatment with HAL may cause changes in their gait pattern or daily activities. Therefore the risk of falls may be increased during or after HAL therapy. Tables 26 and 27 summarize the fall-related adverse events that occurred during the clinical trial.

Table 26. Fall-related adverse events (unrelated to treatment)

Patient ID Group	Event term in case report/ Preferred term (MedDRA/J)	Case description (monitoring report)
[redacted] Group A	Bruise of head/Contusion	The event occurred on the day following the seventh visit in Treatment Period 2 The patient hit a housekeeping cart while in a wheelchair, lost balance, fell, and received a blow to the hip and the head. The blow to the hip was not regarded as an adverse event because the hip only touched the ground and left no bruise. This event was accidental and determined as "unrelated."
[redacted] Group A	Right patella fracture/ Patella fracture	The event occurred in the follow-up period (6 days after the ninth visit in Treatment Period 2). The patient forgot to activate the stopper of the electric lift chair before standing up, resulting in a fall. This event was due to carelessness and was determined as "unrelated."
[redacted] Group B	Bruise of buttock/Contusion	The event occurred 7 days after the eighth visit in Treatment Period 2. The patient fell on the buttocks at home. This event was determined as "unrelated."
[redacted] Group A	Bruise pain (left arm)/ Contusion	The event occurred after the eighth visit in Treatment Period 1. The patient fell and bruised the arm. This event was accidental and determined as "unrelated."
[redacted] Group A	Fall/Fall	The event occurred on the day following the fourth visit in Treatment Period 2. The patient tripped on furniture and fell forward but experienced no bruising or pain. This event was accidental and determined as "unrelated."
[redacted] Group A	Bruise on lips/Contusion	The event occurred 2 days after the sixth visit in Treatment Period 2. The patient fell in the bathroom and received a blow to the mouth, resulting in swelling of the inner lip. The swelling was due to the blow. This event was accidental and determined as "unrelated."
[redacted] Group B	Fall/Fall	The event occurred the day after the third visit in Treatment Period 1. The patient fell at home. This event was accidental and determined as "unrelated." An additional event secondary to this event, namely "pain (in

		hip and right popliteal region)" (the term in the case report) was reported separately.
[redacted] Group B	Bruise (left upper arm)/ Contusion	The event occurred 4 days after the second visit in the run-in period. This event was caused by fall due to knee buckling associated with progression of primary disease; it was determined as "unrelated."
[redacted] Group B	Fall/Fall	The event occurred 6 days after the seventh visit in Treatment Period 1. No pain accompanied the fall; it was accidental and determined as "unrelated."
[redacted] Group B	Right wrist sprain/ Ligament sprain	The event occurred 4 days after the second visit in the run-in period. The patient fell off a bicycle. This event occurred before the beginning of HAL therapy; it was determined as "unrelated."

Table 27. Fall-related adverse events (possibly or probably related to treatment)

Patient ID Group	Event term in case report /Preferred term (MedDRA/J)	Case description (monitoring report)
[redacted] Group A	Bruise of back of head/ Contusion	The event occurred on the day following the sixth visit in Treatment Period 2. The patient failed to sit in a chair properly, lost balance, and fell without unconsciousness or nausea. This event occurred while the patient was on HAL therapy. This event was determined as "possibly related," because causal relationship cannot be ruled out.
[redacted] Group A	Fall//Fall	The event occurred in the follow-up period (10 days after the ninth visit in Treatment Period 2) The patient fell on a snowy day but had no bruising or other adverse events. This event was determined as "probably related" because HAL therapy resulted in longer strides, causing the patient to lose balance and fall.

Besides the 4 events of "fall," some of the adverse events termed "contusion," etc. were caused by a fall. When these events are combined, the total number of fall-related events is 12. Of these, 9 events occurred during or after HAL therapy. A causal relationship could not be ruled out for 2 events: "fall" in 1 patient and "contusion" in 1 patient (see Table 27). The fall in a patient (Patient ID [redacted]) was considered by the investigator to be due to a change in strides as a result of HAL therapy. This suggests that a change in gait pattern caused by HAL therapy may increase the risk of falls. However, the use of a hoist in Treatment Period 1 may also have increased strides, and the risk of falls is not necessarily attributable to HAL alone.

The risk of falls is of concern, given that fall-related events occurred in daily life during and after the treatment and they were attributable to changes in gait pattern or increased activities as a result of improved gait function. Using the label (in the "Important Precautions" section) and the guidelines for the proper use, the applicant plans to inform healthcare professionals and patients of fall-related events occurring in the clinical trial and advise them to take appropriate actions to reduce the risk of fall not only during treatment but also in everyday life.

PMDA's views are summarized in the discussion on safety in the latter part of section 6.B.(3).1).(D).

6.B.(3).1).(C) Serious adverse events

Any causal relationship was ruled out between HAL for Medical Use and all serious adverse events occurring in the clinical trial, but PMDA asked the applicant to report whether similar events (e.g., stroke) occurred in association with HAL for Living Support, which has been on the market.

The applicant replied that no relevant events occurred in association with HAL for Living Support.

PMDA's views are summarized in the discussion on safety in the latter part of Section 6.B.(3).1).(D).

6.B.(3).1).(D) Other adverse events

PMDA asked the applicant to provide data on the occurrence of other adverse events, analyze the cause of the events, and identify preventive and corrective measures to address the events, in order to facilitate the proper use of HAL based on its risks and benefits.

The applicant's response:

Of 19 adverse events for which a causal relationship with HAL could not be ruled out, 10 events were muscle pain or other pain, as described above, and 2 events were fall-related events. The remaining 7 events consist of 4 events of dermatitis, etc. caused by the attached electrodes or marking tape; 1 event of skin exfoliation on the posterior thigh caused by wearing of HAL; 1 event of excoriation on external malleolus that occurred when HAL was fitted; and 1 event of excoriation in the lower leg where the lower leg cuff was attached. The risk of dermatitis, etc. on electrode attachment sites will be reduced by examining the skin at every visit, applying ointment if it does not heal spontaneously, and suspending HAL therapy in the event of worsening condition. Excoriation observed in 2 patients in the clinical trial occur infrequently; the risk of the event will be reduced by careful examination of patients and adjusting the fitting of HAL based on feedback from the patient. The label will describe the occurrence of adverse events during the clinical trial.

PMDA's view on the safety of HAL based on 6.B.(3).1).(A) through (D):

As per the applicant's explanation on muscular overload, myalgia and other muscular adverse events observed during the clinical trial were transient without evidence for muscle injury. Meanwhile, HAL is designed to assist patients only by uniaxial rotation of the hip and knee joints and is not always capable of assisting in a way that fits individual patients' gait pattern specific to the affected site. In such conditions, HAL may overload muscles in the entire body (including unaffected muscles), with load levels that would not be expected in daily life or conventional walking therapies, and may increase the risk of myalgia and other pain as compared with the conventional walking therapies. Furthermore, patients with muscle disorders are vulnerable to excessive load. Thus HAL should be used under the appropriate supervision of a physician and a physiotherapist to prevent excessive loads on the muscles of patients [see "6.B.(5) Treatment program and usage"]. Muscular overload may be detected early by measuring creatine kinase and aldolase in serum, markers for the degree of muscle injury, although these markers were not used in the clinical trial. Therefore the use-results survey of HAL should include a

muscle disorder-related investigation item [see "7. Data on planning of post-marketing surveillance, etc. specified in Article 2-1 of the Ministerial Ordinance on Good Postmarketing Study Practice for Medical Devices"].

As shown in Table 26, fall-related adverse events include those occurring before starting HAL therapy or obviously not attributable to HAL, and some with unknown cause. When considering events listed in Table 27 together, the possibility remains that HAL therapy may cause a change in the patient's gait pattern and daily activities. Given that HAL is intended for patients with impaired gait function who are at high risk of falls, appropriate measures should be specified to address a possible increase in the risk of falls. Physicians and physiotherapists should be informed of the risk in addition to precautionary advice in the label, and patients should be provided with relevant information and guidance by physicians and physiotherapists. Thus, the applicant's response is reasonable.

In the clinical trial, HAL was not used for >9 times. However, repetitive treatment is expected for patients with slowly progressive nerve and muscular diseases depending on disease progression [see "6.B.(5) Treatment program and usage"]. Given this fact, the long-term safety of HAL should be investigated in the use-results survey. In particular, treatment of neuromuscular diseases is expected to involve risks of muscle weakness due to excessive physical activity (overwork muscle weakness). In the use-results survey, the applicant should assess not only the risks of muscle disorders in short-term treatment but also the risk of overwork muscle weakness resulting from the long-term use of HAL, and investigate the proper amount of exercise (degree of loads and frequency) [7. Data on planning of post-marketing surveillance, etc. specified in Article 2-1 of the Ministerial Ordinance on Good Postmarketing Study Practice for Medical Devices].

Most of other adverse events were mild in severity (without interfering with daily life). All events for which a causal relationship with HAL could not be ruled out were mild and are unlikely to cause any great problems. However, because the number of patients enrolled in the clinical trial was limited, post-marketing data should be collected to identify unknown adverse events and new trend in the occurrence of events so that appropriate measures are taken [see "7. Data on planning of post-marketing surveillance, etc. specified in Article 2-1 of the Ministerial Ordinance on Good Postmarketing Study Practice for Medical Devices].

In the clinical trial, there was no event caused by an interaction between HAL and a cardiac pacemaker or implantable cardioverter defibrillator (ICD). However, because HAL is designed to be activated by the power unit used in close contact with the patient's body, PMDA asked the applicant to explain possible interactions between HAL and the mentioned devices.

The applicant's response:
Some myogenic disorders are accompanied by abnormal cardiac muscles. In particular, patients with Duchenne muscular dystrophy and myotonic dystrophy may be wearing an ICD or pacemaker. During

the development of HAL for Living Support (study model), the applicant and a pacemaker manufacturer agreed that there would be no risk of device malfunction caused by an interaction between the HAL for Living Support and a pacemaker. The mentioned risk in the treatment with HAL for Medical Use is controllable as long as the device is used at medical facilities under instructions of physicians or used in the presence of healthcare professionals. HAL is probably free from problems with these cardiac devices structurally, but the possibility to affect them cannot be ruled out. The applicant thus plans to include precautionary advice in the "Interaction" section of the label that patients with a cardiac pacemaker, etc., should use HAL under the instructions and supervision of a cardiac specialist.

PMDA's conclusion:
The above measures proposed by the applicant are appropriate to address any possible interaction between HAL and a cardiac pacemaker, ICD, etc. at present. Data on the interactions should be collected and new findings should be communicated to healthcare professionals, by revising the label as necessary.

6.B.(3).2) Malfunctions
PMDA asked the applicant to explain the occurrence of malfunctions and errors, actions taken, and any abnormal behavior in the clinical trial.

The applicant's response:
During the clinical trial, 22 malfunctions were reported. Of these, 8 led to the stop of assistance. These malfunctions did not cause adverse events, but the device was replaced. Another 8 malfunctions were due to misalignment at an adjustable area; the affected area was fixed in the proper alignment position. Five malfunctions were poor connection, wearing, or breakage caused by vibration and shock; the device was replaced. The remaining malfunction was abnormal noise from the ankle joints due to the specifications rather than a breakdown. HAL was modified according to collected information on the malfunctions.

All patients who wore HAL experienced an error leading to the stop of assistance, but none of them encountered unintended abnormal behavior. HAL stopped assistance when it detected abnormal BES or a defect in the power unit as an error, and this is considered the appropriate response to the error. A total of 5 cases of an error leading to the invalidation of treatment program occurred in 2 patients, but did not result in the discontinuation of clinical trial. Perspiration of the wearer may cause instability of the electrodes leading to abnormal behavior of the device, but there was no such error. The record of error history revealed that there were 170 BES-related errors, and one of these was recorded as a malfunction (stop of assistance). Other BES-related errors were corrected by the reattachment of electrodes and the modification of cable routing (for removal of tension), so that treatment could be continued. When an electrode becomes detached from the skin, the electrode error detection function alerts the error to the user while the corresponding torque unit changes to a mode equivalent to CIC; HAL therefore is unlikely to force the patient to move his/her limbs in bigger strides. Appropriate setting of torque limit and assist angle range reduces the risk of exerting excessive mechanical energy.

PMDA considers that the nature of the 22 malfunctions and 202 errors that occurred during the clinical trial are unlikely to cause serious problems. As many as 170 errors were BES-related but were not serious because none of these errors led to the discontinuation of clinical trial. However, because many malfunctions and errors were reported, relevant information should be further collected.

6.B.(4) Intended use or efficacy

Based on the clinical trial results and the discussions above, PMDA concluded that the descriptions of the intended use or efficacy be revised as shown in Table 28 below. The applicant agreed.

Table 28. Revision of intended use or efficacy

Before change	After change
1. Intended use HAL suppresses the progression of muscle atrophy and weakness by assisting muscle contraction in patients with slowly or chronically progressive intractable neuromuscular disease. Patients wear HAL regularly, intermittently, and therapeutically to receive assistance in muscle contraction. 2. Eligible patients HAL is indicated for patients with unsteady gait who receive treatment to suppress the progression of intractable rare neuromuscular disease. Patients with target disease, namely slowly or chronically progressive neuromuscular disease, are eligible for HAL therapy if they (1) have symptoms attributable to spinal muscular atrophy (SMA), spinal and bulbar muscular atrophy (SBMA), amyotrophic lateral sclerosis (ALS), Charcot-Marie-Tooth (CMT) disease, distal myopathy, inclusion body myositis (IBM), congenital myopathy, or muscular dystrophy, and (2) meet all the criteria below: (a) Patients weighing 40 to 100 kg (b) Patients approximately 150 to 190 cm tall who are able to wear HAL. Patients shorter or taller than this height range but able to wear HAL with an appropriate body size (e.g., upper/lower leg length, hip width).	1. Intended use HAL is used to improve gait function*1 in patients with slowly progressive*2 neuromuscular disease.*3 HAL improves gait function by assisting the movement of lower limbs according to bio-electric signals during gait training. Patients wear HAL intermittently to repeat the training.*4 2. Eligible patients HAL is indicated for patients with impaired gait function*5 due to slowly progressive*2 neuromuscular disease.*3 Patients are eligible for HAL therapy if they (1) have a diagnosis*6 of slowly progressive*2 neuromuscular disease,*3 namely spinal muscular atrophy (SMA), spinal and bulbar muscular atrophy (SBMA), amyotrophic lateral sclerosis (ALS), Charcot-Marie-Tooth (CMT) disease, distal myopathy, inclusion body myositis (IBM), congenital myopathy, or muscular dystrophy; (2) need human assistance with walking or a walking aid*7; and (3) meet all the criteria below: (a) Patients weighing 40 to 100 kg (b) Patients approximately 150 to 190 cm tall or with an appropriate body size (e.g., upper/lower leg length, hip width) who are able to wear HAL

*1 The clinical trial evaluated the improvement in gait function.

*2 The clinical trial was considered to have conducted in patients with slowly progressive neuromuscular disease.

*4 To clearly define clinical positioning [“V.(1) Appropriateness of conducting a collective evaluation of the target diseases”]

*5 HAL is used to improve impaired gait function.

*7 To specify the degree of impaired gait function [“V.(1) Appropriateness of conducting a collective evaluation of the target diseases”].

*3, *6 Improvements in wording

6.B.(5) Treatment program and usage

6.B.(5).1) Appropriate treatment program and guidelines for proper use

The desired effect of HAL is achieved through repeated training. The clinical trial suggested that the usage (treatment intervals) of HAL had affected the efficacy. An appropriate treatment program is important to obtain the optimum effect of HAL. PMDA asked the applicant to establish guidelines for tailoring a treatment program according to the disease or the degree of disease progression of individual patients. The guidelines should define the basic or appropriate amount of therapy in the post-marketing settings, specifically, the details, hours, frequency, and duration of training based on those used in the clinical trial. The actual effect of treatment and the prevention of overuse should also be taken into consideration.

The applicant's response:

In the clinical trial, a 40-minute training session consisting of warming-up, gait training, and cooling down was performed 9 time per treatment period. Each patient was allowed to take a rest for <20 minutes according to the degree of fatigue. The degree of fatigue was judged by patients themselves, because no fatigue criteria were established for the clinical trial. The healthcare professional assisting the patient monitored the patient's facial expression and spoke to the patient occasionally.

A potential risk for worsening of the primary disease due to overloaded muscles must be avoided during HAL therapy. The degree of fatigue or myalgia was checked to adjust treatment frequency (intervals) within the defined upper limit. In Week 1, up to 3 treatment sessions were allowed (not on consecutive days). From Week 2 onward, up to 4 treatment sessions were allowed per week (not on three consecutive days), depending on the degrees of muscle pain, joint pain, and fatigue. Inpatients received 2.7 treatment sessions per week on average in Treatment Period 1 and 2.4 treatment sessions in Treatment Period 2, whereas outpatients received 1.3 treatment sessions per week on average in both Treatment Periods 1 and 2. Approximately 9 treatment sessions are probably needed to achieve the effect of treatment. There was a correlation between treatment interval and treatment efficacy; the shorter the interval, the greater the treatment benefit (see Figure 8). The frequency of treatment is considered to influence the degree of improvement in gait function. However, flexibility in the adjustment of treatment intervals may have differed between inpatients and outpatients, and this may have also affected the treatment efficacy, as stated in "6.B.(2).2).(B) Effects of patient characteristics and usage, etc. of HAL." The optimal frequency of treatment is assumed to be 2 to 3 sessions a week. Four patients received 4 treatment sessions weekly on several occasions, but experienced no adverse events. In contrast, treatment efficacy tended to decrease as the interval increased. Figure 8 suggests that HAL may not produce therapeutic effects if used at $\geq$1 week intervals.

Accordingly, patients are recommended to receive approximately 9 treatment sessions. Treatment frequency should be 1 to 4 sessions per week depending on the patient's condition. In a single treatment session, patients should walk for at least 20 minutes but no more than 30 minutes, with rest as needed depending on their condition.

The following may increase efficacy:

- When HAL is not properly fitted, the device may feel too heavy or the patient may feel exhausted. Then readjustment of fitting is required.
- Patients should walk an adequate distance for an appropriate duration during gait training. However, training should be postponed when the patient feels exhausted or ill.
- The presence and degree of muscle or joint pain and exhaustion should be checked to adjust the frequency (intervals) of treatment for individual patients.
- Patients should maintain good posture while walking. Walking with the head forward or in a posture of carrying HAL on their back will worsen their fatigue.

PMDA asked the applicant to discuss appropriate intervals in hoist-assisted HAL therapy sessions repeated >9 times. (Treatment sessions repeated >9 times have not been evaluated in the clinical trial.)

The applicant's response:

When HAL is used ≥10 times, the patient should be monitored for myalgia and other pain while treatment efficacy is evaluated. In order to prevent patients from being overloaded, the upper limit of treatment frequency should be similar to that in the clinical trial, and every patient should be checked for fatigue, myalgia, etc. to adjust treatment frequency (intervals). In the follow-up period, 2-minute walk distance did not decrease. Therefore, when a patient receives similar treatment repeatedly before his/her condition worsens due to the nature of the disease, his/her gait function may be improved by every treatment. The treatment is worth being repeated until it fails to produce short-term improvement in gait function.

PMDA considers that guidelines should be established for the proper setting and change of tasks, modes, sensitivity to BES (amplification), torque (assist strength), and balance (flexion and extension torque), to obtain the optimal efficacy of HAL. PMDA asked for the applicant's view on this matter.

The applicant's response:

In order to increase efficacy, healthcare professionals are required to precisely adjust assist torque etc. to identify optimal settings for individual patients for implementing a treatment program efficiently. In principle, the optimal settings should help the patient feel easy to walk. Specific setting guidelines for individual parameters are presented below. Of note, in the clinical trial, HAL was always operated in CVC mode, and the operation only in CAC mode was not allowed.

- Amplification should be increased to check for the appearance of BES for extension and flexion of muscles.
- Torque should be gradually increased with the torque tuner when assist force is felt to be insufficient.
- The balance tuner is used to coordinate the balance between the flexion and extension torque of muscles involved. It is also used to increase only the extension assist torque of the supporting leg or for other adjustment.

- Gait speed and other parameters should be adjusted according to how the patient feels.

Taking the above into account, PMDA also considers that a treatment manual should be prepared to inform healthcare professionals of the optimal frequency of HAL therapy identified based on the clinical trial results, the device settings, relevant medical knowledge, etc. PMDA asked for the applicant's opinion on the preparation of the manual in cooperation with related associations specializing in neuromuscular diseases and physiotherapies.

The applicant's response:
The clinical trial was conducted in accordance with a standardized treatment program at all study centers. An instruction manual was prepared to define the proper settings in HAL and provide guidelines for adjustment. The applicant is now working with related associations to prepare and release a treatment manual. The manual contains pre-treatment patient examination, guidance on setting up the device and changing device settings according to the patient's condition, guidance on treatment program, how to maximize walk exercise therapy using HAL, and safety management. The applicant plans to revise the content wherever new information is available and may issue various versions depending on the disease or disease classification.

PMDA's view:
The actions to be taken by the applicant are generally appropriate. Since HAL targets rare diseases and only limited clinical data are available, a treatment manual should be prepared and continually revised based on new safety and efficacy data, with careful consideration to the characteristics of each target disease. While repeated use of HAL for >9 times is not currently prohibited, muscle injury due to overload and muscle weakness after the overuse of the device should be analyzed based on long-term data, as explained in "6.B.(3).1) Adverse events." Given that the long-term efficacy of HAL through repeated use is still unknown, long-term data on safety and efficacy including adverse events associated with overload should be collected to further examine the proper use of HAL in the post-marketing settings. Guidelines for the device adjustment and settings should be established through the practical use of HAL to help patients walk properly while wearing the device. In addition, guidelines that are more specific should be established by analyzing collected data. The guidelines should be communicated to physicians through the treatment manual to allow them to tailor a treatment program for individual patients.

6.B.(5).2) Qualification of physicians and medical institutions
PMDA considers that a patient's eligibility for HAL therapy, treatment prescription, etc. should be determined by a physician specializing in the target disease, while the rareness of the disease and the prevention of overload are taken into consideration. Since HAL is a novel medical device, physicians or physiotherapists involved in the effective prescription of treatment, the fitting, adjustment, and operation of HAL should be thoroughly familiar with its characteristics and operation method. Thus it is advisable that the applicant works with related associations to define required expertise of physicians, qualification

of medical institutions, eligibility criteria, and criteria for the proper use of HAL, including training on the use of the device. PMDA asked for the applicant's opinion.

The applicant's response:
The applicant will continue to work with related associations to establish a standard for its proper use and update the standard based on new data.

PMDA concluded that the applicant's plans were appropriate. In view of Article 79-2 of the Pharmaceutical Affairs Law (Act No. 145, August 10, 1960), PMDA considers qualifications of physicians and medical institutions need not be included in conditions for approval of HAL.

6.B.(5).3) Necessity of using a hoist with HAL
According to the clinical trial data submitted by the applicant, HAL was not used alone. Instead, a hoist was always used when a patient wore HAL and during gait training with HAL, to prevent the patient from falling. However, the proposed label submitted for the application recommended that HAL be used with parallel bars, a walking aid, etc.

PMDA considers that HAL should be used with a hoist or an equivalent non-weight-bearing device for the following reasons: (1) In case of a fall, the patient would be forced to take an extra action of holding the parallel bars or the walking aid to prevent themselves from falling. Such equipment does not eliminate the risk of falls because it does not always prevent falls as effectively as a hoist. (2) No clinical data are available on safety, particularly the risk of falls in the use of HAL without a hoist. (3) Non-weight-bearing effect of a hoist was expected to help improve treatment efficacy in the clinical trial. PMDA asked for the applicant's view.

The applicant's view
HAL should be used with a hoist or any other equipment that prevents falls without requiring any efforts by the patient. This information will be included in "Directions for use" and the label. PMDA concluded that the applicant's response was appropriate.

7. Data on planning of post-marketing surveillance, etc. specified in Article 2-1 of the Ministerial Ordinance on Good Postmarketing Study Practice for Medical Devices

7.A Summary of the submitted data
No data were submitted because the applicant had no plan at the time of application.

7.B Outline of the review by PMDA
PMDA considers a use-results survey should be conducted in the post-marketing settings, for the following reasons: (i) The HAL for Living Support has been used in Japan, but the applicant filed the application for approval of HAL for Medical Use as a new medical device. (ii) Because HAL is indicated for rare diseases, experiences in the use of the device are limited in Japan and overseas. (iii) In light of

the small sample size of the clinical trial, data on the safety and efficacy of HAL should be further collected to optimize its use. As mentioned in "6.B Outline of the review by PMDA," PMDA considers the following (1) to (4) should be investigated through the survey.

(1) The safety of HAL, in particular, risks of adverse events such as muscle injury due to overloading and overwork muscle weakness due to long-term use of HAL should be analyzed. Given that HAL is intended for the treatment of rare diseases and that only a limited number of patients were enrolled in the clinical trial, appropriate measures should be taken for unknown adverse events (including those related to cardiopulmonary function) or malfunctions (including errors), or any new trends in the incidence or severity of known events.
(2) In the clinical trial, HAL was used up to 9 times per treatment period. However, the device is expected to be used more frequently in clinical practice. The safety, appropriate frequency or intervals, cumulative effects, and sustainability of effects should be evaluated in patients who receive >9 treatment sessions with HAL.
(3) The efficacy and safety of HAL should be evaluated by disease. Data should be collected particularly on diseases for which there is no or little data. Influential factors should be also analyzed.
(4) Data on QOL should be collected to analyze benefits in daily lives of patients.

Accordingly, PMDA asked the applicant to summarize the plan for the use-results survey (as a post-marketing surveillance).

The applicant's response:
The above-mentioned investigation items (1) to (4) will be investigated. In the clinical trial, the lowest incidence of adverse events was 3.3%. To detect ≥1 adverse event with the incidence of 3.3%, with a probability of 95%, 89 patients need to be enrolled. The enrolled patients will be grouped into neurogenic disorders (spinal muscular atrophy, spinal and bulbar muscular atrophy, amyotrophic lateral sclerosis, Charcot-Marie-Tooth disease) and myogenic disorders (distal myopathy, congenital myopathy, inclusion body myositis, muscular dystrophy). To obtain sufficient data on adverse events including those caused by overload in both groups, 90 patients per group, a total of 180 patients, need to be enrolled. This sample size ensures a certain number of patients with each disease (≥10 patients per disease), which should be sufficient to collect the required amount of data. Efficacy will be also evaluated in the enrolled patients. HAL is expected to be introduced in up to 50 medical institutions, and approximately 20 of these institutes will participate in the survey. Each medical institution would have an average of 2 to 3 patients annually, thus approximately 50 patients would be enrolled in the survey annually. An enrollment period of 3 years and 6 months is required to achieve the target sample size.

Investigation items include patient characteristics (disease, degree of progression, etc.), adverse events (related to overload and overwork, including unknown adverse events), malfunction and errors, 2-minute walk distance, Barthel Index, and QOL. Markers for the degrees of muscle disorders (e.g.,

creatine kinase) and information on the use of device (date, operation hours, setting, etc.) will also be collected. These data will be used to analyze the effects of HAL therapy sessions repeated >9 times, which were not evaluated in the clinical trial, in terms of the efficacy, safety, and appropriate usage of HAL, effects by disease, benefit, and influential factors.

Patients should be followed for ≥1 year to monitor changes in their slowly progressive diseases. However, HAL is expected to be used for longer periods in some patients. The survey will thus be continued until 1 year after the last enrollment. In order to collect long-term data as much as possible, patients enrolled earlier than the last enrollment should be followed until the end of the survey while they are on HAL therapy. Accordingly, the survey period is to be 5 years (Preparation for launch, 6 months; enrollment, 3 years 6 months; follow-up, 1 year from the last enrollment).

PMDA has concluded that the plan proposed by the applicant is appropriate.

8. Contents of the label as specified in Paragraph 2-1 of Article 63 of the Pharmaceutical Affairs Law

8.A Summary of the submitted data

The attachment of the label (draft) was omitted in accordance with "Application for Approval of Medical Devices" (PFSB Notification No. 1120-5 dated November 20, 2014).

8.B Outline of the review by PMDA

In consideration of comments from the Expert Discussion, PMDA has concluded that there was no particular problem with the descriptions in the label apart from the necessary cautions that should be provided as stated in "6.B Outline of the review by PMDA"

IV. Results of Compliance Assessment by PMDA Concerning the Data Submitted in the New Medical Device Application and Conclusion by PMDA

A document-based inspection and data integrity assessment were conducted in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. As a result, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted documents.

V. Overall Evaluation

HAL is a medical device designed for effective gait training therapy. The device assists the wearer in moving lower limbs by driving the hip and knee power units according to BES and other information.

The main issues in the review of HAL were (1) the appropriateness of evaluating the target patients collectively, (2) efficacy evaluation, (3) safety evaluation, and (4) treatment program and usage. In

consideration of comments from the Expert Discussion, PMDA has reached the conclusions presented below:

V.(1) Appropriateness of evaluating the target patients collectively

The sample size of the clinical trial was small because of the rareness of the target diseases of HAL. It was therefore difficult to evaluate efficacy by disease. The 8 diseases evaluated in the trial, except for amyotrophic lateral sclerosis (ALS), are all characterized by gait disturbance associated with muscle weakness caused by impaired lower motor neurons and muscles. These 8 diseases are assumed to respond to conventional therapies by a common mechanism: restoration of muscle strength deteriorated by disuse and relearning of gait. HAL does not act on the causes of the 8 diseases, but is expected to help improve gait function effectively by assisting gait movement based on BES generated by muscle activity during repetitive walking training. For the treatment of upper motor neuron-dominant ALS, PMDA concluded that the following precautionary advice be provided to healthcare professionals: "The efficacy and safety of HAL have not been demonstrated in upper motor neuron-dominant ALS."

Further, the degrees of disease progression are assumed to vary among patients with any of the 8 diseases. HAL is expected to have similar therapeutic effects across the 8 diseases if used in patients meeting the inclusion criteria of the clinical trial (i.e., unable to walk 10 meter independently but able to walk ≥10 meter with human assistance or a walker, etc.). In addition, measurement of BES, the main feature of HAL, is possible in patients with impaired gait function meeting this criterion.

Accordingly, patients with any of the 8 diseases can be evaluated collectively. Data on each disease should be collected in the use-results survey.

V.(2) Efficacy evaluation

PMDA has concluded that the endpoints used for evaluating the efficacy of HAL are appropriate taking into consideration the Guidance on the Evaluation of Devices for Physical Function Recovery.[1] A concern was that there was no washout between First and Second Treatment Phases in the crossover evaluation. However, the additional effect of HAL was observed in the comparison between the 2 groups in First Treatment Phase (P = [redacted], t-test). HAL was shown to be more effective in improving walking ability than treatment with the hoist alone, demonstrating its efficacy and clinical significance. The additional effect of HAL is expected to be 10% to 16% on average. The improvement in gait function was achieved through HAL therapy with a hoist (not HAL alone). Therefore clinical trial results, the precondition (HAL must be used with a hoist), and the incidences of adverse events should be communicated to healthcare professionals to facilitate the proper use of HAL based on its benefits and risks. It should be noted that treatment efficacy with HAL tended to be better with shorter treatment intervals. This is considered attributable to the design of treatment program, suggesting the importance of an appropriate treatment program.

The secondary endpoints demonstrated overall improvement, but it is difficult to make definite conclusions on these endpoints at present because of the limited number of patients. Treatment benefits in the daily life (e.g., QOL, ADL) of patients receiving HAL therapy should be investigated through the use-results survey.

V.(3) Safety evaluation

Myalgia and other pain were relatively common adverse events in the clinical trial. The safety of HAL must be further analyzed with its long-term use taken into consideration. Adverse events related to overload, muscle impairment, and overwork muscle weakness should be investigated in the use-results survey. Healthcare professionals should be informed of the risk of falls in patients on HAL therapy as well as in patients not wearing HAL after the completion of therapy. Other adverse events such as skin disorders were mild and unlikely to cause great problems. Nevertheless, adverse events, including unknown ones, should continue to be investigated through the use-results survey.

V.(4) Treatment program and usage

The applicant should work with related associations to prepare an operation manual based on the treatment program used in the clinical trial. The manual should include an appropriate prescription tailored to each patient and guidelines for setting the assist strength, and be revised continually based on available new data. In the clinical trial, HAL therapy sessions were repeated ≤9 times in a single treatment period. In clinical practice, repeating treatment sessions >9 times is not prohibited, but the safety and efficacy of treatment sessions repeated >9 times should be evaluated through the use-results survey. The applicant should work with associations to establish guidelines for the proper use of HAL, including knowledge required of physicians, expertise required of medical institutions, criteria to identify eligible patients, and educational training on the use of HAL.

As a result of its regulatory review, PMDA has concluded that HAL may be approved for the intended use as described below.

Intended use

1. Intended use

HAL is used to improve gait function in patients with slowly progressive neuromuscular disease. HAL improves gait function by assisting the movement of lower limbs according to bio-electric signals during gait training. Patients wear HAL intermittently to repeat the training.

2. Eligible patients

HAL is indicated for patients with impaired gait function due to slowly progressive neuromuscular disease. Patients are eligible for HAL therapy if they (1) have a diagnosis of slowly progressive neuromuscular disease, namely spinal muscular atrophy (SMA), spinal and bulbar muscular atrophy (SBMA), amyotrophic lateral sclerosis (ALS), Charcot-Marie-Tooth (CMT) disease, distal myopathy,

inclusion body myositis (IBM), congenital myopathy, or muscular dystrophy; (2) need human assistance with walking or a walking aid; and (3) meet all the criteria below:

(a) Patients weighing 40 to 100 kg

(b) Patients approximately 150 to 190 cm tall or with an appropriate body size (e.g., upper/lower leg length, hip width) who are able to wear HAL

HAL is not classified as a biological product or a specified biological product. HAL should be designated as a product subject to a use-results survey. Use results should be monitored for 5 years.

As a result of its regulatory review, PMDA has concluded that the application should be deliberated at the Committee on Medical Devices and *In-vitro* Diagnostics.

References

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