Citation: Clin Transl Sci (2021) 14, 806–811; doi:10.1111/cts.12898

MINI-REVIEW

Overview of the Premarketing and Postmarketing Requirements for Drugs Granted Japanese Conditional Marketing Approval

Shunsuke Matsushita[1], Keisuke Tachibana[1], Tetsuya Kusakabe[2,†], Ryuichi Hirayama[3], Yasuo Tsutsumi[1] and Masuo Kondoh[1,*]

For drugs that are intended to fill unmet medical needs, such as the treatment of rare diseases or a subtype of cancer, it can take a long time to conduct confirmatory clinical trials due to limited patient availability. Delayed access to these drugs increases the risk of mortality of patients with these diseases. To address this issue, the Ministry of Health, Labour, and Welfare of Japan has decided to implement the Conditional Early Approval System with issuing the Ministry Notification in 2017. Drugs eligible for conditional early approval are those that are indicated for the treatment of a serious disease, have proven safety and efficacy, and cannot be examined easily by confirmatory clinical trials. When the benefit of immediate availability outweighs the risk of having less comprehensive data with which to confirm the clinical benefit of a product in the premarketing phase, products can be approved under the Conditional Early Approval System, accompanied by postmarketing regulatory requirements to manage postmarketing risks and, if needed, conduct postmarketing confirmatory clinical studies. Overview of the pre-approval and post-approval regulatory considerations will promote to more efficiently develop pharmaceutical products that fill unmet medical needs, leading to the prompt delivery of safe and effective drugs to patients who often have few therapeutic options available. As of March 2020, four drugs had been approved under the Conditional Early Approval System. In this review, we describe the premarketing and postmarketing requirements of these drugs and discuss the regulatory landscape around the Conditional Early Approval System.

Confirmatory clinical studies are used to investigate whether a pharmaceutical product provides a clinically meaningful therapeutic effect on patient survival, function, and quality of life. These studies are designed to include a statistically appropriate number of patients, taking into consideration the target indication, putative safety, and efficacy profiles of the pharmaceutical product. However, when the target indication is a rare disease or a subpopulation of a disease, it can take a long time to recruit the required number of patients and therefore to complete a confirmatory study. Furthermore, if the indication is a serious disease with few current therapeutic options, delayed access to a novel pharmaceutical product could increase the risk of mortality in these patients.

To address this issue, there are several systems in global level that allow for conditional marketing approval for novel pharmaceutical products that fill unmet medical needs. In the United States, the US Food and Drug Administration has the Accelerated Approval Program.[1] Under the Accelerated Approval Program, a surrogate end point or an intermediate clinical end point that are considered reasonably likely to predict clinical benefit are evaluated to predict the clinical benefit of a product. Once a product is granted approval, the applicant is required to conduct confirmatory studies during the postmarketing phase to verify the clinical benefit of the product. If the postmarketing studies just show a benefit smaller than what was expected or fail to show a clinical benefit, the label indication is changed based on the postmarketing clinical data or the product is withdrawn.

In Europe, the European Medicines Agency has the Conditional Marketing Authorization scheme.[2] When immediate availability outweighs the risk of less comprehensive data accumulation, an application for conditional marketing authorization can be made. Under this scheme, conditional marketing authorization can be granted if the product meets the following four conditions: (i) the benefit–risk balance of the product is positive; (ii) the applicant will be able to provide comprehensive data from the postmarketing phase; (iii) an unmet medical need will be filled; and (iv) the benefit to public health of the medicinal product's immediate availability on the market outweighs the risks due to the need for further data collection. Conditional marketing authorizations under this system are valid for 1 year and can be renewed annually. Once conditional approval is granted, the applicant is required to conduct postmarketing clinical studies to provide comprehensive data confirming that the benefit–risk balance is positive. If a positive benefit–risk balance is confirmed, all obligations related to the conditional approval are removed. If a positive benefit–risk balance is not confirmed, the product is withdrawn from the market.

[1]Graduate School of Pharmaceutical Sciences, Osaka University, Osaka, Japan; [2]Graduate School of Medicine, Osaka City University, Osaka, Japan; [3]Graduate School of Medicine, Osaka University, Osaka, Japan; [†]Present address: Pharmaceuticals and Medical Devices Agency (PMDA), Tokyo, Japan. *Correspondence: Masuo Kondoh (masuo@phs.osaka-u.ac.jp)
Received: July 28, 2020; accepted: September 9, 2020. doi:10.1111/cts.12898

In Japan, the Ministry of Health, Labour, and Welfare (MHLW) operates the Conditional Early Approval System. A drug granted conditional approval under this system must meet the following four conditions: (i) it must be indicated for the treatment of a serious disease; (ii) it must have proven clinical utility; (iii) conducting confirmatory clinical trials for the product must be difficult or take a considerable amount of time; and (iv) there must be a reasonable prospect of a certain degree of efficacy and safety (**Table 1**).[3–5] This regulatory system was implemented by Notifications of the MHLW, in 2017, under administrative framework.[3,4] It was also legislated in December 2019, and came into effect in September 2020.[6,7] As of March 2020, the MHLW has approved four drugs under the Notifications of the Conditional Early Approval System (**Table 2**), with the applicants obliged to conduct confirmatory postmarketing clinical studies and other regulatory tasks to manage risks during the postmarketing phase.

In parallel to the Conditional Early Approval System, the MHLW has established the SAKIGAKE Designation System, which was designed to promote Japanese research and development with the goal of increasing early patient access to innovative medical products in 2015.[8] A drug granted approval under the SAKIGAKE Designation System must meet four conditions: (i) it must be innovative; (ii) it must address a serious indication; (iii) it must have prominent effectiveness; and (iv) application for approval must have been submitted in Japan before anywhere else in the world (**Table 1**).[8] Comparing the requirements of the SAKIGAKE Designation System with those of the Conditional Early Approval System reveals differences in the evidence level required for the evaluation of clinical benefit. That is, drugs granted approval under the Conditional Early Approval System require a certain degree of efficacy and safety as evidenced through clinical trials other than confirmatory clinical trials, whereas drugs granted approval under the SAKIGAKE Designation System require to be confirmed prominent effectiveness. Thus, this difference between two approval frameworks in evidence level to evaluate clinical benefit of products in the premarketing phase may affect differences between them in postmarketing regulatory requirements.

Overview of the approval requirements of products already marketed under the conditional approval regulatory system will contribute to the future development of drugs that fill unmet medical needs, leading to prompt access of patients to novel drugs for the treatment of serious diseases that are tolerant to current therapeutic options. In this review, we compared the regulatory requirements of products between these two approval schemes, and we overview the premarketing and postmarketing requirements for drugs approved under the Japanese Conditional Early Approval System.

THE APPROVED DRUGS

As of March 2020, eight drugs have been approved under the SAKIGAKE Designation System (Tepotinib Hydrochloride Hydrate, Entrectinib, Tafamidis Meglumine, Gilteritinib Fumarate, Baloxavir Marboxil, Sirolimus, Viltolarsen, and Borofalan (^{10}B)) and four drugs (Pembrolizumab, Lorlatinib, Trastuzumab Deruxtecan, and Viltolarsen) have been approved under the Conditional Early Approval System (**Tables 2** and **3**). Viltolarsen was approved under both systems. Borofalan (^{10}B) was approved under the SAKIGAKE Designation System, but the dossier was not available at the time of this review (March 2020); therefore, Borofalan (^{10}B) was excluded from the following investigation.

COMPARISON OF PRE-APPROVAL CLINICAL TRIAL PHASE AND INDICATION OF THE DRUGS

Of the seven drugs that have been approved under the SAKIGAKE Designation System, four were approved based on clinical data from phase III trials and three were approved based on those from phase II trials (**Table 3**). All four drugs that received conditional approval under the Conditional Early Approval System were approved based on clinical data from phase II trials (**Table 2**).

In terms of clinical trial phase, SAKIGAKE designation seems to be more confirmative than conditional approval because some SAKIGAKE designated drugs were evaluated in phase III trials. Comparing the cancer drugs, all of those approved under the Conditional Early Approval System are indicated for the treatment of malignant tumors that are tolerant to current standard treatments, whereas none of those drugs approved under the

Table 1 Requirements for approval of drugs under the Conditional Early Approval System and SAKIGAKE Designation System

Regulatory framework	Requirements
Conditional Early Approval System	All of the following 4 conditions
	1. The drug must be indicated for the treatment of a serious disease, such as a disease with high mortality or an irreversible progressive disease.
	2. The drug must have proven clinical utility in line with the following points: There must be few therapeutic, preventive, or diagnostic options currently available for the drug's indication. The clinical utility of the drug is superior to that of current therapeutic, preventive, or diagnostic options with respect to efficacy, safety, and tolerability.
	3. Conducting confirmatory clinical trials for the drug must be difficult or take a considerable amount of time.
	4. There must be a reasonable prospect of a certain degree of efficacy and safety, as evidenced through clinical trials other than confirmatory clinical trials.
SAKIGAKE Designation System	All of the following 4 conditions
	1. The drug must be innovative. In principle, the drug must include a new mode of action.
	2. The drug must address a serious indication, such as a disease with high mortality or a disease with few therapeutic option and continuous severe symptoms.
	3. The drug must have prominent effectiveness.
	4. Application for approval must have been submitted in Japan before anywhere else in the world.

Table 2 Drugs approved under the Conditional Early Approval System (as of March 2020)

Product	Application classification	Indication	Outline of the clinical trial included in the approval submission				
			Region	Phase	Design	Primary endpoint	Number of patients enrolled (name of study)
Pembrolizumab	Prescription drug, (4) Drug with new indications, (6) Drug with a new dosage	Advanced or recurrent microsatellite instability-high solid tumors that have progressed after cancer chemotherapy (limited to patients who are refractory or intolerant to standard treatments)	Global	II	Open-label, uncontrolled study	Response rate	61 (including 7 Japanese patients) (KEYNOTE-164) 94 (including 7 Japanese patients) (KEYNOTE-158)
Lorlatinib	Prescription drug, (1) Drug with a new active ingredient	*ALK* fusion gene-positive unresectable advanced and/or recurrent non-small cell lung cancer with resistance or intolerance to ALK tyrosine kinase inhibitor(s)	Global	I/II	Open-label, uncontrolled study	Response rate	276 (including 39 Japanese patients) (1001)
Trastuzumab Deruxtecan	Prescription drug, (1) Drug with a new active ingredient	*HER2*-positive, unresectable or recurrent breast tumors that have treated chemotherapy (limited to patients who are refractory or intolerant to standard treatments)	Global	II	Open-label, uncontrolled study	Response rate	253 (including 56 Japanese patients) (U201)
Viltolarsen	Prescription drug, (1) Drug with a new active ingredient	Duchenne muscular dystrophy with a deletion in the dystrophin gene amenable to exon 53 skipping therapy	Japan	I/II	Open-label, uncontrolled study	Dystrophin protein level	16 (P1/2)
			United States and Canada	II	Period 1 (until week 4) Placebo-controlled, randomized, double-blind, parallel group study Period 2 (weeks 5–24) Open-label, uncontrolled study	Dystrophin protein level	Period 1: Placebo, 5; Drug, 11 Period 2: Drug 16 (201)

Table 3 Drugs approved under the SAKIGAKE Designation System (as of March 2020)

Product	Application classification	Indication	Outline of the clinical trial included in the approval submission				
			Region	Phase	Design	Primary end point	Number of patients enrolled (name of study)
Tepotinib Hydrochloride Hydrate	Prescription drug, (1) Drug with a new active ingredient	Unresectable, advanced or recurrent *MET* exon 14 skipping mutation-positive non-small cell lung cancer	Global	II	Open-label, uncontrolled study	Response rate	130 (including 17 Japanese patients) (VISION)
Entrectinib	Prescription drug, (1) Drug with a new active ingredient	*NTRK* fusion-positive, advanced/ recurrent solid tumors	Global	II	Open-label, uncontrolled study	Response rate	207 (including 16 Japanese patient) (STARTRK-2)
Tafamidis Meglumine	Prescription drug, (4) Drug with a new indication, (6) Drug with a new dosage	Delay of peripheral neurologic impairment in patients with transthyretin familial amyloid polyneuropathy or transthyretin amyloid cardiomyopathy (wild-type or variant)	Global	III	Placebo-controlled, randomized, double-blind, parallel-group study	All-cause mortality Frequency of cardiovascular-related hospitalizations	Placebo, 177 (including 5 Japanese patients) Drug, 264 (including 12 Japanese patients) (B3461028)
Gilteritinib Fumarate	Prescription drug, (1) Drug with a new active ingredient	*FLT3* mutation-positive relapsed or refractory acute myeloid leukemia	Global	III	Open-label, randomized study	Overall survival	Control, 86 Drug, 169 (0301)
Baloxavir Marboxil	Prescription drug, (1) Drug with a new active ingredient	Influenza A or B virus infection	Global	III	Placebo-controlled and oseltamivir phosphate-controlled, randomized, double-blind, parallel-group study	Duration of influenza illness	Placebo, 231 Oseltamivir, 377 Drug: 456 (T0831)
			Japan	III	Open-label, uncontrolled study	Duration of influenza illness	104 (T0822)
Sirolimus	Prescription drug, (3) Drug with a new route of administration	Tuberous sclerosis complex-associated skin lesions	Japan	III	Double-blind, parallel group study	Improvement in angiofibromas	Placebo, 32 Drug, 30 (NPC-12G-1)
				III	Open-label, uncontrolled study	Improvement in angiofibromas	Placebo, 32 Drug, 62 (NPC-12G-2)
Viltolarsen	Prescription drug, (1) Drug with a new active ingredient	Duchenne muscular dystrophy with a deletion in the dystrophin gene amenable to exon 53 skipping therapy	Japan	I/II	Parallel group study	Dystrophin protein level	16 (P1/2)
			United States and Canada	II	Period 1 (until week 4) Placebo-controlled, randomized, double-blind, parallel group study Period 2 (week 5–24) Open-label, uncontrolled study	Dystrophin protein level	Period 1: Placebo, 5; Drug, 11 Period 2: Drug 16 (201)

Borofalan (^{10}B) was approved in March 2020, but the approval dossier was unavailable at the time of this review.

SAKIGAKE Designation System have such an indication (**Tables 2** and **3**). There is no therapeutic option available at all for Duchenne muscular dystrophy, which is the indication of Viltolarsen approved under the Conditional Early Approval System. Thus, the Conditional Early Approval System appears to be targeting diseases with fewer therapeutic options compared with the diseases targeted by the SAKIGAKE Designation System.

COMPARISON OF APPROVAL CONDITIONS

To examine how the benefit of early availability is balanced against the risk associated with less comprehensive data accumulation, we compared the approval conditions for each drug granted approval under the Conditional Early Approval System and the SAKIGAKE Designation System. For all of the drugs approved under the two systems, the applicants are required to implement an appropriate risk management plan in the postmarketing phase. In addition, for all of the drugs, except Baloxavir Marboxil (SAKIGAKE Designation System) and Pembrolizumab (Conditional Early Approval System), the applicants are also required to conduct a postmarketing use-results survey of all patients treated with the product.[9–18] Furthermore, for each of the drugs approved under the Conditional Early Approval System, the applicants have additional requirements that must be fulfilled as described below.

Pembrolizumab is indicated for advanced or recurrent microsatellite instability-high (MSI-High) solid tumors that are tolerant to standard treatments. The pre-approval clinical study design for Pembrolizumab is a basket trial, in which cancers are classified by common genomic mutation rather than by the conventional approach of classifying by tissue of origin. Two global phase II trials were conducted for Pembrolizumab, one examining the efficacy and safety of Pembrolizumab in patients with MSI-High colorectal cancer (KEYNOTE-164) and the other examining the efficacy and safety of Pembrolizumab in patients with MSI-High noncolorectal cancer (KEYNOTE-158). In KEYNOTE-158, the study was limited to 20 types of MSI-High noncolorectal cancer.[15] Thus, Pembrolizumab appears to be effective in MSI-High solid tumors, including colorectal and noncolorectal tumors[15]; however, data on noncolorectal tumors was limited in the application for conditional approval. Thus, the MHLW and Pharmaceuticals and Medical Devices Agency of Japan (PMDA) require postmarketing confirmation of the efficacy and safety of Pembrolizumab in patients with noncolorectal cancer, and, if the expected clinical benefit is not confirmed in MSI-High noncolorectal cancers, the current label indication will be changed.

Lorlatinib is an anaplastic lymphoma kinase-tyrosine kinase (ALK-TK) inhibitor indicated for use in patients with unresectable non-small cell lung cancer that is tolerant to standard therapies. A global phase I/II clinical trial was conducted to investigate the efficacy of Lorlatinib in patients with *AKK* fusion gene-positive advanced and/or recurrent non-small cell lung cancer that had progressed after ALK-TK inhibitor therapy. Although the response rate was 47.2%, 38.9% of all patients showed central nervous system (CNS) disorders, including memory impairment, cognitive disorder, irritability, amnesia, and anxiety.[16] Other ALK-TK inhibitors do not show CNS disorders.[16] The underlying mechanism of Lorlatinib-induced CNS disorders remains unknown. To manage the risks of Lorlatinib treatment during postmarketing, the applicant is required to ensure that the product is prescribed by physicians with sufficient experience treating non-small cell lung cancer and that the product is available only at specified medical institutes and pharmacies, which themselves have specific requirements to manage risks associated with the product during the postmarketing phase.[16]

Trastuzumab Deruxtecan is indicated for the treatment of HER2-positive malignant breast tumors tolerant to standard treatments. A global phase II clinical trial was conducted to evaluate the clinical benefit of Trastuzumab Deruxtecan. Trastuzumab Deruxtecan was administered to patients with HER2-positive, unresectable, and/or metastatic breast cancer who had received two or more prior anti-HER therapies.[17] The main efficacy outcome was objective response rate, which was 60.6%, including a complete response rate of 4.4% and a partial response rate of 56.1%. Although the true end point of anticancer drug trials is overall survival rate, data on the true end point was not provided in the approval submission. Therefore, the applicant is required to conduct a postmarketing phase III clinical trial and provide healthcare professionals with the results soon after completion of the trial.[17] If the phase III trial fails to show the expected clinical benefit, the product will be withdrawn or the label indication will be changed.

Viltolarsen is indicated for the treatment of Duchenne muscular dystrophy amenable to dystrophin exon 53 skipping. A Japanese phase I/II clinical trial and a US/Canada phase II clinical trial were conducted to evaluate the efficacy and safety of Viltolarsen. The primary efficacy end point was the increase of dystrophin protein in the muscle after injection of Viltolarsen. In both trials, immunoblot analysis revealed that dystrophin increased. The US/Canada trial showed that function improved in patients treated with Viltolarsen with respect to walking and standing up from the floor compared with individual patient data recorded prior to the study.[18] Patients with Duchenne muscular dystrophy show severe muscle weakness, which typically leads to death before the age of 30 years.[18,19] Considering the seriousness of Duchenne muscular dystrophy, Viltolarsen was granted conditional approved with the requirement that the applicant evaluates the efficacy, safety, and clinical tolerability of Viltolarsen via a postmarketing phase III clinical trial and a registry study of Japanese patients with dystrophinopathy.[20]

Taken together, drugs approved under the Conditional Early Approval System are required more approval conditions specific to each drug than those under the SAKIGAKE Designation.

DISCUSSION

Unmet medical needs include rare diseases with few therapeutic options, subpopulations of diseases that are tolerant to conventional pharmaceutical treatments, serious diseases that are irreversibly progressive, and diseases with a high rate of mortality. For medicinal products filling these unmet medical needs, waiting for the completion of confirmatory clinical trials with a statistically rational experimental design is incompatible with the concept of providing patients

with prompt access to potentially lifesaving products because of the often-limited size of these patient populations. When there are no therapeutic options available, clinical benefit must be evaluated by considering whether the benefit of early provision of the product outweighs the risk of having a less comprehensive set of data than conventionally required data for marketing approval. Under the Conditional Early Approval System, the usual premarketing regulation to confirm clinical benefit is partly substituted with postmarketing regulations, such as the requirement to implement a postmarketing risk-management plan, conduct a postmarketing use-results survey, or evaluate clinical benefit via postmarketing confirmatory clinical trials.

Indeed, the drugs so far approved under the Conditional Early Approval System were approved with such conditions. That is, the applicant for Pembrolizumab is required to provide data on clinical benefit in MSI-High noncolorectal tumors through ongoing phase II studies and a use-results survey after postmarketing; the applicant for Lorlatinib is required to minimize the risk of CNS injury by cooperating with specified physicians, medical institutions, and pharmacies; and the applicants for Trastuzumab Deruxtecan and Viltolarsen are required to perform confirmatory clinical trials in the postmarketing phase. Thus, the Conditional Early Approval System might mark a paradigm shift from macro-regulation to micro-regulation of drug approval, leading to a precision regulatory system.

Unforeseeable risks are important regulatory concerns in the postmarketing phase of drugs granted approval under the Conditional Early Approval System. However, registry data and the Medical Information Database Network (MID-NET) can facilitate risk surveillance and mitigate some of these risks. For example, a registry-based postmarketing surveillance system has been initiated for amyotrophic lateral sclerosis.[21] In Japan, many scientific societies are currently preparing frameworks to collect real-world data and collect them in registries for efficient postmarketing surveillance.[22] MID-NET has been developed for the assessment of drug safety with the cooperation of 23 hospitals that provide real-world electronic medical record data, administrative claims data, and diagnosis procedure combination data.[23] The data are updated every 3 weeks or 1–3 months depending on the type of data. MID-NET is expected to be a major data resource for postmarketing drug safety assessments conducted by the PMDA.[24] Thus, this postmarketing surveillance infrastructure will be useful for making regulatory decisions on the benefit–risk balance of the products granted marketing approval under the Conditional Early Approval System.

The regulatory framework of the Conditional Early Approval System was legislated in December 2019 and came into effect in September 2020. It is expected that this regulatory framework will push forward the research and development of pharmaceutical products fulfilling unmet medical needs in Japan. Future accumulation of regulatory experiences with the Conditional Early Approval System will promote precision regulatory considerations and contribute to providing patients with prompt access to innovative medical products.

Funding. No funding was received for this work.

Conflict of Interest. The authors declared no competing interests for this work.

Disclaimer. The views mentioned here do not necessarily represent the views and findings of the Ministry of Health, Labour, and Welfare or the Pharmaceuticals and Medical Devices Agency of Japan.

1. US Food and Drug Administration. Fast track, breakthrough therapy, accelerated approval, priority review. <https://www.fda.gov/ForPatients/Approvals/Fast/default.htm>.
2. European Medicines Agency. Conditional marketing authorization <https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation>.
3. Notification No. 1020-1 of 2017 of the PSHEB/PED <https://www.pmda.go.jp/files/000227089.pdf>.
4. Notification No. 0731-1 of 2017 of the PSEHB <https://www.pmda.go.jp/files/000227090.pdf>.
5. Matsushita, S., Tachibana, K., Nakai, K., Sanada, S. & Kondoh, M. A review of the regulatory framework for initiation and acceleration of patient access to innovative medical products in Japan. *Clin. Pharmacol. Ther.* **106**, 508–511 (2019).
6. The Pharmaceutical and Medical Devices Act. Article 23–26, Act No. 63 of 2019 <https://www.mhlw.go.jp/content/000489905.pdf>.
7. Cabinet Order No. 39 of Reiwa 2 <https://www.mhlw.go.jp/hourei/doc/hourei/H200311I0020.pdf>.
8. Ministry of Health, Labour, and Welfare. Strategy of SAKIGAKE <https://www.mhlw.go.jp/english/policy/health-medical/pharmaceuticals/dl/140729-01-01.pdf>.
9. Information on the deliberation results of Tepmetko tablets 250 mg <https://www.info.pmda.go.jp/go/pack/42910E0F1028_1_01/>.
10. Report on the deliberation results of Rozyltrek capsules 100 mg, 200 mg <https://www.pmda.go.jp/files/000232794.pdf>.
11. Report on the deliberation results of Vyndagel capsules 20 mg <https://www.pmda.go.jp/files/000231029.pdf>.
12. Report on the deliberation results of Xospata tablets 40 mg <https://www.pmda.go.jp/files/000228502.pdf>.
13. Report on the deliberation results of Xofluza tablets 10 mg, 20 mg <https://www.pmda.go.jp/files/000225380.pdf>.
14. Report on the deliberation results of Rapalimus gel 0.2% <https://www.pmda.go.jp/files/000225368.pdf>.
15. Report on the deliberation results of Keytruda injection 20 mg, 100 mg <https://www.pmda.go.jp/files/000231921.pdf>.
16. Report on the deliberation results of Lobrena tablets 25 mg, 100 mg <https://www.pmda.go.jp/files/000228981.pdf>.
17. Information on the deliberation results of Enhert for intravenous drip infusion 100 mg <https://www.info.pmda.go.jp/go/pack/42914D0D1026_1_02/>.
18. Information on the deliberation results of Viltepso Injection <https://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/530263_19004A0A1029_1_03>.
19. Emery, A.E. The muscular dystrophies. *Lancet* **359**, 687–695 (2002).
20. Registry of Muscular Dystrophy; Remudy <http://www.remudy.jp/>.
21. Matsuhita, S., Tachibana, K. & Kondoh, M. The clinical innovation network: a policy for promoting development of drugs and medical devices in Japan. *Drug Discov. Today* **24**, 4–8 (2019).
22. A report of the conference of improvements and promotions in the clinical trial environment and developing platform, March 13 2019 <https://www.mhlw.go.jp/content/10801000/000487614.pdf>.
23. Yamaguchi, M. *et al*. Establishment of the MID-NET® medical information database network as a reliable and valuable database for drug safety assessments in Japan. *Pharmacoepidemiol. Drug Saf.* **28**, 1395–1404 (2019).
24. Ishiguro, C., Takeuchi, Y., Uyama, Y. & Tawaragi, T. The MIHARI project: establishing a new framework for pharmacoepidemiological drug safety assessments by the Pharmaceuticals and Medical Devices Agency of Japan. *Pharmacoepidemiol. Drug Saf.* **25**, 854–859 (2016).