December 6, 2023
Medical Device Evaluation Division
Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Instrument & Apparatus 12, Apparatus for Physical Therapy
Term Name	Transcutaneous peripheral nerve stimulator for head
Brand Name	Relivion
Applicant	Sawai Pharmaceutical Co., Ltd.
Date of Application	December 26, 2022 (Application for marketing approval)

Results of Deliberation

In its meeting held on December 6, 2023, 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 and Food Sanitation Council.

The product is designated as a medical device subject to a use-results survey. The product is not classified as a biological product or a specified biological product.

The use-results survey period should be 6 years. The following approval conditions should be attached.

Approval Conditions

1. The applicant is required to take necessary measures, including the dissemination of the guideline for proper use developed jointly with relevant academic societies and offering seminars for physicians with adequate knowledge and experience in the diagnosis and treatment of acute migraine attacks, which will ensure the selection of eligible patients and the provision of appropriate information and instructions to patients to be treated.
2. The applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product until data are gathered from a certain number of cases with chronic migraine and patients aged <18 years, report the survey results to the Pharmaceuticals and Medical Devices Agency, and take other necessary measures.

Review Report

October 27, 2023
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following medical device submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

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Reviewing Office	Office of Medical Devices II

Review Results

October 27, 2023

Classification	Instrument & Apparatus 12, Apparatus for Physical Therapy
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Results of Review

Relivion is a head-worn external neurostimulator for the acute treatment of migraine, which is designed to stimulate the trigeminal and occipital nerve branches on the head surface.

The applicant submitted non-clinical data of Relivion supporting its physicochemical properties, electric safety, electromagnetic compatibility, biological safety, mechanical safety, stability, durability, and performance. The data revealed no particular problems.

For clinical evaluation of Relivion, the applicant submitted the results of a multicenter, prospective, randomized, double-blind, parallel-group study conducted outside Japan in patients with migraine with or without aura (the RIME study).

The primary efficacy endpoint "the proportion of subjects reporting the reduction of migraine headache pain 2 hours from the start of treatment" was 60.00% in the Relivion group and 37.29% in the control group (between-group difference 22.71 points, $P = 0.0180$). The between-group difference was greater than the pre-defined threshold of 20 points. A secondary endpoint "the proportion of subjects who were migraine pain-free 2 hours from the start of treatment" was also higher in the Relivion group (46.00%) than that in the control group (11.86%), demonstrating the clinical efficacy of the Relivion therapy.

The safety endpoint was "the incidence of adverse events from the subject enrollment throughout the end of the study (regardless of a causal relationship to the study device)." A total of 12 adverse events were reported in 8 subjects (11.94%) in the Relivion group and 9 events in 2 subjects (3.13%) in the control group. All of these were mild or moderate known events, most of which resolved without intervention. The results indicated no particular safety concern.

However, the RIME study did not fully evaluate the consistency of the efficacy of Relivion against recurrent migraine. Approximately 30% of the subjects used rescue drugs, which was allowed when the headache persisted. The acute treatment of migraine aims to resolve migraine attacks robustly and quickly and minimize impacts on daily activities, etc., which is, however, difficult to achieve with Relivion alone. For patients who are inadequately responding to the Relivion therapy or unable to wear

Relivion, a treatment strategy must be developed by combining pharmacotherapy with Relivion. At this time, the pharmacotherapy established for migraine treatment should remain the first-line therapy, and the Relivion therapy should be positioned as a new therapeutic option that supplements the pharmacotherapy.

The pharmacotherapy, being established for acute treatment of migraine, has also issues including poor response, ineligibility, decreased treatment adherence due to adverse drug reactions/adverse reactions, and medication-overuse headache (MOH). For patients whose daily activities are interfered by these problems, Relivion is considered a useful and relatively safe non-pharmacotherapy.

Relivion is Japan's first neuromodulation (a therapy that modulates nerve functions by electrical or magnetic stimuli) device for the acute treatment of migraine. For its effective and safe introduction to Japan, treating physicians are required to have adequate knowledge and experience in the diagnosis and standard treatment of migraine, fully understand the clinical positioning, usage, treatment outcomes, etc. of Relivion, provide appropriate information and instructions to patients treated with Relivion, and thereby ensure the proper use of Relivion.

A use-results survey must be conducted to evaluate sufficiency of the proposed safety measures as well as the efficacy and safety of Relivion in Japanese clinical settings, covering the patient populations excluded from the RIME study, while additional measures for risk reduction and proper use are taken as necessary.

As a result of its review, PMDA has concluded that Relivion may be approved for the intended use shown below with the following approval conditions, and that the results should be presented to the Committee on Medical Devices and *In-vitro* Diagnostics for further deliberation.

Intended Use

Relivion is used in the acute treatment of migraine attacks with or without aura to relieve pain by transcutaneous electrical nerve stimulation to the head.

Approval Conditions

1. The applicant is required to take necessary measures, including the dissemination of the guideline for proper use developed jointly with relevant academic societies and offering seminars for physicians with adequate knowledge and experience in the diagnosis and treatment of acute migraine attacks, which will ensure the selection of eligible patients and the provision of appropriate information and instructions to patients to be treated.
2. The applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product until data are gathered from a certain number of cases with chronic migraine and patients aged <18 years, report the survey results to the Pharmaceuticals and Medical Devices Agency, and take other necessary measures.

Review Report

October 27, 2023

Product for Review

Classification	Instrument & Apparatus 12, Apparatus for Physical Therapy
Term Name	Transcutaneous peripheral nerve stimulator for head
Brand Name	Relivion
Applicant	Sawai Pharmaceutical Co., Ltd.
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Proposed Intended Use	Relivion is used in the acute treatment of migraine with or without aura to relieve pain by transcutaneous electrical nerve stimulation to the head.

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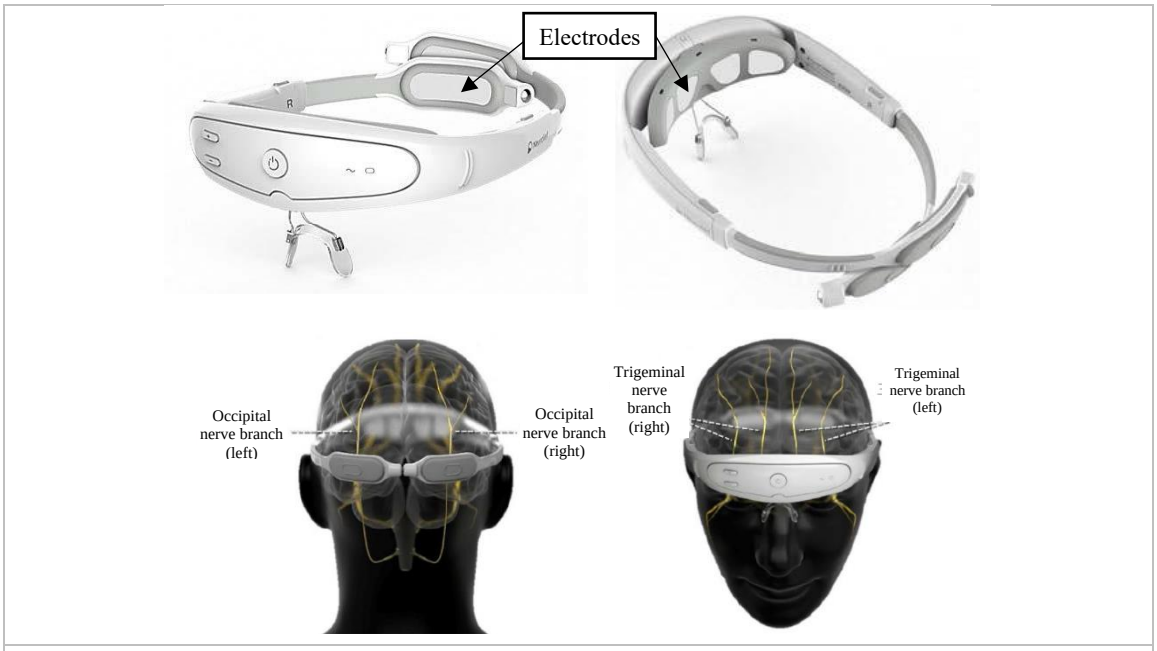
List of Abbreviations

BMI	Body Mass Index
FAS	Full Analysis Set
ICHD	International Classification of Headache Disorders
ITT	Intention To Treat
MBS	Most Bothersome Symptom
mITT	modified Intention To Treat
MOH	Medication Overuse Headache
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs

I. Product Overview

Relivion is a head-worn external neurostimulator used for the acute treatment of migraine that electrically stimulates the trigeminal and occipital nerves on the head surface. Relivion consists of a Relivion device (headset), a charger, electrode pads, a patient mobile application, and a physician interface (Figure 1).

The Relivion headset incorporates 3 pairs of output electrodes that come in contact with the patient's scalp at the frontal region (2 pairs) and occiput (1 pair). When the headset is attached to the head, the 2 pairs of the frontal electrodes are placed over the trigeminal (supraorbital and supratrochlear nerve) branches, and the other pair of the occipital electrodes over the greater occipital nerve branches. The stimulator generates electrical pulses, which are delivered to the scalp via the electrodes and stimulate the trigeminal and occipital nerve branches. The headset electrodes are distant from one another so that optimum nerve stimulation is provided on the head surface layer. Electrical stimuli act on the trigeminocervical complex in the brain stem for the release of antinociceptive neurotransmitters, including norepinephrine (locus coeruleus) and serotonin (raphe nucleus) to suppress pain.



Relivion device (headset)

Electrode pads

Charger

Patient mobile application

Physician interface

Figure 1. Appearance of Relivion

The patient mobile application and physician interface are provided as options for better user convenience. The main functions of the patient mobile application are tracking of treatment protocol, including treatment frequency, intensity level, and duration, and recording of patient's headache status, medication, etc. The physician interface allows physicians to check data entered on the patient mobile application and send information about recommended treatment regimens, such as treatment duration, to the patient mobile application.

II. Summary of the Data Submitted and Outline of the Review Conducted by the Pharmaceuticals and Medical Devices Agency

The following summarizes data submitted by the applicant for the present application and the applicant's responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA).

The expert advisors present during the Expert Discussion on Relivion declared that they did not fall under Item 5 in Chapter 3 of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1. History of Development, Use in Foreign Countries, and Other Information

1.A Summary of the data submitted

1.A.(1) History of development

Migraine is a primary headache disorder that interferes with daily activities, and is the third cause of daily activity interference in people aged <50 years.[1] The reported annual prevalence of migraine is 8.4% in people aged ≥15 years in Japan,[2] and the disease most commonly occurs in young to middle-aged women. At the same time, migraine is also characterized by high prevalence in high school students (9.8%) and junior high school students (4.8%).[3,4]

The diagnosis of migraine has been globally standardized based on the classification system and diagnostic criteria proposed by the International Headache Society. Japan also introduced the diagnostic criteria provided in the third edition of the International Classification of Headache Disorders (ICHD-3).[5] In the migraine classification in the ICHD-3, major migraines are "migraine without aura" and "migraine with aura." "Migraine without aura" is recurrent headache attacks persisting for 4 to 72 hours, typically with unilateral, throbbing, and moderate or severe pain. In "migraine with aura," headache is preceded by unilateral, fully-reversible attacks affecting visual and sensory symptoms, etc. that persist for minutes. The ICHD-3 defines "chronic migraine" as headache occurring on ≥15 days each month for >3 months, which, on ≥8 days per month, has the features of migraine headache.[5] Although the pathophysiological mechanism of migraine has yet to be elucidated, cortical spread depression is thought to be associated with aura, while the trigeminal nerve, which is distributed in the intracranial and epidural blood vessels, are thought to be involved migraine attacks.[6]

In the acute treatment of migraine, it is important to resolve migraine attacks robustly and quickly to promote the patient's functional recovery. The first-line therapy for the acute treatment of migraine is pharmacotherapy both in Japan and overseas, with acetaminophens, non-steroidal anti-inflammatory drugs (NSAIDs), and triptan drugs.[6] Generally known issues in pharmacotherapy are inadequate

response in some patients, patient's decreased adherence due to adverse events, and the potential MOH resulting from regular drug overuse over >3 months.

Neuromodulation is a treatment modality by which electrical or magnetic stimuli are applied to the peripheral or cranial nerve fields to modulate nerve functions. It is a non-pharmacotherapy that has been employed in the treatment of migraine overseas in recent years. Non-invasive neuromodulation devices clinically applied to the treatment of migraine include non-invasive vagal nerve stimulators, transcutaneous trigeminal nerve stimulators, single-pulse transcranial magnetic stimulators, transcutaneous complex occipital/trigeminal nerve stimulators, and remote electrical neuromodulation devices. According to the American Headache Society Consensus Statement, non-invasive neuromodulation provides all patients diagnosed with migraine with access to treatment,[7] and is recommended to patients who wish to avoid pharmacotherapy and those who have a low tolerance to triptans or in whom triptans are contraindicated.

Relivion is a neuromodulation device for the acute treatment of migraine, which relieves pain by simultaneously stimulating the occipital and trigeminal nerves in a non-invasive manner. The RIME study began in 2018 to evaluate the efficacy and safety in the acute treatment of migraine with Relivion. During and after the RIME study, the designs of the occipital electrodes and headset frame were modified 3 times to improve poor electrode contacts encountered in the study. Table 1 compares Relivion with the study devices. The efficacy in the RIME study was evaluated by analyzing the data collected after Modification (1) in the table, while safety was evaluated by analyzing both the population with and without the data collected before Modification (1). The applicant explained that the efficacy and safety evaluations of Relivion were feasible based on the results of the RIME study because the conditions of electric stimulation remained unchanged before and after the modifications as per Table 1.

Table 1. Differences between the study devices used in the RIME study and Relivion

	Timing of modification	Purpose of modification	Main modification
(1)	[redacted] 20[redacted] (During the RIME study)	Improvement of poor electrode contacts observed in the RIME study	The gold coating at the electrode contact point was changed to erosion-resistant [redacted].
(2)	[redacted] 20[redacted]	Complementary modification of (1) and improvement in productivity	[redacted], a component of electrodes, was removed, and alternatively introduced a method using [redacted].
(3)	[redacted] 20[redacted]	Resolutions of a conductivity problem due to electrode deterioration and improvement in productivity	• [redacted] used in the occipital electrodes was changed. • [redacted] of the housing of frontal electrode was changed.

1.A.(2) Use in foreign countries

After the clearance of 510(k) in February 2021, Relivion has been used for the acute treatment of patients with migraine since September 2021 in the US. In Europe, despite the approval in July 2019, Relivion has yet to be on the market because of its sales system not ready for the launch. Table 2 shows the intended use and the number of units used.

Table 2. Intended use and the number of units used overseas (as of June 30, 2023)

Country	Intended use or indication	Approximate number of units used
US	The Relivion® transcutaneous electrical nerve stimulator is indicated for the acute treatment of migraine with or without aura in patients 18 years of age or older. It is a prescription device to be self-used at home.	Number of units shipped: [redacted] Number of patients treated: [redacted] Number of treatments: [redacted]
Europe	Relivion MG cephalic transcutaneous neurostimulator is intended for the treatment of migraine and is indicated for self-administered treatment by patients 18 years of age or older.	No sales

1.A.(3) Malfunctions and adverse events in foreign countries

A total of [redacted] Relivion-related malfunctions and adverse events were reported in the US by June 30, 2023. Table 3 shows the incidences based on the number of patients treated with Relivion and the total number of treatments. Post-treatment malaise, ear-related complaints (pain, muffled hearing, and tinnitus), eye irritation, eye twitching, and neuralgia were unexpected events. All other events were expected. No serious adverse event was reported.

Table 3. Relivion-related malfunctions and adverse events reported in the US

Event	Number of events	Incidence (%)*1	Incidence (%)*2
Post-treatment blurry vision and malaise	[redacted]	0.069	0.001
Dizziness		0.069	0.001
Ear-related complaints (pain, muffled hearing, and tinnitus)		0.206	0.004
Eye irritation		0.069	0.001
Eye twitching		0.137	0.003
Headache/migraine		2.745	0.052
Headache/migraine and nausea		0.137	0.003
Headache and dizziness		0.069	0.001
Nausea		0.069	0.001
Peri- or post-treatment nausea and dizziness		0.069	0.001
Muscle activation		0.069	0.001
Neuralgia		0.137	0.003
Pain		1.167	0.022
Pain (caused by over-tightening of the device)		0.206	0.004
Post-treatment persistent tingling sensation		0.069	0.001
Peri- or post-treatment numbness of the head skin		0.137	0.003
Skin irritation/skin reaction		1.784	0.034
Peri-treatment discomfort		0.755	0.014

*1 Incidence based on the number of patients treated ([redacted])
*2 Incidence based on the total number of treatments ([redacted])

1.B Outline of the review conducted by PMDA

The above data, including the incidences, are discussed later in Section 6.

2. Specifications

2.(1) Performance and safety specifications

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

The proposed performance and safety specifications for Relivion were stimulation output (stimulation parameters and output characteristics), electrical current distribution, durability of the electrodes (frontal and occipital electrodes), [redacted], electrical safety, electromagnetic compatibility, the

requirements for medical electrical equipment and medical electrical systems used in home healthcare settings, particular requirements for the basic safety and essential performance of nerve and muscle stimulators, and biological safety.

2.(1).B Outline of the review conducted by PMDA

PMDA asked the applicant to explain the justification of electrode durability specifications, which differ between the frontal and occipital electrodes.

The applicant's response:

At the beginning, the occipital and frontal electrodes underwent durability testing employing the same method and acceptance criteria ([redacted]). The RIME study, however, revealed a malfunction and deterioration in the occipital electrodes (increased [redacted] of the electrodes due to eroded gold coating). After that, the durability testing of the occipital electrodes employed [redacted] instead of [redacted] as an acceptance criterion. The proposed specifications for the occipital electrodes in the present application are based on the method and acceptance criteria employed in the test conducted.

PMDA's view:

The applicant's explanation is reasonable, in view of the proposed specifications for the occipital electrodes different from those for the frontal electrodes, for easier detection of malfunctions in the occipital electrodes. The review of the tests and acceptance criteria for other performance and safety specifications revealed no particular problem.

2.(2) Physicochemical properties

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

The applicant submitted the test results on the physical parameters pertaining to the physicochemical properties of Relivion. The test samples used were the headset before Modification (3) in Table 1. The applicant explained that the use of the headset before the third modification was reasonable because the modification involved no change in measurement sites and items for the physical parameters. The test results met the predefined acceptance criteria, showing that the physical parameters of Relivion met the product specifications.

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

PMDA reviewed the data supporting the physicochemical properties and concluded that there was no particular problem.

2.(3) Electrical safety and electromagnetic compatibility

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

The applicant submitted data pertaining to the electrical safety and electromagnetic compatibility of Relivion. The data have demonstrated that Relivion meets the international standards that define the general requirements for the basic safety and essential performance of medical electrical equipment (IEC 60601-1:2005/(R)2012+A1:2012), the international standards that define the requirements for the electromagnetic compatibility of medical electrical equipment (IEC 60601-1-2:2014), and the

international standards that define the requirements for the basic safety and essential performance of nerve and muscle stimulators (IEC 60601-2-10:2016). The applicant also submitted operation verification data from a test using the headset and the patient mobile application connected via Bluetooth. The test sample used was the headset before Modification (2) in Table 1. Modifications (2) and (3) would have no impact on Relivion's structure or specifications that assure its electric safety or electromagnetic compatibility. Given this, the applicant explains that it was reasonable to evaluate the electrical safety and electromagnetic compatibility of Relivion, as well as the basic safety and essential performance of the stimulator based on the test results with the headset before the design modifications. All test results met the specifications and assured electrical safety and electromagnetic compatibility of Relivion.

2.(3).B Outline of the review conducted by PMDA

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

2.(4) Biological safety

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

Biological safety of the headset and electrode pads of Relivion were evaluated based on test items for surface-contact medical devices that come into contact with healthy skin surface for a long period (>30 days), The results of cytotoxicity, sensitization, and intradermal reaction tests submitted showed no problematic findings.

2.(4).B Outline of the review conducted by PMDA

PMDA reviewed the biological safety data and concluded that there was no particular problem.

2.(5) Mechanical safety

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

The applicant submitted data pertaining to the mechanical safety of Relivion. The data have demonstrated that Relivion meets the international standards that define the requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment (IEC 60601-1-11:2015+A1:2022) and the results of environment tests. The test samples used were the headset before Design Modification (2) in Table 1. The Modifications (2) and (3) would have no impact on Relivion's structure or specifications that assure its mechanical safety. Thus, applicant explains that it was reasonable to evaluate the mechanical safety of Relivion based on the test results with the headset before the design modifications. All test results met the specifications and assured mechanical safety of Relivion.

2.(5).B Outline of the review conducted by PMDA

PMDA reviewed the mechanical safety data and concluded that there was no particular problem.

2.(6) Stability and durability

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

The applicant submitted the following test results for the durability of Relivion: [redacted], [redacted], [redacted], [redacted], [redacted],

[redacted], [redacted], and [redacted].
The test samples used, in other than [redacted], were the headset before Modification (2) or (3) in Table 1. It has been confirmed that the modifications made after the tests had no impact on the test results, and the applicant explains that the evaluation of Relivion's durability based on the test results with the headset before modifications is reasonable. All test results met the specifications, assuring the durability of Relivion.

2.(6).B Outline of the review conducted by PMDA

The applicant's explanation about the stability evaluation of Relivion:
The part of Relivion that comes into contact with the patient's skin surface is made of materials, including silicon and polyamides with well-known long-term stability warranted for ≥3 years.

PMDA accepted the applicant's explanation, reviewed the stability and durability data, and concluded that there was no particular problem.

2.(7) Performance

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

The applicant submitted test results for the performance of Relivion, including hardware function verification, electrical current distribution, durability of the electrodes (non-single use components), [redacted], and the software of the headset, mobile application, and physician interface. The electrical current distribution test ([redacted]), electrode durability test ([redacted]), and [redacted] used the headset before Modification (2) in Table 1 as sample. The only difference before and after Modifications (2) and (3) was the occipital electrodes. The applicant thus explains that it was reasonable to assess these performance parameters based on the test results with the headset before modifications. All test results met the specifications and assured the performance of Relivion.

2.(7).B Outline of the review conducted by PMDA

PMDA reviewed the performance data and concluded that there was no particular problem.

2.(8) Usage

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

The applicant omitted data on the usage of Relivion because the usage have been shown to meet the international standards pertaining to usability (IEC 60601-1-6:2013 and IEC 62366:2015).

2.(8).B Outline of the review conducted by PMDA

PMDA concluded that there was no particular problem in the omission of data related to the usage of Relivion.

2.(9) Conformity to IEC 62304

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

The applicant submitted the data showing that Relivion meets the international standards that define the software life-cycle process of medical device software (IEC 62304:2015).

2.(9).B Outline of the review conducted by PMDA

PMDA reviewed the data on the conformity to IEC 62304 and concluded that there was no particular problem.

3. Conformity to the Requirements Specified in Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices

3.A Summary of the data submitted

The applicant submitted a declaration of conformity declaring that Relivion meets the standards for medical devices as stipulated by the Minister of Health, Labour and Welfare in accordance with Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (hereinafter referred to as "the Essential Principles") (MHLW Public Notice No. 122, 2005).

3.B Outline of the review conducted by PMDA

PMDA reviewed the conformity of Relivion to the Essential Principles.

1) PMDA's view on the conformity of Relivion to Article 1, which stipulates preconditions, etc. for designing medical devices (particularly requirements for users, such as the expected level of technical knowledge and experience, and the expected level of education and training for users):
   As described later in Sections "6.B Outline of the review conducted by PMDA" and "7.B Outline of the review conducted by PMDA," the selection of eligible patients, user training, and adherence to the guideline for proper use are important to maintain a risk-benefit balance of Relivion. To this end, necessary measures will be requested in the attached approval conditions.

2) PMDA's view on the conformity of Relivion to Article 2, which stipulates requirements for risk management throughout the product life cycle of medical devices:
   As described later in Sections "6.B Outline of the review conducted by PMDA" and "7.B Outline of the review conducted by PMDA," the efficacy and safety of Relivion must be evaluated in clinical practice in Japan because of the lack of data on clinical efficacy or safety of Relivion in Japan. To this end, PMDA instructed the applicant to conduct a use-results survey.

3) PMDA's view on the conformity of Relivion to Article 3, which stipulates requirements for the performance and functions of medical devices, and to Article 6, which stipulates the efficacy of medical devices:
   As described in Section "2.(7).B Outline of the review conducted by PMDA," the performance of Relivion has been confirmed. In addition, as described later in Sections "6.B Outline of the review conducted by PMDA" and "7.B Outline of the review conducted by PMDA," the clinical study showed favorable outcomes with Relivion. The study confirmed that the selection of eligible patients would ensure the effective and safe use of Relivion. The product conforms to Articles 3 and 6.

4) PMDA's view on the conformity of Relivion to Article 4, which stipulates the shelf-life or durability of medical devices:
   As described in Section "2.(6).B Outline of the review conducted by PMDA," the stability and durability of Relivion have been confirmed. The product conforms to Article 4.

5) PMDA's view on the conformity to Article 7, which stipulates the chemical properties, biological safety, etc. of medical devices:
As described in Section "2.(4).B Outline of the review conducted by PMDA," the justification of the biological safety, etc. of Relivion have been confirmed. The product conforms to Article 7.

6) PMDA's view on the conformity of Relivion to Article 17, which stipulates requirements for information including precautionary advice, etc. to be provided to users through publication or the instructions for use ("Information for Precautions, etc."):
As described later in Sections "6.B Outline of the review conducted by PMDA" and "7.B Outline of the review conducted by PMDA," treating physicians' adequate knowledge and experience in the diagnosis and treatment of acute migraine attacks, the selection of eligible patients, and appropriate instructions to users on the use of Relivion are important to maintain its risk-benefit balance. To this end, relevant information should be provided through the Information for Precautions, etc., the guidelines for proper use, training, and by other means. Accordingly, PMDA instructed the applicant to provide the Information for Precautions, etc. to remind of the use of Relivion strictly in accordance with the guidelines for proper use that contain requirements on treating physicians, eligible patients, training, etc.

Based on the above, PMDA concluded that there is no particular problem with the conformity of Relivion to the Essential Principles.

4. Risk Management

4.A Summary of the data submitted

The applicant submitted a summary of risk management, the risk management system, and its progress in accordance with ISO 14971:2019 "Medical devices—Application of risk management to medical devices."

4.B Outline of the review conducted by PMDA

PMDA comprehensively reviewed the document on risk management taking into account the discussion presented earlier in Section "3.B Outline of the review conducted by PMDA" and concluded that there was no particular problem.

5. Manufacturing Process

5.A Summary of the data submitted

The applicant submitted the data pertaining to the in-process tests of Relivion.

5.B Outline of the review conducted by PMDA

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

6. Clinical Data or Alternative Data Accepted by the Minister of Health, Labour and Welfare

6.A Summary of the data submitted

The applicant submitted the results of the RIME study that evaluated the efficacy and safety of Relivion (study period, November 29, 2018 to August 4, 2020).

6.A.(1) Study methodology

The RIME study was a multicenter, prospective, randomized, double-blind, parallel-group study conducted at 12 study sites in the US and Israel to evaluate the efficacy and safety of Relivion in patients with migraine with or without aura. Table 4 is the outline of the RIME study.

Table 4. Outline of the RIME study

Item	Outline
Type of the study	Multicenter, prospective, 2-arm randomized, double-blind, parallel-group, sham-controlled study
Study population	Patients aged ≥18 years with migraine with or without aura
Major inclusion criteria	• ≥18 years of age • Meeting the International Classification of Headache Disorders, the third edition (ICHD-3) (2018) diagnostic criteria for migraine with or without aura • Reporting 1 to 6 migraine attacks per month and other headaches ≤6 days per month
Major exclusion criteria	• Botox treatment in the head region in the prior 3 months • Supraorbital or occipital nerve blocks in the prior month • Migraine, new daily persistent headache, and chronic tension-type headache per the International Classification of Headache Disorders, the third edition (ICHD-3) (2018) diagnostic criteria in the prior 6 months • Onset of headaches >10 days per month • Ongoing medication overuse headache • Use of opioid medications in the prior month • Use of barbiturates in the prior month • Use of implantable metal/shrapnel or electrical devices in the head (excluding dental implants), a cardiac pacemaker or an implantable or wearable defibrillator • Parenteral infusions for migraine within the prior 2 weeks • History of neurosurgical interventions • Use of implantable neurostimulators, surgical clips (above the shoulder line), or medical pumps • Skin lesion or inflammation at the region of the stimulating electrodes • Recent brain or facial trauma (≤3 months prior to the study) • Head circumference <51 or >60 cm
Number of patients enrolled	187
Study period	• Run-in period: 28 + 10 days • Self-practice period after subject enrollment (randomization): ≤14 days • Treatment period: 5 migraine attacks or 70 ± 10 days after randomization visit, whichever comes earlier
Primary efficacy endpoint	Proportion of subjects reporting the reduction of migraine headache pain 2 hours after the start of treatment
Secondary efficacy endpoints	• Proportion of subjects reporting improvement in MBS other than headaches 2 hours after the start of treatment • Proportion of subjects reporting the reduction of migraine headache pain 1 hour after the start of treatment • Proportion of subjects who were migraine pain-free 2 hours after the start of treatment
Safety endpoint	Incidence of adverse events from the subject enrollment (randomization) throughout the end of the study (regardless of a causal relationship to the study device)
Exploratory endpoints	• Proportion of subjects free from most bothersome symptom (MBS), other than headaches, at 2 hours after the start of treatment • Proportion of subjects who were pain-free 1 hour after the start of treatment • Proportion of subjects reporting a positive overall impression on the effect of Relivion • Proportion of subjects reporting the reduction of migraine headache pain at 2 to 24 hours after the start of treatment

Figure 2 is the flowchart of the RIME study. In the RIME study, subjects were randomized after the run-in period (28 + 10 days) in which their eligibility was assessed based on the characteristics of migraine and the frequency of migraine attacks, and trained for the use of Relivion. This was followed by a self-practice period of ≤14 days, during which subjects used Relivion twice, each over 30 to 60 minutes when they had no migraine attacks. In the following treatment period, subjects used Relivion at each onset of migraine attack either up to 5 times or until 70 ± 10 days after randomization visit, whichever came earlier. Subjects were instructed to record migraine pain levels at baseline, and 1, 2, and 24 hours after the start of treatment (0 = none, 1 = mild, 2 = moderate, 3 = severe) after each use of Relivion.

Migraine-related baseline symptoms (nausea, photophobia [brightness], phonophobia, and most bothersome symptom [MBS]) were also recorded. Improvement or no improvement in these symptoms was recorded 1 and 2 hours after the start of treatment. The use of rescue drugs was recorded at each assessment point.

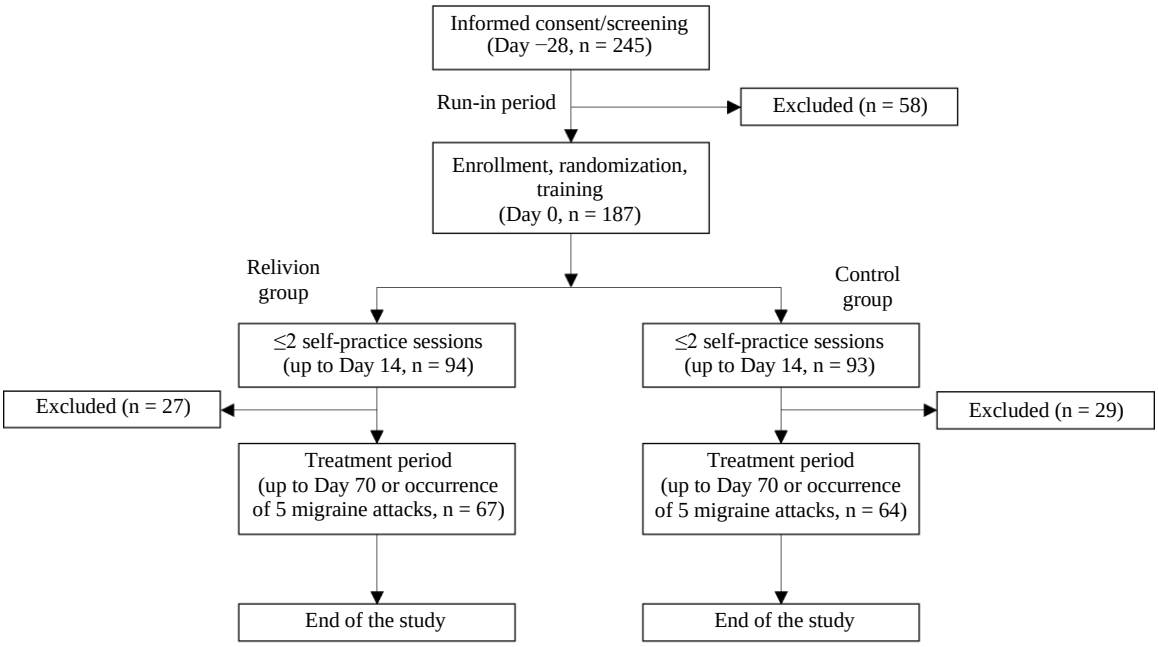


Figure 2. Flowchart of the RIME study

The primary efficacy endpoint of the RIME study was the "proportion of subjects reporting the reduction of migraine headache pain 2 hours after the start of treatment." The superiority of Relivion over the control (sham[i]) was assessed. The sample size of the RIME study was determined with reference to the literature references on the therapeutic effects of non-invasive neuromodulation devices[8-9,10] and pharmaceutical drugs[11] approved in the US (Table 5). Assuming that 45% of the subjects in the Relivion group and 25% of the subjects in the control group achieve pain reduction, 180 subjects are required with a power of 80%, two-sided significance level of 5%, and the randomization ratio of 1:1. Allowing for a dropout of approximately 10%, the sample size was determined as 200.

[i] A group that used weaker output conditions [redacted] than those in the Relivion group (pulse width, [redacted] μs; pulse frequency, 80 Hz; maximum current, 6 mA [frontal region] and 12 mA [occipital region])

Table 5. Reference data used to estimate the pain reduction rates based on the primary endpoint of the RIME study

References	Device/drug		Pain reduction at the start of treatment or 2 hours after the end of treatment	
			Relivion	Control
8	Transcutaneous trigeminal nerve stimulation (e-TNS)		-50%[*1]	-32%[*1*2]
9	Non-invasive vagal nerve stimulation (nVNS)		40.8%	27.6%[*2]
10	Single-pulse transcranial magnetic stimulation (sTMS)		72%	67%[*2]
11	Standard-dose drugs	Almotriptan	48.3%	26.7%
		Eletriptan	60.4%	
		Frovatriptan	42.4%	
		Naratriptan	44.5%	
		Rizatriptan	57.1%	
		Sumatriptan	49.7%	
		Zolmitriptan	50.0%	
	Standard-dose ODTs	Rizatriptan	69.0%	
		Zolmitriptan	65.8%	
	Standard-dose nasal sprays	Sumatriptan	52.6%	
		Zolmitriptan	51.3%	
	Standard-dose subcutaneous injectables	Sumatriptan	75.7%	
	Non-triptans	NSAID	48.0%	
		Acetaminophen	51.7%	
		Aspirin	46.1%	
		Ergot	38.4%	

*1 Change in pain intensity from baseline to 2 hours
*2 The control group received the sham treatment.

A device malfunction occurred in the early stage of the study. It was attributed to the erosion of the gold coating at the electrode contact point, leading to a partial decrease in the electrical output delivered to the treatment site. Corrective and preventive measures were taken against the malfunction by [redacted], 20[redacted] (Modification [1] in Table 1). The subjects who started the study treatment before [redacted], 20[redacted] were excluded from the analyses due to the possibility of faulty treatment with Relivion, and additional 50 subjects were scheduled to be enrolled as replacements. However, the emergence of the COVID-19 pandemic in 2020 had led to the termination of subject enrollment before the planned sample size was reached, considering that the continuation of the study was ethically inappropriate according to the FDA guidance on COVID-19.[12] The statistical analysis report was prepared with the analysis of numeric headache scores added to the endpoints, according to the FDA guidance on statistical analysis.[13]

The full analysis set (FAS) of the RIME study was defined as all subjects randomized, including those who had the treatment before [redacted], 20[redacted]. The intent to treat (ITT) analysis set was defined as subjects included in the FAS who used Relivion or the sham device at least once after the above-mentioned malfunction, including the use for self-practice. The modified intent to treat (mITT) analysis set was defined as subjects in the ITT analysis set who used Relivion or the sham device at least once, except for self-practice, to treat migraine attacks that met the following criteria.

Criteria for migraine attacks

- The subject did not use any analgesics, other pain killers, or cannabis in 4 hours prior to the study treatment.

- No more than 30 minutes has passed after the onset of migraine attack.
- The subject has been pain-free for >48 hours after the last migraine attack.
- The migraine attack did not cause the subject to wake up (to ensure that <30 minutes has passed after the onset of the migraine attack).
- The device log records the study treatment over the total stimulation time of ≥30 minutes in the "pass" session (pass, ≥[redacted] mA stimulation intensity delivered).

The FAS included 187 patients enrolled in the RIME study and randomized. The ITT analysis set included 131 subjects excluding 56 subjects from the FAS. The mITT analysis set included 109 subjects, except 22 subjects in the ITT analysis set whose migraine attacks eligible for the treatment had not been treated during the treatment period. The mITT analysis set was used for the analysis of the efficacy endpoints. The safety endpoint was analyzed using the FAS and ITT analysis set to avoid possible underestimation of Relivion's safety caused by the inclusion of the subjects who started the study treatment before [redacted], 20[redacted].

6.A.(2) Patient characteristics

Table 6 shows the patient characteristics of the ITT analysis set.

Table 6. Patient characteristics (mITT analysis set)

	Relivion (N = 50)	Control (N = 59)
Age (years)	39.9 ± 11.92	40.7 ± 13.05
BMI (kg/m^2)	28.1 ± 7.46	25.0 ± 5.10
Head circumference (cm)	55.4 ± 1.75	55.5 ± 1.94
Sex		
Male	16.0% (8/50)	18.6% (11/59)
Female	84.0% (42/50)	81.4% (48/59)
Race		
Asians	0% (0/50)	5.1% (3/59)
Africans or African Americans	8.0% (4/50)	5.1% (3/59)
Caucasians	90.0% (45/50)	88.1% (52/59)
Others	2.0% (1/50)	1.7% (1/59)
Diagnostic criteria		
Migraine without aura	54.0% (27/50)	62.7% (37/59)
Migraine with aura	46.0% (23/50)	37.3% (22/59)
Use of migraine prophylactic agents	30.0% (15/50)	27.1% (16/59)

6.A.(3) Study results

6.A.(3).1) Efficacy evaluation

The primary endpoint of the RIME study was the proportion of subjects reporting the reduction of migraine headache pain 2 hours after the start of treatment. The "reduction of migraine headache pain" was defined as a decrease in pain intensity from severe/moderate to mild/no pain or mild to no pain.

The secondary efficacy endpoints were the proportion of subjects reporting improvement in their MBS other than headaches 2 hours after the start of treatment, the proportion of subjects reporting the reduction of migraine headache pain 1 hour after the start of treatment, and the proportion of subjects who were migraine pain-free 2 hours after the start of treatment. The exploratory endpoints were the proportion of subjects who were MBS-free, other than headaches, 2 hours after the start of treatment;

the proportion of subjects who were pain-free 1 hour after the start of treatment; the proportion of subjects reporting a positive global impression of the effect of Relivion; and the proportion of subjects reporting the reduction of migraine headache pain 2 to 24 hours after the start of treatment.

In the RIME study, the subjects were allowed to use Relivion up to 5 times. The subject's impression on the effect of Relivion, an exploratory endpoint, was assessed at the end of the study, regardless of treatment frequency. The other endpoints were assessed at the first use of Relivion for a migraine attack that met the above-mentioned eligibility criteria. The endpoints related to pain intensity and MBS were judged as no improvement if the subjects used a rescue drug in 2 hours after the start of treatment.

6.A.(3).1).(a) Primary endpoint

The primary efficacy endpoint "the proportion of subjects reporting the reduction of migraine headache pain 2 hours after the start of treatment" was 60.00% in the Relivion group and 37.29% in the control group, and was significantly higher in the Relivion group ($P = 0.0180$) (Table 7). The baseline migraine severity in the analysis of the primary endpoint was moderate in approximately 50% of the Relivion group and ≥50% of the control group (Table 8). The sample size was determined on the assumption that 45% of the Relivion group and 25% of the control group would achieve pain reduction. The RIME study showed an approximately 15-point higher result in each group. In clinical research in patients with migraine, headaches decreased in placebo groups as well. Because subjects in the control group in the RIME study also wore a device on the head and perceived electrical currents, the subjects' expectation led to the greater-than-anticipated reduction of headache in both groups. Of 5 subjects with missing primary endpoint data, 3 subjects (2 in the Relivion group, 1 in the control group) were evaluated based on the pain intensity 1 hour after the start of treatment used as primary endpoint data. As a result, the treatment was successful in 1 subject in the Relivion group, while failed in the other 2 subjects. The treatment in the remaining 2 subjects was considered as failure because their data on pain intensity 1 hour after the start of treatment were also missing. As per the protocol, multiple imputation for binary data was performed in 3 ways; i.e., by handling all 5 subjects as data missing, handling all 5 subjects as treatment success, or handling all 5 subjects as treatment failure. All analyses showed a higher improvement rate in the Relivion group than the control group with a significant difference, indicating no impact of the missing data on the interpretation of the study results.

Table 7. Proportion of subjects reporting the reduction of migraine headache pain 2 hours after the start of treatment (mITT analysis set)

Relivion [95% CI]	Control [95% CI]	Between-group difference [95% CI]	*P*-value (χ^2 test)	*P*-value (Fisher's exact test)
60.00% (30/50) [46.18%; 72.39%]	37.29% (22/59) [26.08%; 50.05%]	22.71 [4.36; 41.06]	0.0180	0.0217

Table 8. Baseline migraine severity in the analysis of the primary endpoint (mITT analysis set)

Severity	Relivion	Control
Mild	19	14
Moderate	24	37
Severe	7	8
Total	50	59

6.A.(3).1).(b) Secondary endpoints

Table 9 is the results of the secondary endpoints. All secondary endpoints tended to show a better outcome in the Relivion group than the control group.

Table 9. Results of secondary endpoints (mITT analysis set)

	Relivion	Control	*P*-value (χ^2 test)	*P*-value (Fisher's exact test)
Proportion of subjects reporting improvement in MBS other than headaches 2 hours after the start of treatment	80.56 % (29/36*)	60.00% (27/45*)	0.0466	0.0558
Proportion of subjects reporting the reduction of migraine headache pain 1 hour after the start of treatment	42.00% (21/50)	25.42% (15/59)	0.0677	0.1014
Proportion of subjects who were migraine pain-free 2 hours after the start of treatment	46.00% (23/50)	11.86% (7/59)	<0.0001	<0.0001

* Number of subjects after the exclusion of subjects without baseline MBS from the mITT analysis set

6.A.(3).1).(c) Exploratory endpoints

Table 10 shows the results of the exploratory endpoints. The impression on the effect of Relivion was evaluated using the simplified Likert Scale (1 = very dissatisfied, 2 = dissatisfied, 3 = neither dissatisfied nor satisfied, 4 = satisfied, 5 = very satisfied). Positive impression was defined as score ≥4. The proportion of subjects reporting the reduction of migraine pain 2 to 24 hours after the start of treatment was calculated using the number of subjects who achieved headache reduction without a rescue drug 2 hours after the start of treatment and had no moderate to severe headache without a rescue drug or additional stimulation with Relivion in subsequent 22 hours. All exploratory endpoints showed a better outcome in the Relivion group than in the control group.

Table 10. Results of exploratory endpoints (mITT analysis set)

	Relivion	Control	*P*-value (χ^2 test)
Proportion of subjects who were MBS-free, other than headaches 2 hours after the start of treatment	75.00% (27/36*)	46.67% (21/45*)	0.0099
Proportion of subjects who were pain-free 1 hour after the start of treatment	18.00% (9/50)	3.39% (2/59)	0.0116
Proportion of subjects reporting a positive global impression of the effect of Relivion	60.00% (30/50)	28.81% (17/59)	0.0011
Proportion of subjects reporting the reduction of migraine headache pain 2 to 24 hours after the start of treatment	48.00% (24/50)	25.42% (15/59)	0.0143

* Number of subjects after the exclusion of subjects without baseline MBS from the mITT analysis set

6.A.(3).2) Safety evaluation

6.A.(3).2).(a) Safety endpoint

The safety endpoint was "the incidence of adverse events observed after subject enrollment (randomization) through the end of the study (regardless of a causal relationship with the study device)." A total of 21 adverse events were reported from 10 subjects (Table 11); 12 from 8 subjects (11.94%) in the Relivion group and 9 from 2 subjects (3.13%) in the control group. Of these, 7 events were moderate and 14 events were mild in severity. All adverse events but inner ear scratches resolved without intervention. A causal relationship to Relivion could not be ruled out for 7 of 12 events in the Relivion group, but these events were anticipated with Relivion. Note that "migraine" refers to the events that

occurred in the use of Relivion during the self-practice period, while “pain” refers to the events that caused pain at the site where Relivion was worn.

Table 11. Summary of adverse events (mITT analysis set)

			Relivion (N = 67)			Control (N = 64)		
Type of adverse event	**Severity**	**Causality**	**Number of events**	**Number of subjects**	**Incidence**	**Number of events**	**Number of subjects**	**Incidence**
Peri-treatment discomfort	Mild	Related	1	1	1.49%	3	1	1.56%
Numbness of the head skin		Related	1	1	1.49%	-	-	-
Redness of skin		Related	-	-	-	3	1	1.56%
Tingling sensation		Probably related	1	1	1.49%	-	-	-
Spasm		Probably unrelated	1	1	1.49%	-	-	-
Numbness of lips		Probably unrelated	1	1	1.49%	-	-	-
COVID-19, upper respiratory tract infection, and inner ear scratches		Unrelated	3	3	4.48%	-	-	-
Sensation of pressure/ discomfort of the head	Moderate	Related	-	-	-	3	1	1.56%
Migraine		Possibly related	2	1	1.49%	-	-	-
Pain		Possibly related	2	1	1.49%	-	-	-
		Total	12	8*	11.94%	9	2*	3.13%

* Because of multiple adverse events observed in some individual subjects, the total number of subjects does not match the simple sum of the number in the columns above.

In the FAS, 51 adverse events were reported from 21 subjects; 35 from 12 subjects (12.77%) in the Relivion group and 16 from 9 subjects (9.68%) in the control group. Of these, 14 events were moderate and 37 events were mild in severity. A causal relationship to Relivion could not be ruled out for 30 of the 35 adverse events in the Relivion group. All these events were anticipated with Relivion. Adverse events other than those reported in the ITT analysis set were headache, skin irritation, skin lesion, and itchiness (1 event each) in the Relivion group, and chest pain, dizziness, acute pharyngitis streptococcal, impetigo, diarrhoea, orthostatic hypotension, and spondyloarthropathy (1 event each) in the control group. Acute pharyngitis streptococcal, impetigo, diarrhoea, orthostatic hypotension, and spondyloarthropathy required intervention. Spondyloarthropathy was only the event persisting even after interventions. However, the event was moderate and insignificant, and was considered to have no impact on the safety of Relivion. The adverse events other than spondyloarthropathy resolved with or without intervention.

6.A.(3).2).(b) Malfunctions

In the FAS, 19 device malfunctions were reported (12 in the Relivion group, 7 in the control group). The malfunctions were poor contact of the occipital electrodes (12 events), poor response of the application (2 events), device damage (2 events), failure to power on the device (1 event), poor connection between the device and the application (1 event), and battery depletion (1 event). Each malfunction was addressed by replacing the device, instructing how to wear the device, or reinstalling the application. No malfunction-related adverse event was reported.

6.B Outline of the review conducted by PMDA

PMDA's focused on the following points:

(1) Justification of the study design
(2) Extrapolation of foreign clinical data
(3) Efficacy and safety
(4) Clinical positioning
(5) Target patients
(6) Post-marketing safety measures

6.B.(1) Study design

6.B.(1).1) Justification of blinding

The applicant's explanation about the justification of the RIME study designed in a blinded manner:

The RIME study was designed with reference to clinical studies of CEFALY (unapproved in Japan),[8,14] which is a US-approved device with a mechanism of action similar to Relivion. Accordingly, the protocol of the RIME study allowed the use of a sham device to deliver a certain level of electrical stimuli. To ensure the blindness of the study, subjects in both treatment and control groups needed to feel that they were treated. Subjects were tested for the perception of electrical current,[15] based on which all participants of the RIME study were to be stimulated at ≥[redacted]-mA as perceivable level. This condition was included in the eligibility criteria for migraine attacks. Table 12 shows the output conditions of Relivion in the Relivion group and the sham device in the control group in the study. The parameters for the sham device were determined taking account the difference in the number of the electrodes, with reference to the study design of CEFALY.

In the RIME study, to confirm the blindness, each subject was questioned which treatment group they thought they had been allocated to. This blindness assessment was conducted after device training while subjects were migraine-free after randomization. Once the migraine treatment had started, subjects could become aware of which group they were in based on the degree of the reduction of migraine pain, and that could make the blindness assessment inaccurate during the actual treatment. For the same reason, the primary endpoint was evaluated after the first treatment in the study, although the study device could be used for up to 5 migraine attacks. Both in the Relivion and control groups, each subject chose the intensity of electrical current they felt comfortable with during the training session and the actual treatment. As shown in Table 12, the output conditions of electrical current differed between the 2 groups. However, in the non-cross-over study in which subjects had no chance to compare Relivion and the sham device, the subjects were very unlikely to judge on the group they were in based on the current intensity. Therefore, when the blindness was maintained during the migraine-free period, the blindness was considered to have been maintained throughout the treatment period.

Table 13 shows the results of blindness assessment. The answers to the question, and interactions between the answer and the treatment were added to a logistic regression model. The *P*-value for Type III test of the interactions calculated by using this model was 0.9171. The possible loss of blindness can be ruled out for the following reasons: While 38.00% of the Relivion group answered that they were in the Relivion group, 60.00% of this group answered that they could not know their assigned treatments; and as described above, the test showed no statistical difference. In the control group, only 10.17% of

the subjects answered that they were in the control group. Those results indicated that the use of the sham device was effective in maintaining the blindness. The subjects' impression on their treatment is not considered to have affected the results of the RIME study.

Table 12. Output conditions in the Relivion, CEFALY and control groups in clinical studies

		Relivion (RIME study)		CEFALY (ACME study)		CEFALY (PREMICE study)	
		Relivion	Control	CEFALY	Control	CEFALY	Control
Pulse width (μs)		[redacted]		250	250	250	30
Pulse frequency (Hz)		80		100	3	60	1
Maximum intensity (mA)	Trigeminal nerve channel	6		16	Unknown	16	1
	Occipital nerve channel	12		-	-	-	-

Table 13. Blindness assessment (mITT analysis set)

Blindness assessment	Relivion	Control
Unable to judge	60.00% (30/50)	77.97% (46/59)
Probably the control group	2.00% (1/50)	10.17% (6/59)
Probably the Relivion group	38.00% (19/50)	11.86% (7/59)

PMDA's view:

The study blindness was assessed during the migraine-free training session prior to the treatment, which was appropriate. Subjects could have guessed which group they were in based on the therapeutic effects if the assessment was conducted after the start of the treatment. The results of the blindness assessment (Table 13) indicate that greater number of subjects in the Relivion group were able to guess their treatment group correctly than those in the control group. This is considered an inevitable result in view that the Relivion group could receive higher-power stimuli than the control group did. Because 60.00% of subjects in the Relivion group and 77.97% of those in the control group answered that they could not know the group they were in, a certain level of blindness was considered maintained.

6.B.(1).2) Effects of the premature termination of subject enrollment

Subject enrollment in the RIME study was terminated before reaching the planned sample size of 200 because of the COVID-19 pandemic. Finally, the FAS included 187 subjects, the ITT analysis set 131 subjects, and the mITT analysis set 109 subjects. The applicant explained the impact of the smaller-than-planned sample size on the clinical evaluation of Relivion as follows:

The following are anticipated statistical impacts of the smaller number of subjects enrolled than planned:

- The power decreases to approximately 66%, which increases the possibility that a significant difference between the Relivion and control groups is not detected (Type II error) even when such difference is present.
- *P*-values tend to be high, increasing the possibility of failing to meet the original significance level, $\alpha = 0.05$.

Although the possibility of Type II error increases, the originally planned statistical analysis showed the *P*-value for the primary endpoint of approximately 0.0180, indicating a significant difference. This result suggests that the impact of the decreased sample size was negligible. Because the significance level, $\alpha = 0.05$, remained unchanged, there was no impact on Type I error.

PMDA's conclusion:
The applicant's explanation was acceptable. The smaller-than-planned sample size did not give an advantage in the hypothesis verification in the RIME study, and no question will arise over the interpretation of the results of the RIME study.

6.B.(2) Extrapolation of foreign clinical data

The applicant's explanation about the extrapolation of the foreign data from the RIME study into Japan:
The Japanese Clinical Practice Guideline for Headache Disorders[6] bases on the international treatment evidence. Albeit different approval status of drugs or medical devices, the treatment selection do not differ largely between Japan and overseas. The medical environment for migraine treatment in Japan also does not substantially differ from other countries. The diagnostic criteria for migraine are based on the ICHD-3,[5] as in other regions outside Japan.

Relivion is a medical device using physical stimuli (electrical stimuli). There is no racial difference in the courses of the supraorbital nerve and greater occipital nerve to which stimuli are applied. Racial and individual differences have been taken into consideration in the arrangement of the electrode pads of Relivion. The size of Relivion arm is adjustable to fit for use in Japanese patients. In fact, the head circumferences of the subjects of the RIME study did not differ from the average head circumference of Japanese people.

Relivion delivers modulated electrical signals to the major nerve pathways around the head to activate the occipital and trigeminal (supraorbital) nerves through both sides of the head. The activated nerves release antinociceptive neurotransmitters, such as norepinephrine and serotonin, to suppress pain. Currently, however, a definite pathophysiological mechanism of migraine has yet to be shown, and the therapeutic mechanism of the Relivion also remains unclear. At the same time, CEFALY, a foreign-approved neuromodulation device similar to Relivion, was reported to have demonstrated a favorable outcome in the treatment (prevention) of migraine in Japan.[16] There is no logical evidence suggesting a racial difference that is significant enough to affect the therapeutic effect of Relivion.

In summary, the extrinsic factors, e.g., the differences in diagnosis, treatment, or treatment environment for migraine, and the intrinsic factors e.g., the racial differences, are considered to have limited influence on the efficacy and safety of Relivion. It is thus possible to extrapolate the results of the foreign clinical study results into Japan.

PMDA's view:
The differences in definitions, diagnosis, treatment modalities, and treatment environment for migraine (extrinsic factors) as well as racial or ethnic differences in the usage and effect of Relivion (intrinsic factors) are not as substantial as to affect the evaluation of Relivion in and outside Japan. It is reasonable to use the results of the RIME study for clinical evaluation in Japan, taking into consideration the comments raised in the Expert Discussion.

6.B.(3) Efficacy and safety of Relivion

6.B.(3).1) Efficacy

PMDA's view:

According to the Japanese Clinical Practice Guideline for Headache Disorders,[6] the acute treatment of migraine is expected to resolve pain and accompanying symptoms immediately. The RIME study demonstrated a therapeutic effect with a between-group difference of >20 points in the proportion of subjects reporting the reduction of migraine headache pain 2 hours after the start of treatment, which was determined as a clinically significant value based on the therapeutic effect, etc. of medication. The result indicates the efficacy of Relivion.

The Guidelines of the International Headache Society for controlled trials of acute treatment of migraine attacks in adults[17] and the Guidelines of the International Headache Society for clinical trials with neuromodulation devices for the treatment of migraine[18] recommend "pain freedom 2 hours after the start of treatment" as primary endpoint. In the RIME study, this was set as a secondary endpoint. The difference between the Relivion and control groups was 34.14 points (95% confidence interval [CI], 16.23-50.18 points). In the acute treatment of migraine, the change in the proportion of subjects who were free from pain 2 hours after the start of treatment was 6.9 to 39.6 points (placebo, 10.6%; active, 17.5%-50.2%) with triptans,[11] approximately 20 points (placebo, 16.6%; active, 200 mg 40.8% in the phase II study: placebo, 8.4%-21.3%; active 200 mg, 29.3%-38.8% in the phase III study) with "Reyvow Tablets."[19] These results suggest a clinically significant therapeutic effect of Relivion.

In comparison with published articles, etc. on the medication for the acute treatment of migraine (triptans and Reyvow Tablets), Relivion yielded a pain reduction rate of 76% and a pain-free rate of 55% 2 hours after the start of treatment,[ii] while these drugs' pain reduction rate and pain-free rate were 42% to 80% and 18% to 50%, respectively.[11, 20, 21] The comparison, although indirect, suggested comparable therapeutic outcomes.

PMDA has concluded that the results of the RIME study demonstrated the clinically significant efficacy of Relivion.

6.B.(3).2) Safety

PMDA's view:

Adverse events anticipated with Relivion were dermatitis and pain around the area covered by the headset, and nerve-related events (e.g., transient numbness, tingling sensation, and spasm of the head skin). In the ITT analysis set of the RIME study, migraine and pain other than those anticipated occurred at a certain rate. No particular safety concern with Relivion was raised because there were neither adverse events reported as causally related to Relivion and required treatment, nor serious adverse event for which a causal relationship to Relivion could not be ruled out.

[ii] To assure the consistency with the evaluation on the medications, the data of subjects with mild migraine at baseline were excluded.

6.B.(3).3) Long-term efficacy and safety

In the RIME study, the efficacy and safety of Relivion were evaluated for up to 70 ± 10 days. The Relivion therapy is a non-radical, symptomatic therapy, and is expected to be repeated for a long term in the post-marketing settings. PMDA asked the applicant to explain the efficacy and safety in repeated use of Relivion.

The applicant's explanation:

The subjects in the RIME study used Relivion up to 70 ± 10 days including the self-practice period and the treatment period. In the self-practice period, subjects used Relivion twice when they were migraine attack-free and ≤5 times at the onset of migraine attacks in the treatment period. Table 14 shows the correlation of pain reduction rates with the frequency of Relivion therapy. The number of subjects decreased with the increased treatment frequency, precluding accurate comparison. However, the pain reduction rates did not tend to decrease with the increased treatment frequency. There was also no clear correlation between treatment frequency and therapeutic effect. An additional analysis of the proportion of subjects reporting the reduction of migraine headache pain 2 hours after the start of treatment, including the results in subjects who had undergone all 5 treatments, showed a pain reduction rate of 64.81% in the Relivion group and 43.85% in the control group (mITT analysis). These results were consistent with the analysis results on first migraine attacks that were treated with Relivion (primary endpoint; 60.00% in the Relivion group, 37.29% in the control group), although a clear conclusion cannot be reached due to the limited number of subjects who used Relivion for multiple times. The results are not suggestive of attenuated therapeutic effect after repeated treatment. The RIME study indicated no clear correlation between the incidence of adverse events and the treatment frequency (Table 15).

Table 14. Pain reduction/resolution at 2 hours after the start of treatment by the frequency of migraine attacks

	Relivion		Control	
Treatment frequency	**Patients achieving pain reduction (resolution)***	**Reduction (resolution) rate (%)**	**Patients achieving pain reduction (resolution)***	**Reduction (resolution) rate (%)**
1	29 (23)/50	58 (46)	22 (7)/59	37 (12)
2	19 (12)/29	66 (41)	15 (5)/36	42 (14)
3	10 (5)/18	56 (28)	11 (1)/21	52 (5)
4	6 (2)/7	86 (29)	6 (3)/10	60 (30)
5	3 (1)/4	75 (25)	2 (1)/4	50 (25)

* Subjects with missing pain intensity data 2 hours after the start of treatment were counted as treatment failure.

Table 15. Number of adverse events and of subjects with adverse events by treatment frequency

	Relivion		Control	
Treatment frequency	**Number of events**	**Number of subjects with events**	**Number of events**	**Number of subjects with events**
0 (self-practice)	9	6/94 (6.4%)	5	5/93 (5.4%)
1	11	5/77 (6.5%)	4	3/81 (3.7%)
2	6	3/51 (5.9%)	4	3/56 (5.4%)
3	4	2/33 (6.1%)	3	2/34 (5.9%)
4	3	1/18 (5.6%)	0	0/15 (0%)
5	2	1/7 (14.3%)	0	0/6 (0%)

The clinical use of Relivion began in September 2021 in the US. Relivion was used in a total of [redacted] cases (total number of treatments, [redacted]) by [redacted] 2022, with the longest duration of use per patient of

approximately [redacted] years. The number of adverse events reported as related to Relivion was [redacted] (incidence based on the number of patients, 4.0%; incidence based on the total treatment frequency, 0.1%). This extremely low frequency of events and the absence of serious events indicate high safety of Relivion. Because patients can discontinue the Relivion therapy anytime, it is unlikely that the therapy is continued when it fails to provide a therapeutic effect. The continuation rate (number of patients continued/[number of patients continued + number of patients discontinued]) by use duration of in the clinical settings shows no tendency to decrease in the long-term use of Relivion. In addition, there has been no serious adverse event or any concern denying the long-term use of CEFALY, the product which works on a principle similar to Relivion's, since its approval in March 2016 in the US. On the basis of these findings, the introduction of Relivion to Japan will require no restriction on the duration or frequency of use.

PMDA's view:
The results of the RIME study and the post-marketing clinical data in the US, although limited, indicate no obvious decrease in the therapeutic effect of Relivion or increase in adverse events with increased treatment frequency or duration. The applicant has expressed their view that no restriction is necessary on the treatment duration or frequency with Relivion for its launch in Japan, which is acceptable. However, the possibility remains that the long-term use of Relivion leads to attenuated pain reduction effect or less frequent use. As described later, patients eligible for the Relivion therapy include those with chronic migraine, who are expected to use Relivion more frequently than the subjects in the RIME study. Treatment outcomes in these patients should be investigated via the use-results survey.

6.B.(4) Clinical positioning

6.B.(4).1) Clinical positioning in comparison with pharmaceutical therapy

The applicant's explanation:
Relivion should be added to the first-line therapeutic options for the acute treatment of migraine regardless of prior pharmacotherapy and the severity or frequency of migraine, for the following reasons:

- Relivion is a non-invasive neuromodulation device. Patients can discontinue the treatment anytime. If the Relivion therapy fails to relieve pain, rescue drugs are available for acute treatment.
- Even in the case where the use of Relivion causes a delay in the start of pharmacotherapy, the patient can choose to switch to pharmacotherapy easily if Relivion fails to relieve pain. Therefore, such delay, even if it occurs, will be no longer than several weeks to several months or is very unlikely to accelerate the progression of migraine symptoms, etc., and thus is clinically acceptable. From the viewpoints of the clinical significance of Relivion and burden on patients (time and cost), it is very unlikely that patients who are already satisfied with existing pharmacotherapy will use Relivion after its launch in Japan. Furthermore, because potential users of Relivion are also assumed to receive medication for acute treatment, a delay in the start of existing pharmacotherapy is unlikely to occur in reality.
- The Relivion therapy has the following clinical significance in pain reduction in the acute treatment of migraine in general:
  - Issues in pharmacotherapy include: inadequate therapeutic effect in some patients; decreased adherence to the treatment due to adverse events; and a certain number of patients ineligible for

pharmacotherapy for some reasons. Relivion can provide a therapeutic option for acute treatment of migraine with a non-pharmaceutical, novel mechanism of action.
  - MOH is one of the issues in the pharmacotherapy. Relivion is expected to reduce the frequency of medication.
- Pain reduction by Relivion in the acute treatment of migraine is not inferior to that of the drugs for acute treatment of migraine (triptans and lasmiditan succinate [brand name, Reyvow Tablets]), although in indirect comparisons.

PMDA's view on the clinical positioning of Relivion:
The Japanese Clinical Practice Guideline for Headache Disorders[6] recommends that patients with migraine be treated regardless of severity whenever pain develops. Particularly, the purposes of the acute treatment of migraine are robust and quick elimination of migraine attacks and the minimization of their impact on daily activities, etc. Pharmacotherapy is the first-line therapy for the acute treatment.

Although the RIME study demonstrated the efficacy and safety of neuromodulation by Relivion, it is difficult to make clear the clinical positioning of Relivion and the pharmacotherapy at this point because of no study directly comparing Relivion with the pharmacotherapy, the standard therapy. Relivion is considered highly safe and effective to reduce or resolve migraine to a certain degree, but it cannot fulfill the purpose of acute therapy by itself for the reasons below. A treatment strategy must be developed by combining the pharmacotherapy with Relivion, bearing in mind the possible cases with inadequate response to the Relivion therapy and difficulty wearing Relivion.
- Some subjects in the RIME study poorly responded to the Relivion therapy. Approximately 30% of the study population used rescue drugs.
- Relivion has not been shown to reduce or resolve pain consistently in each recurrent migraine attack.
- There will be more than a few situations where patients are unable to wear Relivion at the onset of migraine attacks.

At this stage, the pharmacotherapy is the established treatment for migraine and should remain the first-line therapy, while Relivion should be recognized as a new therapeutic option that supplements the pharmacotherapy. The pharmacotherapy established for the acute treatment of migraine has some issues, including poor response, ineligibility, decreased treatment adherence due to adverse drug reactions/adverse reactions, and MOH. For patients whose daily activities are interfered by these problems, Relivion is a useful, safe non-pharmacological therapy.

6.B.(4).2) Use of medication in combination with the Relivion therapy
The applicant's explanation about how drugs should be used in combination with the Relivion therapy:
(1) Albeit no safety concern, the concurrent use of Relivion with a drug is not recommended because of unknown efficacy.
(2) The on-demand use of a drug after the Relivion therapy should preferably be withheld until approximately 2 hours after the start of the Relivion therapy to see the result, taking into account the time to the onset of headache relief effect.

(3) Relivion can be used after medication when the drug does not show adequate therapeutic effect, but the time to the onset of the effect of medication (generally approximately 2 hours) should be taken into consideration.

In the RIME study, subjects used rescue drugs when they had an inadequate response to the Relivion therapy according to (2). However, because of no data on pain reduction 2 hours after the use of rescue drugs, the effect of Relivion cannot be determined based only on the data from those who used rescue a drug. Nevertheless, Relivion is a medical device that physically delivers stimuli (electrical stimuli) and provides a therapeutic effect through its action different from the pharmacological action of drugs. Thus, the efficacy of the drug can be expected even in use when Relivion is ineffective. The RIME study raised no safety concerns on the use of rescue drugs. The real-world data collected in the app after the launch of Relivion in the US market (period, [redacted] 2021 to [redacted] 2023; number of patients, [redacted]; number of cases reported in the mobile application, [redacted]) show that approximately [redacted]% of the patients used drugs in addition to Relivion (at unknown timing). Given no information raising any efficacy or safety concern, the use of drugs needs not be restricted. Although there is no scientific evidence that requires a time interval from the end of the Relivion therapy to the drug administration, it is preferable to have an interval of approximately 2 hours from the start of the Relivion therapy to see the result because the therapeutic effect of the acute treatment of migraine is generally assessed based on the elimination or obvious reduction of headache 2 hours after the start of the treatment.

In the context of the use of drugs according to (3), the efficacy of the Relivion therapy after medication has not been assessed, and the add-on effect of the Relivion therapy remains unclear. Therefore, as mentioned in (1), the concurrent use of the Relivion therapy with a drug in expectation of the add-on effect of the drug is not recommended. Nevertheless, Relivion, acting by a mechanism different from that of drugs, is expected to have efficacy and intended to be used only when medication is not effective enough. Although the time to the onset of therapeutic effects varies by drug, it is recommended that Relivion be used 2 hours after medication because the therapeutic effect of the acute treatment of migraine is generally assessed 2 hours after medication.

PMDA's view:
The applicant's explanation (1) is reasonable. As explained by the applicant in (2), the use of medication to treat migraine persisting after the Relivion therapy is also appropriate, in view of the safety in the use of rescue drugs after the Relivion therapy demonstrated in a certain number of subjects in the RIME study. The study did not use the Relivion therapy in the way mentioned in (3), and the efficacy and safety of Relivion in such use remain unevaluated. As explained by the applicant, however, Relivion may provide a therapeutic effect in patients poorly responding to medication, through its action different from that of drugs. US post-marketing data have raised no significant safety issues in patients who used medication. Inevitably, patients in situations where are they are unable to wear Relivion, e.g., at work or out of the house, will have to choose medication first. Considering such cases, it is acceptable that patients poorly responding to the drug use relatively safe Relivion before taking other additional dug, because it may lead to the prevention of a decrease in treatment adherence due to adverse drug reactions/adverse reactions and MOH, the issues in medication. The applicant's explanation about the time interval between the Relivion therapy and the on-demand medication is reasonable because the

Japanese and overseas guidelines recommend that the therapeutic effect of acute treatment be generally assessed 2 hours after the medication.

PMDA concluded that the applicant's proposed policies on the use of drugs with the Relivion therapy in (1) to (3) are acceptable, taking into consideration the comments raised in the Expert Discussion.

6.B.(5) Target patients

6.B.(5).1) Inclusion of patients with chronic in the target population

PMDA asked the applicant to explain the justification of the target population for the Relivion therapy, which includes the populations excluded from the RIME study, i.e., patients with chronic migraine and those with headache on ≥10 days per month.

The applicant's explanation:

The RIME study excluded patients with chronic migraine and those with headache on ≥10 days per month. The reason for the exclusion was to limit the frequency of migraine attacks in study participants to assure the validity of evaluation. Patients with chronic migraine or frequent migraine attacks often have difficulty in clearly noticing the start of attack and are not sure whether the attack has been persisting due to poor therapeutic effect or it is another episode. The inclusion of these patients in the study could cause complexity for the efficacy analysis. The Guidelines of the International Headache Society for controlled trials of acute treatment of migraine attacks in adults recommend a frequency of ≤8 attacks per month so as to decrease the probability to enroll patients with chronic migraine in clinical studies.

Chronic migraine occurs as a result of the progression of recurrent migraine in some cases. The therapeutic effect of Relivion therapy has been demonstrated in the acute treatment of recurrent migraine. Furthermore, the efficacy of Relivion have been demonstrated in patients with chronic migraine,[22] and although by different principles from Relivion's, direct stimulation and neuromodulation of the trigeminal and occipital nerves have been reported to improve chronic migraine.[23,24] The acute treatment of chronic migraine is the same as that of recurrent migraine. To prevent the progression to MOH, the restriction on the number of days on acute treatment medication is recommended (≤2 days per week). In view of less frequent use of acute treatment drugs, the use of Relivion is possible in accordance with the treatment policy in Japan, and is of clinical significance. The RIME study showed improvement in MBS, a secondary endpoint, suggesting a potential contribution of Relivion to improvement in symptoms accompanying headache.

Relivion is used for chronic migraine in the same manner as for migraine, i.e., starting at the onset of migraine attack and continuing until pain free or 1 hour after the start of the therapy. There is no restriction on the treatment frequency per month, which will likely increase the duration and frequency of use in patients with chronic migraine. Meanwhile, US post-marketing data showed the incidence of adverse events of 0.1% based on the total number of treatments. The data included those from approximately [redacted] patients who used Relivion on ≥90 days with an average treatment frequency of [redacted] per month. Therefore, safety concerns on the frequent use of Relivion in a certain time period is considered negligible.

After launching in Japan, the Relivion therapy will be prescribed and supervised by physicians who fully understand the characteristics of the product. The use of a headache diary, etc. will allow physicians to give patients with chronic migraine appropriate guidance and supervision on the use of Relivion according to their headache types. Physicians will decide to discontinue the Relivion therapy when it is considered ineffective, thus prolonged use of Relivion in non-responders will be prevented.

PMDA's view:
The applicant's explanation is acceptable, and patients with chronic migraine are also eligible for the Relivion therapy, taking into consideration the comments raised in the Expert Discussion. However, patients with chronic migraine suffer headaches more frequently than those with recurrent migraine, precluding accurate assessment of its therapeutic effect. Including this point, the appropriate use of Relivion must be communicated to patients. Such information must be offered through the instructions for use and training, and post-marketing treatment outcomes must be investigated via the use-results survey.

6.B.(5).2) Inclusion of patients aged <18 years in eligible patients

While the RIME study targeted patients aged ≥18 years, there is no age restriction for the Relivion therapy. PMDA asked the applicant to explain the justification of the inclusion of patients aged <18 years in the target population for the Relivion therapy.

The applicant's explanation:
There are no efficacy or safety data of Relivion from patients aged <18 years, and as a general rule, Relivion should be used only in patients aged ≥18 years. However, in light of its promising efficacy, few safety concern, and clinical significance, patients aged <18 years should also deserve careful use of Relivion at physician's discretion. According to the Scammon's growth curve, the development of human nerve system is nearly completed by the age of 12 years. The nerve distribution and response to nerve stimulation in those ages are not considered to differ substantially from those in adults, and Relivion is thus expected to have a therapeutic effect in patients aged <18 years. For the same reasons concerning the efficacy, there is minimal safety concern associated with neurodevelopment. While the skull thickness depends on age, the skull has a high impedance regardless of its thickness. Relivion is designed so that electrical stimuli do not stimulate the nerves inside the skull. On the other hand, the skin on the forehead tends to thicken with age,[25] and patients aged <18 years will be more sensitive to electrical stimuli. However, the electrical current of Relivion is adjustable, allowing patients to select an appropriate current intensity, thus they are very unlikely to be affected by the excessive electrical current. The therapy can be easily discontinued, which keeps the risk of adverse events low. The Relivion therapy is of clinical significance in view of its potential demand in patients aged <18 years, because the prevalence of migraine does not substantially differ between high school students or older and adults.

The eligibility criteria for patients aged <18 years will be specified in the guideline for proper use jointly with relevant academic societies and provided in the instructions for use.

PMDA's conclusion:

Relivion relieves pain through electrical stimuli delivered to the trigeminal and occipital nerves. Given this, the Relivion therapy will have a promising therapeutic effect in patients aged <18 years with anatomically similar nerve distribution to that of patients aged ≥18 years. With the applicant's explanation taken into account, patients aged <18 years are unlikely to have increased risks associated with Relivion. As there are limited medications indicated for patients aged <18 years, the introduction of Relivion as a new therapeutic option is significant. In the issue of the eligibility of patients aged <18 years, it is rather important that physicians with expertise in pediatric migraine select patients who are able to wear and operate Relivion properly, based on their physical and mental growth levels, and give guidance to both patients and parents. No particular age restriction is necessary for the use of Relivion, taking the comments raised in the Expert Discussion into account. Post-marketing treatment outcomes must be investigated via the use-results survey.

6.B.(6) Post-marketing safety measures

Table 16 outlines the training programs for patients and physicians proposed by the applicant. Table 17 is a summary of the draft guideline for proper use developed by relevant academic societies (the Japanese Headache Society, Japanese Society of Neurology, the Japan Neurosurgical Society, and Japan Society of Pain Clinicians).

Table 16. Outline of the training programs

	Item	Timing	Remarks
Patients	Training by physician using the actual device	At prescription	Essential
	Training on how to use the device using paper electronic materials	At prescription	Essential
	Training by a call center staff member via phone or Web	Between prescription and use	Information provision to patients by physicians: essential Optimization of information provided: optional
	Web video training	Between prescription and use	
	Training on the patient app procedure	Between prescription and use	
Physicians	Training by a sales person dedicated for medical devices	At contract between a physician and the marketing authorization holder	Essential
	Training on how to use the physician app (PMI) using paper or electronic materials	At contract between a physician and the marketing authorization holder	It is essential for the marketing authorization holder to provide with Information provision to physicians: essential Optimization of information provided: optional

Table 17. Summary of the guideline for proper use (draft)

	Description
Requirements for medical institutions	There is a physician responsible for the Relivion therapy, who has full understanding of the pathology, course, prognosis, diagnosis, and treatment of migraine (refer to the Japanese Clinical Practice Guideline for Headache Disorders 2021) and adequate knowledge about Relivion (See the requirement for physicians below).
Requirements for physicians	● ≥5-year clinical experience in the treatment of diseases with headache after being licensed as a physician and the completion of a 2-year internship program. ● Ability to make appropriate decisions on whether to continue the therapy based on periodic assessment of the outcome of the Relivion therapy. ● Certified as a specialist doctor by the academic societies related to the treatment of diseases with headache including; • The Japanese Headache Society • Japanese Society of Neurology • The Japanese Society of Internal Medicine (Fellow of the Japanese Society of Internal Medicine) • The Japan Neurosurgical Society • Japan Society of Pain Clinicians
Target patients	Patients to be prescribed with the therapy should meet all of the following criteria: 1. Confirmed to have migraine with or without aura, chronic migraine, or suspected migraine based on thorough examination with reference to the International Classification of Headache Disorders (ICHD-3). 2. Receiving non-pharmacotherapies, such as guidance on sleep and diet, maintenance of proper body weight, stress management, etc. to reduce factors that induce or aggravate migraine (refer to the Japanese Clinical Practice Guideline for Headache Disorders 2021). 3. Having difficulty using or continuing with the medication for the acute treatment of migraine attacks approved in Japan (triptans and lasmiditan) for any of the following reasons ([1] to [4]), or difficulty in daily life activities despite appropriate medication: (1) Inadequate response to triptans or lasmiditan taken 3 times (headache attacks) at appropriate timing* (2) Low tolerance (3) Contraindication or strong safety concerns due to adverse drug reactions (4) Reluctance to use medication 4. Understanding the characteristics of migraine and the proper usage of Relivion. 5. Patients aged <18 years who is old enough for positive diagnosis of migraine. * For patients who have inadequate response to the acute treatment and experience migraine attacks frequently, preventive therapy must also be considered.

Currently, pharmacotherapy has been established for the acute treatment of migraine, but issues remain, i.e., poor response, decreased treatment adherence due to adverse drug reactions/adverse reactions, and MOH. Neuromodulation, safer than pharmacotherapy, is a new therapeutic option that is expected to solve these problems when combined with the pharmacotherapy. For the effective and safe introduction of Relivion to Japan, physicians must have adequate knowledge and experience in the treatment of migraine, fully understand the clinical positioning, usage, treatment outcomes, etc. of Relivion, and provide appropriate information and instructions to patients to be treated with the therapy so as to ensure the proper use of Relivion.

PMDA's conclusion:

The applicant's proposed training programs will provide patients and physicians with essential information, including the usage and the indication, or necessary procedures before use or as needed, which is reasonable. The draft guideline for proper use developed by the relevant academic societies were also reasonable, in view that Relivion be prescribed to eligible patients selected by physicians and

at medical institutions with proven experience in migraine treatment, and taking the comments raised in the Expert Discussion into account. A statement to this effect is to be attached as Approval Condition 1.

7. Plan for Post-marketing Surveillance, etc. Stipulated in Paragraph 1 of Article 2 of Ministerial Ordinance on Good Post-marketing Study Practice for Medical Devices

7.A Summary of the data submitted

The applicant's explanation:

Relivion was a new medical device and there was no similar medical device approved in Japan. The use-results survey is scheduled as per the Table 18.

Table 18. Use-results survey plan

Objective	To evaluate efficacy and safety in patients treated with Relivion in clinical settings
Population	Patients using Relivion according to the intended use or indication and the usage approved
Methodology	Patients aged <18 years and those with chronic migraine: All cases Others: Central registration Patients on the Relivion therapy are registered, and data pertaining to patient characteristics, efficacy, and safety are collected.
Sample size (planned)	300 (including ≥30 patients aged <18 years and ≥100 patients with chronic migraine) Rationale: The incidence of adverse events in the pivotal study was 1.49% to 4.48%. A total of 300 patients are required to detect adverse events with the incidence of 1% in ≥1 patient, with a probability of ≥95%.
Planned survey period	6 years (preparation, 1 year; registration, 3 years and 6 months; follow-up, 1 year; analysis, 6 months)
Key survey items	• Pain reduction rate 2 hours after the start of treatment • Change in efficacy in long-term use (change in pain reduction rate 2 hours after the start of treatment and change in the frequency of migraine attacks) • Seriousness, causal relationship to the therapy, and outcome of adverse events • Malfunctions
Survey items	• Patient information • Migraine status before the Relivion therapy • Relivion therapy status (e.g., duration, presence/absence of aura, use of concomitant or rescue drugs) • Efficacy (pain assessment and MBS) • Safety (adverse events and malfunctions)

7.B Outline of the review conducted by PMDA

Relivion is a first neuromodulation device in Japan for the treatment of migraine. The RIME study in patients with migraine (except chronic migraine) aged ≥18 years was the only clinical study that produced data submitted for the regulatory review. The use-results survey should aim to collect the following information and to take additional measures for risk reduction and proper use as necessary:

- Safety and proper use of Relivion in the medical environment in Japan
- Efficacy and safety against chronic migraine
- Efficacy and safety in patients aged <18 years

The planned sample size of 300 based on the incidence of adverse events in the RIME study is reasonable. It includes 30 patients aged <18 years, the population assumed to have a risk comparable to that in patients aged ≥18 years, to investigate the usage and outcome, and 100 patients with chronic migraine, who develop headache and use Relivion more frequently, to analyze and confirm the tendency of adverse

events. There are no sufficient clinical data of patients aged <18 years and those with chronic migraine, and thus all-case surveillance is considered reasonable.

The follow-up period of 1 year is reasonable. In the clinical settings, expected long-term use of Relivion may raise a concern about possible resistance to the Relivion therapy.

Taking into consideration the other survey items proposed and the comments raised in the Expert Discussion, PMDA has concluded that the applicant's draft use-results survey plan is appropriate and that this survey plan be attached as Approval Condition 2.

III. Results of Compliance Assessment Concerning the New Medical Device Application Data and Conclusion Reached by PMDA

PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The medical device application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

IV. Overall Evaluation

Relivion is a transcutaneous peripheral nerve stimulator that delivers electrical nerve stimuli percutaneously to the head for pain reduction in the acute treatment of migraine with or without aura. The review primarily focused on (1) the efficacy and safety, (2) clinical positioning, and (3) post-marketing safety measures. The following describes PMDA's conclusions based on the comments raised in the Expert Discussion.

(1) Efficacy and safety of Relivion

The RIME study demonstrated the efficacy of Relivion in pain reduction in patients with migraine. There was no particular safety concern with Relivion in view of no serious adverse event for which a causal relationship to Relivion could not be ruled out nor events requiring treatment, despite some causally related to Relivion.

The RIME study excluded patients with chronic migraine due to their frequent headache attacks, which could cause complexity in the judgment and assessment of treatment outcomes. Chronic migraine is a pathological condition resulting from the progression of recurrent migraine symptoms. In light of reported efficacy of Relivion in patients with chronic migraine, Relivion's pain reduction effect in patients with migraine in the RIME study will also be expected in those with chronic migraine. The US post-marketing data revealed no particular safety concerns after frequent use of Relivion over a certain time period. Chronic migraine can be included in the indication of Relivion in the present application, with the condition on the use-results survey to be conducted to confirm Relivion's efficacy and safety in patients with chronic migraine.

(2) Clinical positioning

The RIME study demonstrated a certain degree of efficacy and safety of Relivion. The study, however, did not fully evaluate the consistency in Relivion's efficacy in recurrent migraine, and approximately 30% of the subjects used rescue drugs. The acute treatment of migraine is aimed to resolve migraine attacks robustly and quickly, and minimize their impact on daily activities, etc., which is, however, difficult to achieve with Relivion alone. A new treatment strategy must be developed by employing the combination of pharmacotherapy with Relivion to address cases of inadequate response to the Relivion therapy or inability to wear Relivion. Currently, pharmacotherapy, the established treatment for migraine, should remain the first-line therapy, and Relivion should be recognized as a new therapeutic option that supplements pharmacotherapy.

(3) Post-marketing safety measures

Relivion is the first neuromodulation device in Japan for the acute treatment of migraine. Effective and safe introduction of Relivion to Japan involves physicians with adequate knowledge and experience in the diagnosis and standard treatment of migraine as well as full understanding of the clinical positioning, usage, treatment outcomes, etc. of Relivion. Such physicians should offer appropriate information and instructions to target patients to ensure that Relivion is used properly. To this end, it is essential to adhere to the guideline for proper use developed by the relevant academic societies. This requirement is to be attached as Approval Condition 1.

In addition, the sufficiency of proposed safety measures and the efficacy/safety in clinical use of Relivion in Japan must be confirmed through the use-results survey, involving the patient populations excluded from the RIME study. Additional measures should be taken for risk reduction and proper use as necessary. The period of the use-results survey on Relivion should be 6 years (preparation period, 1 year; patient enrollment period, 3 years and 6 months; follow-up period, 1 year; analysis period, 6 months). These requirements should be attached as Approval Condition 2.

As a result of the above review, PMDA has concluded that Relivion may be approved for the following intended use.

Intended Use

Relivion is used in the acute treatment of migraine attacks with or without aura to relieve pain by transcutaneous electrical nerve stimulation to the head.

Approval Conditions

1. The applicant is required to take necessary measures, including the dissemination of the guideline for proper use developed jointly with relevant academic societies and offering seminars for physicians with adequate knowledge and experience in the diagnosis and treatment of acute migraine attacks, which will ensure the selection of eligible patients and the provision of appropriate information and instructions to patients to be treated.
2. The applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product until data are gathered from a certain number of cases with chronic migraine and

patients aged <18 years, report the survey results to the Pharmaceuticals and Medical Devices Agency, and take other necessary measures.

The product is not classified as a biological product or a specified biological product. The product is designated as a medical device subject to a use-results survey. The period of use-results survey should be 6 years.

PMDA has concluded that the application should be deliberated at the Committee on Medical Devices and *In-vitro* Diagnostics.

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