November 21, 2022
Medical Device Evaluation Division
Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Instrument & Apparatus 12, Physical Therapy Apparatus
Term Name	Extracorporeal shockwave skin ulcer treatment device (newly created)
Brand Name	Duolith SD1 Ultra
Applicant	Karl Storz Endoscopy Japan K.K.
Date of Application	October 27, 2021 (Application for partial change approval)

Results of Deliberation

In its meeting held on November 21, 2022, 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 applied for partial change should be approved with designation as a medical device subject to a use-results survey.

The use-results survey period should be 5 years.

Review Report

August 15, 2022
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).

Classification	Instrument & Apparatus 12, Physical Therapy Apparatus
Term Name	Extracorporeal shockwave pain treatment device
Brand Name	Duolith SD1 Ultra
Applicant	Karl Storz Endoscopy Japan K.K.
Date of Application	October 27, 2021
Items Warranting Special Mention	None
Reviewing Office	Office of Medical Devices II

Review Results

August 15, 2022

Classification	Instrument & Apparatus 12, Physical Therapy Apparatus
Term Name	Extracorporeal shockwave pain treatment device
Brand Name	Duolith SD1 Ultra
Applicant	Karl Storz Endoscopy Japan K.K.
Date of Application	October 27, 2021

Results of Review

Duolith SD1 Ultra (hereinafter referred to as "Duolith") is an extracorporeal shock wave pain treatment device. It is designed to provide low-energy extracorporeal shock wave treatment by modifying the energy level of the conventional electromagnetic extracorporeal shock wave lithotripsy device. Duolith is approved for use for pain relief in patients with refractory plantar fasciitis in Japan and available in clinical practice. The present application is a partial change application submitted to expand the intended use of Duolith to include the treatment of refractory upper and lower limb ulcers in patients with systemic sclerosis, and to add a dedicated handpiece for the treatment of ulcers as a component of Duolith.

The applicant submitted non-clinical data on Duolith to support the electrical safety, electromagnetic compatibility of the device, and the safety and performance of shock wave therapy. The results showed no particular problem.

The applicant submitted the clinical data of Duolith in the form of the results of the "non-randomized controlled study evaluating outcomes of treatment with Duolith versus standard care as a comparator" (hereinafter referred to as the "pivotal study"), which was an investigator-initiated clinical study in patients with systemic sclerosis involving refractory digital ulcers, conducted in Japan. In the pivotal study, the decrease in the total number of ulcers at Week 8 of treatment, the primary endpoint, was significantly greater in the Duolith group than in the standard care group. Although a bias in the total number of ulcers at baseline in both groups may have affected the decrease in the total number of ulcers, the results suggested a certain level of efficacy of Duolith in the treatment of refractory digital ulcers because the proportion of subjects with a decrease in the total number of ulcers, the secondary endpoint, was significantly higher in the Duolith group than in the standard care group. Since the pivotal study was conducted as a non-randomized controlled study, PMDA assessed biases in baseline patient characteristics as well. Taking account of the results of the assessment and the explanation by the applicant, PMDA considered that the evaluation based on the results from the pivotal study was acceptable. In the pivotal study, no serious adverse events occurred, and adverse events for which a causal relationship to the study device could not be ruled out were mild or moderate in severity. All of

the moderate adverse events resolved with drug therapy. Therefore, PMDA concluded that there was no major problem in the safety of Duolith.

In addition, despite very limited clinical data supporting the efficacy of Duolith in the treatment of foot ulcers, PMDA considered that there is no need to limit the indication of Duolith to the treatment of digital ulcers, on the premise that post-marketing information will be continuously collected for the following reasons: i) The treatment options for refractory foot ulcers in patients with systemic sclerosis are very limited and there is a need for such treatment options in clinical practice; ii) in light of the efficacy of Duolith in the treatment of digital ulcers and its mechanism of action, the device is expected to be effective in some patients with refractory foot ulcers, although the efficacy data for treatment of digital ulcers cannot be simply extrapolated into the treatment of foot ulcers; iii) the results of the pivotal study and a feasibility study showed that the number of foot ulcers decreased in some patients after treatment with Duolith, albeit the results were obtained in only limited patients; and iv) there is no significant problem in the safety of Duolith.

Further, PMDA considered that the applicant should collect information on the characteristics of patients eligible for the use of Duolith and on the safety and efficacy of Duolith used in combination with drugs through the use-results survey and should take risk mitigation measures as necessary, for the following reasons: (a) Systemic sclerosis for which Duolith is indicated is an orphan disease, and the efficacy and safety of Duolith were evaluated in the pivotal study that enrolled only 30 subjects; (b) the treatment outcome for foot ulcers is extremely limited.

As a result of its review, PMDA has concluded that Duolith may be approved for the following intended use and that this conclusion should be presented to the Committee on Medical Devices and *In-vitro* Diagnostics for further deliberation.

Intended Use

Duolith SD1 Ultra is indicated for pain relief in patients with refractory plantar fasciitis who have a history of failed conservative therapy for at least 6 months. Shock waves are extracorporeally applied to the affected area in a non-invasive manner to heal or reduce pain.

<u>Duolith SD1 Ultra is indicated for the treatment of refractory upper and lower limb ulcers in systemic sclerosis.</u>

(Underline denotes additions.)

Review Report

August 15, 2022

Product for Review

Classification	Instrument & Apparatus 12, Physical Therapy Apparatus
Term Name	Extracorporeal shockwave pain treatment device
Brand Name	Duolith SD1 Ultra
Applicant	Karl Storz Endoscopy Japan K.K.
Date of Application	October 27, 2021
Proposed Intended Use	Duolith SD1 Ultra is indicated for pain relief in patients with refractory plantar fasciitis who have a history of failed conservative therapy for at least 6 months. Shock waves are extracorporeally applied to the affected area in a non-invasive manner to heal or reduce pain. Duolith SD1 Ultra is indicated for the treatment of refractory upper and lower limb ulcers in scleroderma. (Underline denotes additions.)

Table of Contents

List of Abbreviations

ACR	American College of Rheumatology
EULAR	European League against Rheumatic Diseases
IEC	International Electrotechnical Commission
ISO	International Organization for Standardization
QOL	Quality of Life
WPW	Wolff-Parkinson-White

I. Product Overview

Duolith SD1 Ultra (hereinafter referred to as “Duolith”) is an extracorporeal shockwave pain treatment device, and it is designed to provide low-energy extracorporeal shock wave treatment by modifying the energy level of the conventional electromagnetic extracorporeal shock wave lithotripsy device. The present application is an application for partial change approval for the medical device (partial change application) submitted to expand the intended use of Duolith to include the treatment of refractory upper and lower limb ulcers in patients with scleroderma. The components of Duolith are shown below. A proposed major change to the components in the present partial change application is the addition of the C-ACTOR handpiece, which was developed for the treatment of refractory skin ulcers in patients with scleroderma.

- Main body
- Handpiece (2 types of handpieces, SEPIA handpiece and C-ACTOR handpiece)
- Stand-off (2 types of stand-offs, I and II, to be attached to the tip of the handpiece during treatment)
- Tablet (optional)

Figure 1 presents the photographs of the main body and the added C-ACTOR handpiece of Duolith.

Figure 1. Overview of Duolith
(top, main body; bottom left, C-ACTOR handpiece; bottom right, handpiece tip with stand-off)

The applicant recommends the following method of use for the treatment of refractory skin ulcers in patients with scleroderma:

- Shock waves are applied to the affected area and its surrounding area once a week.
- In principle, shock waves should be applied at an energy level of 0.25 mJ/mm^2 and at a frequency of 4 Hz, with 100 pulses per site. This may be adjusted according to the patient’s condition.

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

The data submitted by the applicant in support of the present partial change application and the applicant's responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below.

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

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

1.(1) History of development

In Japan, there are an estimated 20,000 patients with systemic sclerosis which is designated as an intractable disease (Ministry of Health, Labour and Welfare Public Notice No. 393 dated October 21, 2014). Patients with systemic sclerosis occasionally manifest ischemic skin ulcers due to peripheral circulatory failure. Skin ulcers is usually resolving in summer because blood vessels are dilated, but worsen in winter. In some cases, skin ulcers may not heal throughout the year. Immunosuppressive therapy for systemic sclerosis (primary disease) may delay wound treatment or cause a condition susceptible to concurrent infection due to decreased immunity. Although skin ulcers associated with systemic sclerosis often become refractory, there are few options such as effective drugs for the treatment of skin ulcers in systemic sclerosis. The development of new treatment options is awaited.

Studies on low-energy shock wave therapy in orthopedics suggest that its mechanisms of action are attenuation of the function of pain-sensing nerve terminals and the induction of neovascularization followed by activation of tissue repair. Based on the latter mechanism of action, Duolith is approved in Europe as a therapeutic device for general ulcers caused by diabetes etc. Duolith is also approved in the United State for the treatment of diabetic foot ulcers.

Based on the above, a partial change application was submitted to expand the indication of the extracorporeal shockwave pain treatment device, which has already been approved for the treatment of refractory plantar fasciitis in Japan (23000BZX00252000), and thereby to include the treatment of refractory ulcers in patients with systemic sclerosis.

1.(2) Use in foreign countries

Table 1 shows the status of approval of or license for Duolith in major foreign countries.

Table 1. Status of approval of or license for Duolith in foreign countries (as of October 2021)

Country	Brand name in the country	Date of approval or licensing	Remarks
Europe	Duolith SD1 T-TOP F-SW ultra	October 2015	CE marking as a therapeutic device for general ulcers
US	Duolith SD1 T-TOP & Tower System with C-ACTOR Sepia Handpiece	February 2021	510(k) clearance as a therapeutic device for diabetic foot ulcers (K202112)

The number of sales of Duolith in Europe is [redacted] (as of [redacted] 20[redacted]) and that in the US is [redacted] (as of [redacted] 20[redacted]), with no serious malfunctions or adverse events reported during the post-marketing periods.

1.(3) Use of approved product in Japan

The number of sales of the approved product (indicated for plantar fasciitis) in Japan is [redacted], with no serious malfunctions reported (as of [redacted] 20[redacted]).

2. Design and Development

2.(1) Performance and safety specifications

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

Additional specifications for the performance and safety of Duolith include focal length, frequency of shock waves, measurement of applied voltage of the shock wave generator, hydrophone measurement of shock wave acoustic field distribution, hydrophone measurement of shock wave pressure at the peak pressure point, and energy flux density for the C-ACTOR handpiece newly added to the components. The applicant submitted the data demonstrating the appropriateness of these specifications.

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

PMDA reviewed the data as addressed later in Section "2.(9) Performance" and concluded that there was no particular problem with the specifications newly included in the present partial change application.

2.(2) Physical and chemical properties

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

The applicant omitted the submission of data on physical and chemical characteristics because Duolith uses general electrical components and the characteristics of the materials used in the components are not related to the nature of the medical device.

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

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

2.(3) Electrical safety and electromagnetic compatibility

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

The applicant submitted the data supporting the electrical safety and electromagnetic compatibility of Duolith. The data have demonstrated that Duolith conforms to the international standard which contains the general requirements for the basic safety and essential performance of medical electrical equipment (International Electrotechnical Commission [IEC] 60601-1:2005+A1:2012) and the international standard which contains the electromagnetic compatibility of medical electrical equipment (EN 60601-1-2:2007). The test samples used were [redacted]. All the test results conformed to the specifications, ensuring the electrical safety and electromagnetic compatibility of Duolith.

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

PMDA reviewed the data supporting the electrical safety and electromagnetic compatibility of Duolith and concluded that there was no particular problem with the data.

2.(4) Biological safety

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

The applicant omitted the submission of data on biological safety because Duolith does not directly or indirectly come into contact with blood or body fluid and there is no change in the raw materials of stand-offs that come into contact with healthy skin compared to those used in the approved product.

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

PMDA concluded that there was no particular problem with omitting the submission of data on biological safety.

2.(5) Radiation safety

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

The applicant omitted the submission of data on radiation safety because Duolith does not use radiation.

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

PMDA concluded that there was no particular problem with omitting the submission of data on radiation safety.

2.(6) Mechanical safety

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

The mechanical safety of Duolith was also evaluated based on the standard (IEC 60601-1:2005+A1:2012) described above in Section "2.(3) Electrical safety and electromagnetic compatibility." The applicant omitted the submission of other data for this section.

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

PMDA concluded that there was no particular problem with omitting the submission of other data on mechanical safety.

2.(7) Stability and durability

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

The function and performance of Duolith are not significantly affected by the issues of stability such as material degradation. Therefore, the applicant omitted the submission of data on stability and durability.

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

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

2.(8) Shock wave safety

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

The applicant submitted data supporting the shock wave safety of Duolith to demonstrate its conformity to the international standard for the basic safety and essential performance of equipment for extracorporeally induced lithotripsy (IEC 60601-2-36:2014). Since there is no international standard specifying the basic safety and essential performance of a shock wave treatment device for the indication of Duolith, the applicant evaluated the approved product by referencing to the above standard. The requirements of the above standard are included in the existing performance and safety specifications. The test samples used were [redacted]. The test results conformed to the specifications, ensuring the shock wave safety of Duolith.

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

PMDA reviewed the data supporting the shock wave safety and concluded that there was no particular problem with the data.

2.(9) Performance

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

The applicant submitted data supporting the performance of Duolith in the form of test results concerning the hydrophone measurement of shock wave acoustic field distribution. The test results showed that the performance of the C-ACTOR handpiece conformed to the specifications, ensuring the shock wave performance of Duolith. The test for evaluation of [redacted] was omitted because [redacted].

To support the mechanism of action of shock wave treatment, the applicant submitted [redacted] because there is no established animal model able to reproduce skin ulcers due to systemic sclerosis. The results suggested that shock wave treatment promotes wound healing and neovascularization.

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

PMDA reviewed the data supporting the performance of Duolith and concluded that there was no particular problem with the data.

2.(10) Method of use

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

The applicant omitted the submission of data on the method of use of Duolith because verification of the method of use of Duolith was not required.

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

PMDA concluded that there was no particular problem with omitting the submission of data on the method of use of Duolith.

2.(11) Conformity to IEC 62304

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

The applicant submitted data showing the conformity to the international standard (IEC 62304:2006) that defines the software life cycle process for medical device software.

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

PMDA reviewed the data showing the conformity to the international standard 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 Duolith 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 of 2005).

3.B Outline of the review conducted by PMDA

PMDA reviewed the conformity of Duolith to the Essential Principles.

(1) PMDA's view on the conformity to Article 3, which defines requirements for the performance and functions of medical devices:

- As described in Section "6.B Outline of the review conducted by PMDA" later in this review report, PMDA instructed the applicant to state that the intended use of Duolith is limited to use in patients with systemic sclerosis.

(2) PMDA's view on the conformity to Article 17, which defines requirements for the provision of information to users through instruction for use, etc.:

- As described in Section "6.B Outline of the review conducted by PMDA" later in this review report, PMDA instructed the applicant to provide advice about information on study sites, selection of patients, method for use, etc.

Based on the above, PMDA concluded that there is no particular problem with the conformity of Duolith to the Essential Principles, as long as necessary modifications are made.

4. Risk Management

4.A Summary of the data submitted

The applicant submitted data summarizing the risk management system and risk management activities implemented for Duolith in accordance with International Organization for Standardization (ISO) 14971:2012 (Medical Devices – Application of risk management to medical devices).

4.B Outline of the review conducted by PMDA

PMDA comprehensively reviewed the risk management documents, taking into account the discussion presented in Section "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" mentioned above, and concluded that there was no particular problem.

5. Manufacturing Process

5.A Summary of the data submitted

The applicant omitted the submission of data on the manufacturing process of Duolith because there was no change in the manufacturing site or inspection process compared to the approved product.

5.B Outline of the review conducted by PMDA

PMDA concluded that there was no particular problem with omitting the submission of data on the manufacturing process.

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

6.A Summary of the data submitted

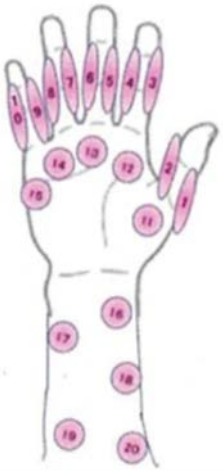
The applicant submitted the clinical data of Duolith in the form of the results of the investigator-initiated clinical study conducted in Japan (hereinafter referred to as "the pivotal study"). The study is summarized in Table 2. The pivotal study aimed to demonstrate the efficacy of Duolith in the treatment of digital ulcers. For the purpose of exploratory assessment, foot ulcers were also treated in patients with digital ulcers and foot ulcers, and such patients were included in the efficacy evaluation. Although [redacted] was used in the pivotal study, [redacted] for Duolith because [redacted] identical with no difference.

Table 2. Summary of the investigator-initiated study

Study design	Non-randomized controlled study using standard care as a comparator
Study population	Patients with systemic sclerosis who have refractory skin ulcer
Study period	November 29, 2013 to May 26, 2015
Number of subjects	[Target sample size] [Number of subjects enrolled] [Analysis population] • A group of subjects treated with the study device ("Duolith group"): 30 subjects Subjects received shock wave treatment with the study device in addition to standard care with medications such as [redacted] • Standard care group: 30 subjects Subjects received standard care with medications such as [redacted]
Study sites	Duolith group • A total of 2 sites: Tohoku University Hospital, [redacted] Standard care group • A total of [redacted] sites: [redacted], and others
Main inclusion criteria	➢ Patients aged ≥18 years at the time of providing informed consent ➢ Patients who meet the diagnostic criteria[1] for systemic sclerosis at the time of providing informed consent ➢ Patients who had digital ulcers at the time of enrollment and who met either of the following 2 criteria: 1) Developed a new ulcer(s) during the use of a drug(s) for treatment of systemic sclerosis-associated ulcers.[2] 2) Have a persistent ulcer despite the use of ≥1 drug for treatment of systemic sclerosis-associated ulcers, which was newly added after the development of the ulcer and used for >4 weeks.
Main exclusion criteria	➢ Patients who started the use of a drug newly added for the treatment of systemic sclerosis-associated ulcers within 4 weeks before enrollment ➢ Patients with concurrent serious cardiac or respiratory dysfunction at the time of enrollment ➢ Patients with concurrent infectious disease at the site of treatment (shock wave application) at the time of enrollment
Prohibited concomitant therapies and prohibited concomitant medications	(1) Prohibited concomitant therapies Therapies with medical devices other than Duolith for the treatment of systemic sclerosis are prohibited throughout the study. (2) Prohibited concomitant medications: None (3) Restricted concomitant medications Do not newly add any of the drugs for treatment of systemic sclerosis-associated ulcers specified in the inclusion criteria during the first 4 weeks of study treatment. Do not start the use of any additional topical agent. However, these do not apply where the use of additional drugs is inevitable for medical reasons

[1] Diagnostic Criteria, Severity Classification, and Treatment Guidelines for Systemic Sclerosis, 2007 Revised Version (in Japanese), 1980 American College of Rheumatology (ACR) Classification Criteria for Systemic Sclerosis, or ACR/European League against Rheumatic Diseases (EULAR) 2013 Classification Criteria for Systemic Sclerosis

[2] Calcium antagonists, antiplatelet agents, anticoagulants, oral prostaglandins, PDE-5 inhibitors, endothelin receptor-blockers, and alprostadil injections. For both the inclusion criteria 1) and 2), patients who had not been previously treated with alprostadil injection were included in the study if they were considered to be ineligible for the use of alprostadil injection.

Study method	(1) Duolith 1) Using the study device, low-energy shock waves are applied to the muscles of both hands. (a) Energy level: [redacted] to 0.25 mJ/mm^2 (b) Number of shock wave impulses and sites of application: Regardless of the presence of ulcers, apply 100 impulses per site (a maximum of 4 impulses per second), for 20 sites each in the right and left hands, 40 sites in total. Start a treatment session with the lateral side of the right thumb, then moves onto the palm, upper arm, and left hand. The session takes up to approximately 60 minutes with breaks.   2) Start the first treatment session at the minimum energy level. Increase the energy level to the maximum level while observing the subject for pain. Start the second and subsequent sessions at the maximum energy level that is tolerable in the subject. 3) Duration of treatment: 7 weeks (once weekly for 7 consecutive weeks, a total of 8 sessions) 4) Follow-up period: Weeks 8 and 12 after the initial shock wave treatment 5) For subjects with foot ulcers, apply shock waves to the feet, following shock wave treatment for the hands. Perform the treatment at a total of 30 sites (15 sites each for the right and left feet) at the same energy level and number of shock wave impulses as those for both hands, regardless of the presence of ulcers. (2) Standard care In the standard care group, informed consent, screening tests, enrollment, and Week 0 of follow-up may occur on the same day. 1) Follow-up/treatment is performed every [redacted] weeks for a total of [redacted] sessions, and the study period ends at Week 12 of follow-up.
Primary endpoint	Decrease in the total number of ulcers at Week 8 of follow-up and treatment [A t-test of the null hypothesis of equal decreases between groups will be performed at a two-sided significance level of 5%]
Main secondary endpoints	• Decrease in the total number of ulcers at Weeks 4 and 12 of follow-up and treatment • Proportion of subjects with a decrease of 20%, 50%, or 70% from baseline in the number of ulcers at Weeks 4 and 8 of follow-up and treatment • Improvement rate in subjective pain assessment using a visual analog scale (VAS), disability assessment using the Health Assessment Questionnaire (HAQ) disability index, and self-assessed QOL based on the EuroQol-5 dimensions (EQ-5D), at Weeks 4 and 8 of follow-up and treatment
Safety endpoints	• Adverse events (including abnormal laboratory finding) • Adverse events related to the study device or malfunctions of the study device

Key results

Major patient characteristics (baseline)

	Duolith	Standard care
Sex	[redacted]	[redacted]
Age	[redacted]	[redacted]
mRSS[3]	[redacted]	[redacted]
Total number of digital ulcers[4]	[redacted]	[redacted]
Number of digital ulcers <5 mm in diameter	[redacted]	[redacted]
Number of digital ulcers ≥5 mm in diameter	[redacted]	[redacted]
Days after diagnosis of systemic sclerosis	[redacted]	[redacted]
Days after development of ulcers	[redacted]	[redacted]

* Mean ± standard deviation (SD), [minimum, maximum]

- The pivotal study enrolled subjects with systemic sclerosis without [redacted]. According to the assessment of the severity of skin thickness at screening, [redacted] of 30 subjects in each group had thickness in the proximal upper and lower limbs (upper arm, thigh) or trunk (anterior chest, abdomen), and subjects with diffuse cutaneous systemic sclerosis accounted for [redacted]% of all subjects, suggesting that the proportion of the patient population was comparable between the groups.

Use of concomitant drugs for treatment of systemic sclerosis-associated ulcers

	Duolith	Standard care
[redacted]	[redacted]	[redacted]

* Use of multiple concomitant drugs in a single subject

Key results

Efficacy

○ Primary endpoint

➢ Decrease in the number of digital ulcers (at Week 8), mean ± SD [minimum, maximum]

Duolith	4.47 ± [redacted] ulcers [redacted]
Standard care	0.83 ± [redacted] ulcers [redacted]
P-value*	$P < 0.0001$

* A t-test of the null hypothesis of equal decreases between groups at a two-sided significance level of 5%

○ Secondary endpoints

➢ Proportion of subjects with a decrease of 20%, 50%, or 70% from baseline in the number of ulcers at Weeks 4 and 8 of follow-up and treatment
  - A significant difference was observed. See Table 3 for details.

➢ Improvement rate in subjective pain assessment (VAS),[5] disability assessment (HAQ),[6] and self-assessed QOL (EQ-5D)[7] at Weeks 4 and 8 of follow-up and treatment

[3] Modified Rodnan Total Skin Thickness Score (mRSS), which is an outcome measure for assessing skin thickness at 17 body sites on a 0 to 3 point scale (0 = normal, 1 = mild, 2 = moderate, 3 = severe) (maximum total score = 51)

[4] The number and size of ulcers were determined based on visual assessment, photography, and central assessment.

[5] Visual Analogue Scale (VAS). A score used for assessment of the severity of pain by subjects. Zero (0) indicates no pain and 100 indicates the worst pain.

[6] Health Assessment Questionnaire (HAQ). A score used to assess the degree of disability in activities of daily living based on the results of a subject questionnaire. Zero (0) indicates the best and 3 indicates the worst.

[7] EuroQol 5 Dimension (EQ-5D). A score used to assess health-related quality of life (QOL) based on the results of a subject questionnaire. One (1) indicates the best and -0.594 indicates the worst.

	• No significant difference at any time point (using the same analysis method as the primary endpoint)
Key results	Safety ➢ Incidence of adverse events • Duolith group: 18 of 30 subjects (60.0%) • Standard care group: 16 of 30 patients (53.3%) ➢ Serious adverse events • Duolith group: 3 events [cardiac failure, worsening of skin ulcer,[8] and anaemia] in 3 of 30 subjects →A causal relationship to Duolith was ruled out for all events. • Standard care group: 1 event [pyrexia] in 1 of 30 subjects ➢ Adverse events for which a causal relationship to the study device could not be ruled out • Six events (5 of 30 subjects) [skin ulcer infection, finger redness, finger swelling, paronychia, Wolff-Parkinson-White (WPW) syndrome, and leg oedema] • Five moderate events resolved with drug therapy • No treatment for mild WPW syndrome.

Table 3. Proportion and number of subjects with a decrease of at least 20%, 50%, or 70% from baseline in the number of ulcers (percentage of subjects to all subjects in each group [%])

Week	Percent decrease from baseline in the number of ulcers	Duolith	Standard care	*P*-value (Chi-square test)
4	20%	26 (86.7%)	10 (33.3%)	< 0.0001
	50%	21 (70.0%)	10 (33.3%)	0.0045
	70%	15 (50.0%)	4 (13.3%)	0.0023
8	20%	28 (93.3%)	15 (50.0%)	0.0002
	50%	26 (86.7%)	13 (43.3%)	0.0004
	70%	21 (70.0%)	8 (26.7%)	0.0008

Figures 2 and 3 show graphs indicating the number of digital ulcers (absolute amount) in each follow-up period. In the Duolith group, a total of 8 sessions of shock wave treatment were performed from Week 0 to Week 7, with follow-up visits at Week 8 and Week 12.

[8] The subject (Case ID: [redacted]) had been hospitalized every winter to prevent cold irritation due to worsening of the primary disease. After the start of study treatment (December 9, 2013), improvement including a decrease in ulcer size was noted, and the subject was discharged from the hospital during the study period (year-end). The subject completed the study on February 3, 2014. Subsequently, the subject was hospitalized due to worsening of ulcers on February 19, 2014, in order to receive local treatment and to prevent cold irritation. Given that the subject had been hospitalized for several months every year to prevent cold irritation, this hospitalization was also considered to be due to worsening of the primary disease. A causal relationship to the study device was ruled out.

Figure 2. Number of digital ulcers (absolute amount) in the Duolith group (abscissa, follow-up period [weeks]; ordinate, number of ulcers)

Figure 3. Number of digital ulcers (absolute amount) in the standard care group (abscissa, follow-up period [weeks]; ordinate, number of ulcers)

Figures 4 and 5 show graphs indicating the number of foot ulcers as exploratory data, not for hypothesis testing. As is the case with digital ulcers, a total of 8 sessions of shock wave treatment for foot ulcers was performed in the Duolith group from Week 0 to Week 7, with follow-up visits at Week 8 and Week 12.

Figure 4. Number of foot ulcers (absolute amount) in the Duolith group (abscissa, follow-up period [weeks]; ordinate, number of ulcers)

Figure 5. Number of foot ulcers (absolute amount) in the standard care group (abscissa, follow-up period [weeks]; ordinate, number of ulcers)

6.B Outline of the review conducted by PMDA

PMDA reviewed the following points mainly, taking account of the comments raised in the Expert Discussion.

6.B.(1) Efficacy and safety of Duolith

The primary efficacy endpoint of the pivotal study of Duolith was "a decrease in the total number of ulcers at Week 8 of follow-up and treatment." The results of the study showed that the total number of ulcers significantly decreased in the Duolith group compared with the standard care group (see the table below). However, there was a bias in the total number of ulcers at baseline in the patients enrolled in the study (see another table below).

Decrease in the number of digital ulcers (at Week 8), mean ± standard deviation (SD) [minimum, maximum]

Duolith	4.47 ± [redacted] ulcers [redacted]
Standard care	0.83 ± [redacted] ulcers [redacted]
P-value*	$P < 0.0001$

* A *t*-test of the null hypothesis of equal decreases between groups at a two-sided significance level of 5%

Number of ulcers at baseline and Week 8, mean ± SD [minimum, maximum]

	Duolith	Usual care
Total number of ulcers at baseline	5.57 ± [redacted] ulcers [redacted]	3 ± [redacted] ulcers [redacted]
Number of digital ulcers at Week 8	1.10 ± [redacted] ulcers [redacted]	2.17 ± [redacted]

In view of the facts that the pivotal study was conducted as a non-randomized controlled study and that the study sites for the Duolith group and those for the standard care group were different, PMDA asked the applicant to explain whether there were biases in patient selection and treatment for ulcers among study sites and whether the efficacy evaluation of Duolith was appropriate based on these biases.

The applicant's explanation:

[redacted]. For this reason, the study sites for the Duolith group were selected and the study was designed as a non-randomized controlled study. [redacted]. In addition, patients with refractory ulcers were enrolled in the study according to certain criteria because the inclusion criteria for refractory ulcers were strictly defined. In the planning stage of the pivotal study, there was a concern that a difference in the total number of ulcers at baseline between the groups would affect the primary endpoint, but the "proportion of subjects with a decrease of >20%, >50%, or 70% from baseline in the number of ulcers" was selected as a secondary endpoint to address the above concern.

Since significant differences were observed in all of these secondary endpoints, the efficacy of Duolith have been demonstrated in the study.

Then, PMDA asked the applicant to explain the impact of seasonal fluctuations in temperature on the efficacy results in consideration of the timing of assessment of subjects in each group and regional differences among study sites because ulcers in patients with systemic sclerosis may worsen or improve with seasonal fluctuations in temperature.

The applicant's explanation:
Figure 6 shows the distribution of the timing of enrollment of subjects in each group.

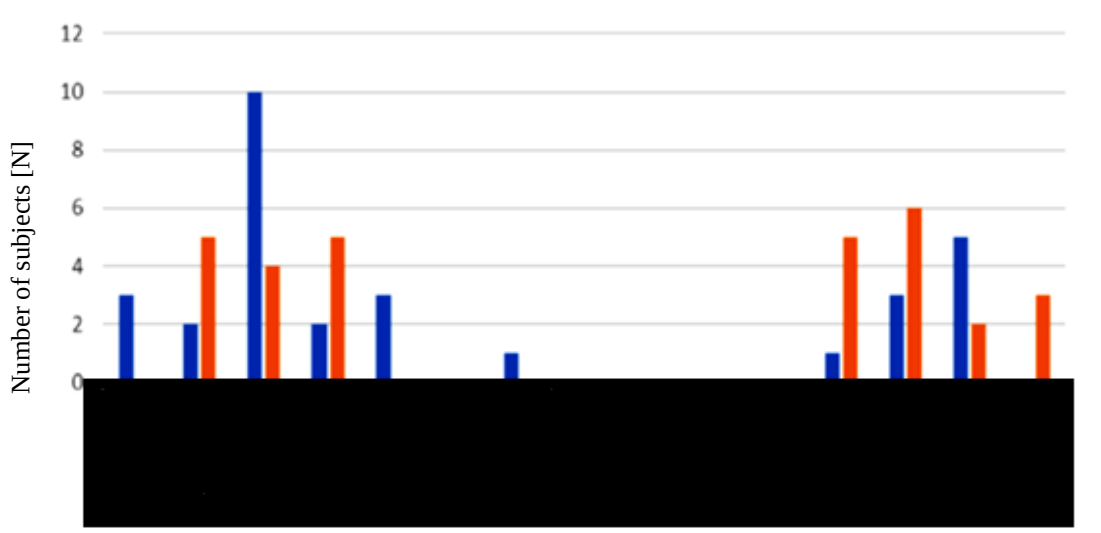


Figure 6. Distribution of timing of enrollment of subjects in each group (blue, Duolith; red, standard care)

In the pivotal study, 23 patients from Miyagi prefecture and 7 patients from Tokyo were included in the Duolith group, while 24 patients from the Tohoku district (Miyagi prefecture, Iwate prefecture, and Aomori prefecture), 3 patients from Gunma prefecture, and 3 patients from Tokyo were included in the standard care group. The above information suggests that there was no significant bias between the Duolith and standard care groups in terms of the timing (season) of enrollment and assessment or regions (sites) where subjects were assessed. Furthermore, according to the results of analysis of individual data from 23 subjects included in the Duolith group at Tohoku University Hospital (Sendai, Miyagi prefecture), ulcers disappeared in 7 of 23 subjects by Week 4 of treatment and in 11 of 23 subjects by Week 8 of treatment. The 23 subjects included 6 subjects who started the treatment in December or January. Ulcers disappeared despite the treatment performed in winter at the study site located in the Tohoku district, suggesting that the improvement of ulcers was attributed to the therapeutic effect of Duolith, not to changes in temperature.

PMDA further asked the applicant to explain the appropriateness of including the treatment of foot ulcers in the indication of Duolith, in view of the fact that the pivotal study was planned to verify the efficacy of Duolith in the treatment of digital ulcers and data on the treatment of foot ulcers were collected in an exploratory manner.

The applicant's explanation:
Although clinical data supporting the efficacy of Duolith in the treatment of foot ulcers are insufficient, Duolith can be expected to be effective in some patients with refractory foot ulcers in light of its efficacy in the treatment of digital ulcers and its mechanism of action. The efficacy of Duolith in the treatment of foot ulcers was also suggested by the following findings: (1) Some of [redacted] subjects with foot ulcers included in the Duolith group of the pivotal study showed a decrease in the number of foot ulcers; and (2) 9 subjects enrolled in the feasibility study conducted prior to the pivotal study received treatment for ulcers using the previous generation of Duolith with equivalent specifications to the current version of Duolith, and of these subjects, [redacted] had a total of [redacted] foot ulcers that all disappeared after treatment. Some patients with systemic sclerosis have a proximal great vessel injury in the lower limb, and the use of Duolith may not be effective in the treatment of ulcers distal to the great vessel in such patients. As a safety measure to address this concern, the following cautionary statements will be included in the instruction for use because the Duolith cannot be expected to effective in treating the peripheral region of the leg in patients with a proximal great vessel injury in the lower limb:

- The efficacy and safety of Duolith in the treatment of foot ulcers have not been evaluated in clinical studies.
- For patients complicated by a condition that could cause arterial ulcer or venous stasis ulcer, the treatment of the condition at the proximal region of the lower limb should precede the treatment with Duolith for foot ulcers in the peripheral region.

Given that the number of patients with systemic sclerosis involving foot ulcers is very limited, and that it is infeasible to evaluate the efficacy of Duolith in the treatment of foot ulcers in a sufficient number of patients as a pre-marketing evaluation, the applicant will collect data on the treatment of foot ulcers in the post-marketing use-results survey.

PMDA's view on the efficacy and safety of Duolith based on the results of the pivotal study:
The pivotal study designed as a non-randomized controlled study was not necessarily appropriate because the study design resulted in biases in patient characteristics. Given the feasibility of an investigator-initiated clinical study on the treatment of a rare disease, however, this study design was probably unavoidable. In addition, seasonal fluctuations in temperature and regional differences among study sites were considered to have only a small impact on the efficacy results.

In the pivotal study, as described earlier, there was a bias in the total number of ulcers at baseline in the study patients between the groups, and the bias may have affected the decrease in the total number of ulcers as the primary endpoint. Therefore, from these results alone, PMDA cannot conclude that the shock wave therapy is effective. However, since the results of the "proportion of subjects with a decrease of >20%, >50%, or >70% from baseline in the number of ulcers," a secondary endpoint, were significantly higher in the Duolith group than in the standard care group (see Table 3), the study demonstrated the efficacy of Duolith in the treatment of digital ulcers. No significant difference was observed between the Duolith group and the standard care group in any of the following secondary endpoints: "improvement rate in subjective pain assessment (VAS), disability assessment (HAQ), and self-assessed QOL (EQ-5D) at Weeks 4 and 8 of follow-up and treatment." However, individual

differences were large in the VAS score, and symptoms associated with systemic sclerosis in areas other than the sites treated with Duolith may have affected the results of the HAQ and EQ-5D, according to the applicant's explanation. In view of the fact that Duolith is not intended to treat systemic sclerosis, which is a systemic disease, but is used as a symptomatic therapy for skin ulcers in systemic sclerosis, the results are acceptable.

There are insufficient clinical data that support the efficacy of Duolith in the treatment of foot ulcers, and the data on the treatment of digital ulcers cannot be simply extrapolated into the treatment of foot ulcers. However, taking into account not only the applicant's explanation mentioned above, but also the facts that there is a need for access to such treatments in clinical practice because of very limited treatment options for refractory foot ulcers in systemic sclerosis, and that there was no significant problem in the safety of Duolith, there is no need to limit the indication of Duolith to the treatment of digital ulcers on the premise that information will be continuously collected in the post-marketing setting.

An analysis was performed on the safety of Duolith. In the pivotal study, a total of 6 adverse events (skin ulcer infection, finger redness, finger swelling, paronychia, Wolff-Parkinson-White [WPW] syndrome, and leg oedema) for which a causal relationship to the study device could not be ruled out occurred in 5 of 30 subjects. All of the events resolved with drug therapy except for mild WPW syndrome for which no additional care was given. No serious adverse events were reported. Therefore, PMDA determined that there was no major problem in the safety of Duolith.

Since patients with systemic sclerosis were enrolled in the pivotal study, "scleroderma" is inadequate for the intended use and "systemic sclerosis" should be used instead. PMDA instructed the applicant to modify the intended use and the applicant accepted the instruction.

6.B.(2) Post-marketing safety measures

6.B.(2).1) Precautions for proper use

PMDA's view:

Since Duolith is indicated for use in patients with systemic sclerosis involving refractory ulcers, the device should be used at institutions where shock wave treatment can be performed in collaboration with physicians who are capable of appropriately diagnosing and treating the conditions of the patient population. In addition, if the term "refractory" is included in the intended use of Duolith, it is necessary to inform users of the diagnostic criteria for the conditions based on the inclusion criteria etc. employed in the pivotal study. PMDA asked the applicant to explain the diagnostic criteria.

The applicant's explanation:

The instruction for use includes a cautionary statement that Duolith should be used at institutions where shock wave treatment is performed in collaboration with physicians who are capable of appropriately diagnosing systemic sclerosis and treating refractory ulcers. The inclusion/exclusion criteria employed in the pivotal study are also clearly stated in the instruction for use. In addition, the instruction for use includes a cautionary statement that whether the use of Duolith is necessary should be determined after treatment with a first-line drug because the efficacy of Duolith in the treatment of

refractory ulcers that were not adequately responsive to drug therapy was evaluated in the pivotal study. However, it is also meaningful to offer access to treatment with Duolith to patients who are ineligible for drug therapy for skin ulcers because they have health conditions such as pregnancy, hypersensitivity, and underlying diseases, although only patients with a history of prior drug therapy were enrolled in the pivotal study.
Based on this claim by the applicant, the following precaution was added:

- Duolith may be used in patients with systemic sclerosis involving refractory ulcers who are ineligible for drug therapy for ulcers or unlikely to have spontaneous cure. However, the efficacy and safety of Duolith in patients with such characteristics have not been evaluated in clinical studies.

PMDA's view:
The applicant's responses are acceptable in view of the fact that appropriate precautions have been added as safety measures for the indication of Duolith.

The safety measures pertinent to the method of use of Duolith were reviewed. The number of ulcers increased in some patients from Week 8 to Week 12 of treatment (see Figures 2 and 4 above). The shock wave treatment in the pivotal study was performed once weekly for up to 7 weeks for a total of 8 sessions. The therapeutic effect of Duolith has been shown to continue for at least 1 week after the treatment period but may be weakened at 5 weeks after the treatment period. The discontinuation of treatment may lead to an increase in the number of ulcers, resulting in a disadvantage for the patient. Thus, PMDA asked the applicant to explain the appropriate method of use, such as the necessity of limiting the number of repeated uses of Duolith.

The applicant's explanation:
In view of the facts that Duolith is not intended to treat the primary disease; that discontinuation of treatment with Duolith resulted in an increase in the number of ulcers in some patients; and that Duolith involves a new treatment method, and therefore the frequency and number of treatment sessions employed in the pivotal study can only be recommended at present, the following cautionary statements are added:

- Duolith is not intended to treat systemic sclerosis but is intended for use in the treatment of refractory ulcers. Since the therapeutic effect of Duolith after the treatment period is temporary, the primary disease should be treated at the same time.
- A single treatment cycle consists of 8 weekly sessions of treatment with Duolith. The necessity of re-treatment should be determined based on follow-up findings.

PMDA's view:
Taking into account that there were no major problems in the safety results of the pivotal study, setting no upper limit of the number of repeated uses of Duolith is appropriate. The applicant's responses are acceptable.

Based on the above review of the safety measures for the indication and method of use of Duolith, there is no problem with the precautions for proper use.

6.B.(2).2) Necessity of approval conditions, requirements for treating physicians/institutions, and guidelines for proper use

PMDA's view:

The basic operation of Duolith is only extracorporeal shock wave application, which is not significantly different from the method of use of the approved product for plantar fasciitis. The procedure for treatment with Duolith is not novel enough to require training for physicians in the post-marketing setting. In addition, if Duolith is generally used by physicians who are capable of appropriately diagnosing systemic sclerosis and treating refractory ulcers at institutions that allows the physicians to do so, it is unnecessary to newly establish requirements for treating physicians and institutions or guidelines for the proper use of Duolith.

As described earlier in Section "6.B.(2).1) Precautions for proper use," it is sufficient to provide a cautionary statement that Duolith should be used at institutions where shock wave treatment can be performed in collaboration with physicians who are capable of appropriately diagnosing systemic sclerosis and treating refractory ulcers. It is unnecessary to impose approval conditions for establishing requirements for treating physicians and institutions as well as guidelines for proper use.

6.B.(2).3) Necessity of post-marketing use-results survey

PMDA's conclusion on this issue is described in Section 7.

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:

Because of the extremely limited number of subjects enrolled in the clinical study, a use-results survey will be conducted as a post-marketing all-case survey until data from a certain number of patients have been gathered.

7.B Outline of the review conducted by PMDA

7.B.(1) Necessity of post-marketing use-results survey

As described above, the results of the pivotal study suggested no major safety concern. Further, Duolith has been approved and used for the treatment of plantar fasciitis without any problem in Japan. However, patient characteristics such as therapeutic drugs used for the treatment of the primary disease differ between systemic sclerosis and plantar fasciitis. Systemic sclerosis for which Duolith is indicated is an orphan disease and only 30 subjects with systemic sclerosis were enrolled in the pivotal study in which the efficacy and safety of Duolith were evaluated. Besides, multiple new drugs for systemic sclerosis have been approved after the conduct of the pivotal study and the safety of Duolith used in combination with these drugs has not been evaluated. The outcome of treatment with Duolith for foot ulcers is extremely limited. For these reasons, information on the characteristics of patients eligible for the use of Duolith and on the safety and efficacy of Duolith in combination with other drugs should be collected through the use-results survey and risk mitigation measures should be taken as necessary.

7.B.(2) Appropriateness of the number of patients to be surveyed

PMDA asked the applicant to explain the rationale for the target sample size for the use-results survey.

The applicant's explanation:

A total of 60 patients were enrolled in the pivotal study over 2 seasons. Given this fact, 120 patients could be enrolled in the survey if the enrollment period spans 4 seasons (48 months). A target sample size of 120 patients was selected for the use-results survey. From the perspective of safety evaluation, adverse events considered possibly causally related to the study device occurred in 5 of 30 subjects (6 events) in the pivotal study. Thus, the target sample size of 120 patients, which is 4 times the number of subjects enrolled in the pivotal study, can detect at least the same number of adverse events and meet the requirement for safety evaluation. In addition, ≥30 patients with foot ulcers will be included in the use-results survey based on the number of subjects (30 subjects) in the Duolith group of the pivotal study. Although it is difficult to make a direct comparison between the outcome of treatment for foot ulcers in the post-marketing setting and that of treatment for digital ulcers in the pivotal study, the use-results survey will allow comparison of the outcomes of treatment for digital and foot ulcers in a single patient, a certain comparison of the post-marketing data with data from the pivotal study, and discussion on the results.

PMDA accepted the applicant's explanation and concluded that the target sample size for this use-results survey is acceptable.

7.B.(3) Appropriateness of survey items

PMDA's view:

The decrease in the total number of ulcers should be defined as the priority survey item because the number of new ulcers was not the primary endpoint of the pivotal study. In addition, the applicant should assess survey participants in terms of the "proportion of subjects with a decrease of 20%, 50%, or 70% from baseline in the number of ulcers at Week 8 of treatment," an endpoint of the pivotal study, which served as a reference for determining the efficacy of Duolith in the study. Thus, PMDA instructed the applicant to do so. There is no problem because the applicant responded that the survey items would be modified and added.

Based on the above review, PMDA concluded that the applicant's use-results survey plan (Table 4) is acceptable.

Table 4. Outline of the use-results survey plan

Objective	To confirm the efficacy and safety of treatment with Duolith in patients with systemic sclerosis involving refractory ulcers in the post-marketing clinical setting.
Patient population	Patients with systemic sclerosis involving refractory ulcers
Sample size (planned)	120 patients (all-case surveillance) At least 30 patients with foot ulcers will be included in the survey based on the number of subjects (30 subjects) in the Duolith group of the pivotal study to confirm the therapeutic effect of Duolith on foot ulcers.
Survey period (planned)	5 years (preparation period of 6 months, patient enrollment period of 48 months, follow-up period of 3 months, and analysis period of 3 months) [Rationale: Since ulcers in systemic sclerosis are characterized by exacerbation in winter, a majority of patients will be enrolled in the survey around December to February. The patient enrollment period spans 4 seasons, i.e., 48 months.]
Key survey items	Confirm that the decrease in the total number of ulcers from baseline to Week 8 of treatment is comparable to the results in the pivotal study, and investigate the decrease in the total number of ulcers at Week 12 of treatment.
Main survey items	• Decrease in the total number of foot ulcers and the number of new foot ulcers at Weeks 8 and 12 of treatment • Proportion of subjects with a decrease of 20%, 50%, or 70% from baseline in the number of ulcers at Week 8 of treatment • Use of concomitant drugs during the treatment and follow-up periods • Serious adverse events for which a causal relationship to Duolith could not be ruled out during the treatment and follow-up periods • Malfunctions of Duolith and adverse events for which a causal relationship to Duolith could not be ruled out that occurred during the treatment and follow-up periods

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

PMDA conducted document-based and on-site inspections and a data integrity assessment for the medical device application data 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

Duolith is an extracorporeal shock wave pain treatment device for use in orthopedics, and it is designed to provide low-energy extracorporeal shock wave treatment by modifying the energy level of the conventional electromagnetic extracorporeal shock wave lithotripsy device. The present application has been submitted as a partial change application to expand the intended use of Duolith to include the treatment of refractory ulcers in patients with systemic sclerosis. The key issues to be discussed in the review of the application for Duolith are (1) the clinical significance of approving Duolith, (2) the efficacy and safety of Duolith, (3) the intended use, (4) post-marketing safety measures, and (5) use-results surveys. PMDA drew conclusions on the key issues based on comments raised in the Expert Discussion, and the conclusions are presented in the subsections below

(1) Clinical significance of approving Duolith

PMDA's conclusion:

In Japan, drugs approved for the treatment of systemic sclerosis include "Tracleer Tablets 62.5 mg" (non-proprietary name, bosentan hydrate) and "Rituxan Intravenous Infusion 100 mg and Rituxan Intravenous Infusion 500 mg" (non-proprietary name, rituximab [genetical recombination]), but only

“Alprostadil Injection 5 μg/10 μg” (non-proprietary name, alprostadil) is approved for the indication of improvement in healing of skin ulcers. Subject enrolled in the pivotal study according to the inclusion/exclusion criteria were those who did not respond to treatment with alprostadil injection (the only drug approved for the indication of improvement in healing of skin ulcers in systemic sclerosis at the time when the pivotal study was conducted) for ≥4 weeks and those who were ineligible for the use of alprostadil injection. Therefore, the efficacy of Duolith was evaluated in subjects with refractory ulcers who had no adequate response to the drug.

Although Duolith is not intended to treat systemic sclerosis as the primary disease, it is meaningful to introduce Duolith in clinical practice as one of symptomatic treatment options for refractory ulcers in patients with systemic sclerosis, because the conventional treatment options are limited.

(2) Efficacy and safety of Duolith

PMDA’s conclusion:

The applicant submitted the clinical data of Duolith in the form of the results of the non-randomized controlled study using standard care as a comparator, which was an investigator-initiated clinical study in patients with systemic sclerosis involving refractory digital ulcers conducted in Japan. In the pivotal study, the decrease in the total number of ulcers at Week 8 of treatment, the primary endpoint, was significantly greater in the Duolith group than in the standard care group. The decrease in the total number of ulcers may have been affected by a bias in the total number of ulcers at baseline in both groups, but the proportion of subjects with a decrease in the total number of ulcers, a secondary endpoint, was significantly higher in the Duolith group than in the standard care group, and thus the study showed a certain level of efficacy of Duolith in the treatment of refractory digital ulcers. Since the pivotal study was conducted as a non-randomized controlled study, the impact of biases in patient characteristics was also examined. Taking into account the explanation by the applicant, the evaluation based on data from the pivotal study is acceptable. In the pivotal study, no serious adverse events occurred, and adverse events for which a causal relationship to the study device could not be ruled out were mild or moderate. All of the moderate adverse events resolved with drug therapy. Therefore, there is no major problem in the safety of Duolith.

In addition, although clinical data supporting the efficacy of Duolith in the treatment of foot ulcers are very limited, there is no need to limit the indication of Duolith to the treatment of digital ulcers on the premise that post-marketing information will be continuously collected, for the following reasons: i) The treatment options for refractory foot ulcers in systemic sclerosis are very limited and there is a need for such treatments in clinical practice; ii) the efficacy data for the treatment of digital ulcers cannot be simply extrapolated into the treatment of foot ulcers, but data on the efficacy of Duolith in the treatment of digital ulcers and its mechanism of action suggest that the efficacy of Duolith is promising in some patients with refractory foot ulcers; iii) in the pivotal study and a feasibility study, some results showed that the number of foot ulcers decreased in some patients after treatment with Duolith; and iv) there is no significant problem in the safety of Duolith.

Based on the above, Duolith can maintain the risk-benefit balance for the treatment of refractory upper and lower limb ulcers in systemic sclerosis.

(3) Intended use

PMDA's conclusion:

Duolith was developed for the treatment of refractory ulcers in patients with systemic sclerosis except for patients with localized scleroderma, and the pivotal study enrolled only patients with systemic sclerosis. Therefore, the primary disease in the statements of the intended use and the indication proposed at the time of submission of the application should be changed to "systemic sclerosis" and the intended use should be modified to the intended use shown in the section of Overall Evaluation.

(4) Post-marketing safety measures

PMDA's conclusion:

The basic operation of Duolith is only extracorporeal shock wave application, which is not significantly different from the method of use of the approved product for plantar fasciitis. The procedure for treatment with Duolith is not novel enough to require training for physicians in the post-marketing setting. In addition, if Duolith is used by physicians who are capable of appropriately diagnosing systemic sclerosis and treating refractory ulcers at institutions that allows the physicians to do so, it is unnecessary to newly establish requirements for treating physicians and institutions or guidelines for the proper use of Duolith. In view of this consideration, the instruction for use includes a precautionary statement that Duolith should be used at institutions where shock wave treatment is performed in collaboration with physicians who are capable of appropriately diagnosing systemic sclerosis and treating refractory ulcers. Therefore, it is not necessary to impose approval conditions. Although only patients with a history of prior drug therapy were enrolled in the pivotal study, it is also meaningful to offer access to treatment with Duolith to patients who are ineligible for drug therapy for ulcers. Besides, there was no problem in the safety of Duolith, regardless of prior drug therapy. If the instruction for use includes precautions for the use of Duolith in such patients, there was no problem with not restricting the indication.

(5) Use-results survey

PMDA's conclusion:

Systemic sclerosis for which Duolith is indicated is an orphan disease, and only 30 subjects with systemic sclerosis were enrolled in the pivotal study that evaluated the efficacy and safety of Duolith. Besides, the outcome of treatment with Duolith for foot ulcers is extremely limited. For these reasons, information on the characteristics of patients eligible for the use of Duolith and on the safety and efficacy of Duolith in combination with drugs should be collected and risk mitigation measures should be taken as necessary, and thus, a use-results survey is necessary. The survey period should be 5 years including the preparation period, enrollment period, follow-up period, and analysis period. The follow-up period should be 3 months for comparison with the study results.

Based on the above results, PMDA has concluded that Duolith may be approved after modifying the intended use as shown below.

Intended Use

Duolith SD1 Ultra is indicated for heel pain in patients with refractory plantar fasciitis who have a history of failed conservative therapy for at least 6 months. Shock waves are extracorporeally applied to the affected area in a non-invasive manner to heal or reduce pain.

Duolith SD1 Ultra is indicated for the treatment of refractory upper and lower limb ulcers in systemic sclerosis.

(Underline demotes additions.)

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 use-results survey period should be 5 years.

PMDA has concluded that the present application should be subjected to deliberation by the Committee on Medical Devices and *In-vitro* Diagnostics.

Review Report (2)

November 2, 2022
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).

Classification	Instrument & Apparatus 12, Physical Therapy Apparatus
Term Name	Extracorporeal shockwave pain treatment device
Brand Name	Duolith SD1 Ultra
Applicant	Karl Storz Endoscopy Japan K.K.
Date of Application	October 27, 2021
Items Warranting Special Mention	None
Reviewing Office	Office of Medical Devices II

Review Results

November 2, 2022

Classification	Instrument & Apparatus 12, Physical Therapy Apparatus
Term Name	Extracorporeal shockwave pain treatment device
Brand Name	Duolith SD1 Ultra
Applicant	Karl Storz Endoscopy Japan K.K.
Date of Application	October 27, 2021

Results of Review

Whether Duolith SD1 Ultra (hereinafter referred to as "Duolith") should be approved was deliberated at a meeting of the Committee on Medical Devices and *In-vitro* Diagnostics held on September 5, 2022 based on the conclusion of the Pharmaceuticals and Medical Devices Agency (PMDA) shown in the Review Report (Review Report on Duolith SD1 Ultra, dated August 15, 2022). At the meeting, the Committee pointed out the reproducibility of shock wave treatment and the appropriateness of the efficacy evaluation in the "non-randomized controlled study using standard care as a comparator" (hereinafter referred to as "the pivotal study"), which was an investigator-initiated clinical study in patients with systemic sclerosis involving refractory digital ulcers conducted in Japan. The conclusion of the meeting was that the efficacy of Duolith should be further discussed based on the additional information including the characteristics of shock waves of Duolith, purpose of use of a stand-off to be attached to the handpiece, usage of the study device in the pivotal study, and appropriateness of the efficacy evaluation for Duolith used for the treatment of ulcers. Consequently, the Committee decided to continue the deliberation.

First, the characteristics of shock waves of Duolith and the purpose of use of a stand-off to be attached to the handpiece are explained to verify the reproducibility of the results of the investigator-initiated clinical study in routine clinical practice. The C-ACTOR handpiece for the treatment of ulcers is designed to be used so that the skin surface coincides with the shock wave focus; however, the handpiece alone does not allow the user to visually determine the focal length. For this reason, the stand-off II to be attached to the handpiece is configured to enable the user to objectively recognize that the shock wave focus is near the tip of the stand-off II. The stand-off II is made of elastic polyether urethane, and it is intended to bring its tip into contact with the skin (without pressing the tip against it). Its method of use is the same as that for the approved indication for use in patients with plantar fasciitis. Non-clinical studies have demonstrated that the pressure difference of a shock wave of Duolith between the focal point and a position [redacted] mm away from the focal point is approximately [redacted]% without significant attenuation. Thus, shock wave treatment does not require rigorous procedures such that the skin surface completely coincides with the shock wave focus.

The pivotal study permitted only the use of the stand-off II attached to the handpiece. The specifications for shock waves that physicians were allowed to set were only “energy level (corresponding to energy flux density),” “number of shock wave impulses,” and “frequency of shock waves.” The focal length of the handpiece (distance from the tip of the handpiece to the shock wave focus) could not be changed arbitrarily by physicians, and the procedures for treatment with the study device, including how the stand-off II was placed on the skin, were standardized to minimize the impact of differences in the procedures on the efficacy of the treatment. The above findings support the reproducibility of shock wave therapy in the pivotal study.

Next, an explanation for the appropriateness of the efficacy evaluation in the investigator-initiated study is provided. The primary endpoint of the pivotal study is the decrease in the number of ulcers assessed visually by the investigator or sub-investigator. The rationales for setting this primary endpoint are as follows: (1) There is no established image assessment method for healing of ischemic digital ulcers as the common symptom of systemic sclerosis; (2) it is difficult to take photographs under standardized conditions, considering that some patients have difficulty in opening their fingers and that there are disease characteristics specific to patients with systemic sclerosis, such as the presence of multiple relatively small ulcers in the fingers; and (3) the number of ulcers assessed visually by the investigator was the primary endpoint of the clinical studies of “Tracleer Tablets 62.5 mg” (Approval No. 21700AMY00170000), a drug approved both in and outside of Japan for the prevention of new ulcers in patients with systemic sclerosis. Against the above background, the rationale for the design of the pivotal study is understandable to a certain extent. Furthermore, the applicant took measures to minimize biases in evaluation between the two groups in the pivotal study. Given this, the efficacy of Duolith is evaluable based on the results of the pivotal study.

As a result of its review, PMDA considers that it is meaningful to introduce Duolith in clinical practice as one of the symptomatic treatment options for refractory ulcers in patients with systemic sclerosis, because of limited conventional treatment options. PMDA concluded that Duolith may be approved for the following intended use and that this conclusion should be presented to the Committee on Medical Devices and *In-vitro* Diagnostics for further deliberation.

Intended Use

Duolith SD1 Ultra is indicated for pain relief in patients with refractory plantar fasciitis who have a history of failed conservative therapy for at least 6 months. Shock waves are extracorporeally applied to the affected areas in a non-invasive manner to heal or reduce pain.

Duolith SD1 Ultra is indicated for the treatment of refractory upper and lower limb ulcers in systemic sclerosis.

(Underline denotes addition.)

Review Report

November 2, 2022

Product for Review

Classification	Instrument & Apparatus 12, Physical Therapy Apparatus
Term Name	Extracorporeal shockwave pain treatment device
Brand Name	Duolith SD1 Ultra
Applicant	Karl Storz Endoscopy Japan K.K.
Date of Application	October 27, 2021
Proposed Intended Use	Duolith SD1 Ultra is indicated for pain relief in patients with refractory plantar fasciitis who have a history of failed conservative therapy for at least 6 months. Shock waves are extracorporeally applied to the affected area in a non-invasive manner to heal or reduce pain. Duolith SD1 Ultra is indicated for the treatment of refractory upper and lower limb ulcers in scleroderma. (Underline denotes additions.)

Table of Contents

1. Content of the Review

Whether Duolith SD1 Ultra (hereinafter referred to as "Duolith") should be approved was deliberated at a meeting of the Committee on Medical Devices and *In-vitro* Diagnostics held on September 5, 2022 based on the conclusion of the Pharmaceuticals and Medical Devices Agency (PMDA) shown in the Review Report (Review Report on Duolith SD1 Ultra, dated August 15, 2022; [Review Report (1)]). At the meeting, the Committee pointed out the reproducibility of shock wave therapy and the appropriateness of the efficacy evaluation in the "non-randomized controlled study using standard care as a comparator" (hereinafter referred to as "the pivotal study"), which was an investigator-initiated clinical study in patients with systemic sclerosis involving refractory digital ulcers conducted in Japan. The conclusion of the meeting was that the efficacy of Duolith should be further discussed based on the additional information including the characteristics of shock waves of Duolith, purpose of use of a stand-off to be attached to the handpiece, usage of the study device in the pivotal study, and appropriateness of the efficacy evaluation for Duolith used for the treatment of ulcers. Consequently, the Committee decided to continue the deliberation.

For the continued deliberation, the outline of the review was presented by PMDA.

(1) Reproducibility of the results of the investigator-initiated clinical study in routine clinical practice

(1).1) Characteristics of shock waves of Duolith and purpose of use of a stand-off to be attached to the handpiece

The shock wave specifications that physicians can set (change) when using Duolith were only "energy level (corresponding to energy flux density)," "number of shock wave impulses," and "frequency of shock waves." Two handpieces included in the configuration of Duolith have different indications for use as shown below, and therefore the focal length and focal size are different for each handpiece. Physicians cannot arbitrarily change the focal length.

- SEPIA handpiece (a component for the approved indication): Used for pain relief in patients with plantar fasciitis
- C-ACTOR handpiece (a component to be added for the proposed indication): Used for the treatment of refractory ulcers in systemic sclerosis

The results of non-clinical studies indicate that shock waves, focused by the parabolic reflector located inside the handpiece of Duolith, have a focal length of 28.5 mm (distance from the tip of the handpiece to the shock wave focus) for the C-ACTOR handpiece used in the treatment of ulcers and the study device. Although the C-ACTOR handpiece is designed to be used so that skin surface coincides with the shock wave focus, the handpiece alone does not allow the user to visually determine the focal length. For this reason, the stand-off II to be attached to the handpiece is configured to enable the user to objectively recognize that the shock wave focus is near the tip of the stand-off II (see Figure 1 on the next page).

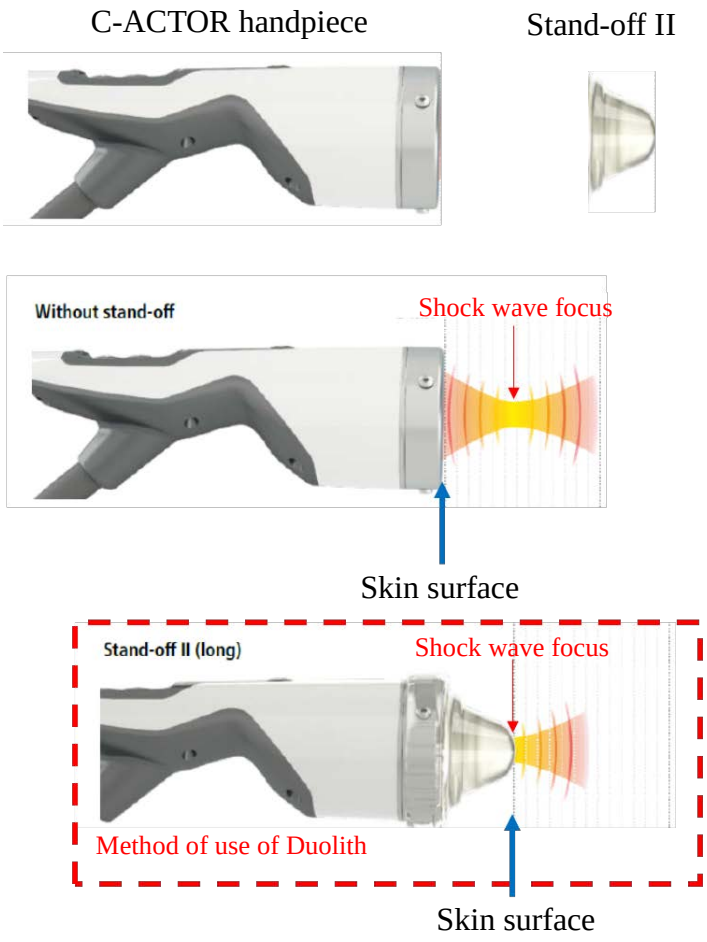


Figure 1. Image showing the relationship between the focus of the C-ACTOR handpiece and stand-off II
(Top, name of each component; middle, when the tip of the handpiece without the stand-off is in contact with the skin surface; bottom, when the tip of the stand-off II attached to the handpiece is in contact with the skin surface)

The yellow part in Figure 1 above shows the shock wave focus. Although the focal length of the C-ACTOR handpiece is unchanged regardless of the use of the stand-off II, a shock wave cannot be focused on the skin surface when the tip of the handpiece without the stand-off is in direct contact with the skin surface (see the middle image in Figure 1) as compared to when the tip of the stand-off II attached to the handpiece is in contact with the skin surface (see the bottom image enclosed by the dashed line in Figure 1). The applicant designed Duolith so that the C-ACTOR handpiece with the stand-off II is used for the treatment of ulcers as it is intended to bring the shock wave focus to near the skin surface.

The raw materials of the stand-off II include elastic polyether urethane, which can easily stick closely to the skin without being pressed against it. In contrast, if the handpiece is pressed against the skin with excessive force, the stand-off II may become deformed, resulting in a substantial separation of the shock wave focus from the skin surface. The stand-off II is intended to provide the user with an appropriate focal length. The applicant developed the stand-off II to bring the tip of the stand-off II into contact with the skin surface during treatment, and not to press the tip of the stand-off II against the skin surface to cause deformation of the stand-off II. The method of use of Duolith for the treatment of ulcers is the same as that for use in patients with plantar fasciitis as the approved

indication. Non-clinical studies have demonstrated that the pressure difference of a shock wave of Duolith between the focal point and a position [redacted] mm away from the focal point is approximately [redacted]% without significant attenuation. Thus, shock wave treatment does not require rigorous procedures such that the skin surface completely coincides with the shock wave focus.

(1).2) Usage of the study device in the pivotal study

In the pivotal study, subjects received a total of 8 weekly sessions of shock wave treatment. As described in Table 2 in Section 6.A of the Review Report (1), 20 sites of application per hand are specified as a guide for the application of shock waves to the upper limb. If an ulcer is present at a planned application site, the user should apply shock waves to the areas around the ulcer, instead of bringing the stand-off II into direct contact with the ulcer to apply shock waves. In the pivotal study, only the stand-off II attached to the handpiece was used, and the usage was consistent among physicians or patients.

- Energy level: [redacted] to 0.25 mJ/mm^2. *Start the first treatment session at the minimum energy level. Increase the energy level to the maximum while observing the subject for pain. Start the second and subsequent treatment sessions at the maximum energy level that is tolerable in the subject.
- Number of shock wave impulses: 100 impulses per site
- Frequency of shock waves: a maximum of 4 Hz

The method of use of Duolith is specified as shown below, based on the usage in the pivotal study:

- Shock waves are applied to the affected area and its surrounding area once a week. In principle, shock waves should be applied at an energy level of 0.25 mJ/mm^2 and at a frequency of 4 Hz, with 100 pulses per site. The shock wave settings may be adjusted according to the patient's condition.

The applicant intends to bring the tip of the stand-off II into contact with the skin. The applicant, therefore, repeatedly confirmed the operation method and procedure of the study device before initiating the study at the study sites for the Duolith group of the pivotal study. In doing so, the applicant confirmed the method of bringing the stand-off II into slight contact with the skin surface, based on the principle of shock wave application with the study device. Therefore, the protocol specified the unified procedures for treatment including how to bring the stand-off II into contact with the skin, and the impact of differences in procedures in the pivotal study on the efficacy of Duolith has been minimized.

Based on the above 1) and 2), PMDA concluded that clinical data were collected through the use of the study device according to the specified method of use in the pivotal study, ensuring the reproducibility of shock wave therapy. Because the use of the C-ACTOR handpiece and the stand-off II is essential for the treatment of ulcers, the method of use of the C-ACTOR handpiece and the stand-off II for this treatment should be clearly stated in the product application and the instruction for use. In addition, since the shock wave focus is positioned at the tip of the stand-off II, information on the appropriate method of use should be provided in the instruction for use so that the stand-off II can be in contact with the skin without causing deformation of the stand-off II.

(2) Appropriateness of efficacy evaluation for the treatment of ulcers in the investigator-initiated study

For the efficacy evaluation including the primary endpoint of the pivotal study, "a decrease in the total number of ulcers at Week 8 of follow-up and treatment," the number of ulcers assessed visually by the investigator or sub-investigator was used.

The applicant's explanation about the following 3 rationales for using the endpoint:

- There is no established image assessment method for healing of ischemic digital ulcers as the common symptom of systemic sclerosis. Various studies have previously reported that accurate assessment of various ulcer conditions (e.g., ulcer depth and ulcer shape) is difficult, and that the only reliable endpoint is the number of ulcers present at the time of follow-up.[1)] For these reasons, the assessment of epithelialization of the sites of ulceration that have been visually confirmed at the time of medical examination was considered appropriate for evaluating the efficacy of Duolith.
- Patients with systemic sclerosis often have swelling and stiffness of fingers, and some of them have difficulty in opening their fingers. In addition, ulcers in systemic sclerosis are smaller than those associated with other primary diseases and involve multiple sites. If image assessment for ulcers is required, photographs of the ulcers have to be taken under these restrictions, and it is difficult to take photographs under uniform conditions.
- In the clinical studies of "Tracleer Tablets 62.5 mg" (Approval No. 21700AMY00170000), a drug approved for the prevention of new ulcers in patients with systemic sclerosis both in and outside of Japan, the number of ulcers assessed visually by the investigator was the primary endpoint. The pivotal study was planned with reference to this assessment method.

The applicant added the explanation as follows:

To adopt the design of a non-randomized study, the applicant at least took measures to minimize biases in evaluation between the groups. Specifically, no investigators were involved in medical examination of both groups in the pivotal study, and data such as changes in the number of ulcers in each individual study subject at study sites for either group were not shared with other sites during the study period.

As reference information, the summary of data from a feasibility study (clinical research) is shown below.[2)] The feasibility study was conducted prior to the initiation of the pivotal study to explore the efficacy of shock wave therapy for refractory ulcers including those in patients with systemic sclerosis. The feasibility study compared the efficacy of shock wave therapy versus the results of standard care with drugs collected in an observational study. Nine patients with systemic sclerosis were included in the shock wave therapy group, and 17 patients in the standard care group, consisting of 14 patients with systemic sclerosis and 3 patients with systemic lupus erythematosus.[1] As the results of efficacy evaluation, the proportion of subjects in whom ulcers disappeared at Week 8 of treatment is shown below. Although differences in protocols and other conditions preclude stringent comparison, there is some consistency between the results of the pivotal study and the published results of the feasibility study.

[1] An autoimmune disease, which is a designated intractable disease as with systemic sclerosis.

- In the feasibility study, 44% (4 of 9 subjects) in the shock wave therapy group and 18% (3 of 17 subjects)* in the standard care group
- In the investigator-initiated study, [redacted]% ([redacted] of 30 subjects) in the shock wave therapy group and [redacted]% ([redacted] of 30 subjects) in the standard care group

  * The result excluding 3 patients with systemic lupus erythematosus was [redacted]% (3 of [redacted] subjects).

PMDA's view on the efficacy evaluation for Duolith:
In a clinical study investigating treatment for skin ulcers, the efficacy of the treatment should be evaluated based on objective indices wherever possible. For example, it is desirable to use outcome measures such as the percentage reduction in wound radius calculated based on the images of a site of ulceration. However, skin ulcers in patients with systemic sclerosis are mainly ischemic digital ulcers and are characterized by a large number of ulcers that have relatively small size. It cannot be said that image assessment methods for the area or number of ulcers have been established not only when the pivotal study was being planned but also at present. Based on these disease characteristics, the number of ulcers assessed visually by the investigator is acceptable as the primary endpoint of the pivotal study, and the efficacy of Duolith is evaluable based on the results of the pivotal study to a certain extent. On that basis, a certain level of efficacy of Duolith has been demonstrated, taking into account (1) that there are limitations in the evaluation of results from the pivotal study conducted in an open-label setting, but treatment options for skin ulcers in patients with systemic sclerosis are limited; (2) that due to the small number of patients with systemic sclerosis, there was no choice but to consider the feasibility of an investigator-initiated study; (3) that the pivotal study was conducted after fully considering the information on the clinical studies of the approved drug, "Tracleer Tablets 62.5 mg"; and (4) that the above-mentioned feasibility study has also suggested a certain level of efficacy of Duolith.

2. Overall Evaluation

Duolith is an extracorporeal shockwave pain treatment device, and it is designed to provide low-energy extracorporeal shockwave treatment by modifying the energy level of the conventional electromagnetic extracorporeal shockwave lithotripsy device. The present application is a partial change application submitted to expand the intended use of Duolith to include the treatment of refractory ulcers in patients with systemic sclerosis. Since the reproducibility of shock wave therapy and the appropriateness of the efficacy evaluation in the pivotal study were pointed out in the meeting of the Committee on Medical Devices and *In-vitro* Diagnostics held on September 5, 2022, PMDA additionally reviewed the characteristics of shock waves of Duolith and the purpose of use of the stand-off to be attached to the handpiece, usage of the study device in the pivotal study, and the appropriateness of the efficacy evaluation for treatment of ulcers. In addition to the results of the Review Report (1), PMDA concluded as shown below.

(1) Reproducibility of shock wave therapy and appropriateness of efficacy evaluation in the investigator-initiated study

PMDA's view:
As described in Section I, the reproducibility of the treatment method employed in the pivotal study has no problems in terms of the role of the stand-off II, the impact of the handpiece on the

characteristics of shock waves, and the usage of the hand-off in the pivotal study. The efficacy of Duolith comparable to that demonstrated in the pivotal study will be ensured as long as the treatment of ulcers in systemic sclerosis is performed according to the method of use of Duolith established based on its usage in the pivotal study. In addition, the fact that the number of ulcers assessed visually by the investigator was used as the primary endpoint for efficacy in the study is understandable to a certain extent, given that (a) there is currently no established image assessment method for healing of ischemic digital ulcers as the common symptom of systemic sclerosis; (b) it is difficult to take photographs under standardized conditions, considering that some patients have difficulty in opening their fingers and that there are disease characteristics specific to patients with systemic sclerosis, such as the presence of multiple relatively small ulcers in the fingers; and (c) the number of ulcers assessed visually by the investigator was used in the studies of the approved drug, and the pivotal study was planned based on this assessment method. Taking into account the fact that the applicant at least took measures to minimize biases in evaluation between the groups, the efficacy of Duolith is evaluable based on the results of the pivotal study.

Based on the above results, PMDA concluded that the product may be approved after modifying the intended use as shown below.

Intended use

Duolith SD1 Ultra is indicated for pain relief in patients with refractory plantar fasciitis who have a history of failed conservative therapy for at least 6 months. Shock waves are extracorporeally applied to the affected area in a non-invasive manner to heal or reduce pain.

Duolith SD1 Ultra is indicated for the treatment of refractory upper and lower limb ulcers in systemic sclerosis.

(Underline denotes additions.)

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 use-results survey period should be 5 years.

PMDA has concluded that the present application should be subjected to deliberation by the Committee on Medical Devices and *In-vitro* Diagnostics.

References

1) M. Matucci-Cerinic, J. R. Seibold, Digital ulcers and outcomes assessment in scleroderma. *Rheumatology.* 2008;47:46-47.

2) Ishii, et al. Development of new treatment for digital ulcer of systemic sclerosis. *Clinical Rheumatology and Related Research.* 2018;30:231-240.